NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease [ID709]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Premeeting briefing

Eliglustat for treating type 1 Gaucher disease

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees, and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Evaluation Committee meeting and should be read with the full supporting documents for this evaluation.

Key issues for consideration

Clinical effectiveness

- Eliglustat was compared with imiglucerase in a non-inferiority trial. Does the committee consider that the observed differences in the trial are clinically important? Does the committee consider that eliglustat and imiglucerase are equivalent in terms of clinical efficacy?
- There is no direct evidence in the treatment naive population eliglustat compared with enzyme replacement therapy (ERT). There is no direct evidence for eliglustat compared with velaglucerase in people who are stable on enzyme replacement therapy. Is the committee satisfied with the company's assumption that eliglustat is equivalent to the comparators for each population?
- Have the benefits of oral treatment been appropriately captured?
- Does the evidence provide enough information to anticipate the likely long-term effects of treatment with eliglustat?

Value

- Is the clinical effectiveness of eliglustat and ERTs appropriately modelled?
  - The company assumes ERT dosing will be the same as in the ENCORE trial. However, there is uncertainty regarding the doses of ERT used in clinical practice. In ENCORE 58% of patients were receiving doses of at least 35 U/kg every two weeks. The marketing authorisations for imiglucerase and velaglucerase recommend a starting dose of 60U/kg every two weeks. However, advice to the ERG suggested that typical doses are 20-40 U/kg. What dose of ERT is generalisable to people with Gaucher disease in England?
- The magnitude of utility benefit associated with taking an oral treatment is assumed to be 0.12. Does the committee consider this to be appropriate?
- Does the committee have confidence in the structure and assumptions of the company's model?
- Does the committee agree that the ERG explorations are appropriate?
- What is the committee's view on the most likely cost and benefit associated with eliglustat?
- What is the committee's view on the most likely budget impact?
- Are there any significant benefits of eliglustat, beyond direct health benefits, which have not been taken into account in the economic analysis?

1 Nature of the condition

1.1 Gaucher disease is an inherited lysosomal storage disorder. It is caused by a deficiency of an enzyme (glucocerebrosidase) which leads to the storage of complex lipids in some types of blood cells. This creates Gaucher cells which occur throughout the liver, spleen, bone marrow and occasionally the lungs. There are 3 subtypes of Gaucher disease, of which type 1 (non-neuropathic) is the most prevalent. All types of Gaucher disease are associated with a variety of symptoms, including pain, fatigue, anaemia,

thrombocytopenia, jaundice, bone damage, and enlargement of the liver and spleen.

1.2 There is limited data available on the epidemiology of Gaucher disease. Over 90% of people affected have type 1 Gaucher disease. The overall frequency of all types of Gaucher disease is approximately 1 in 50,000 to 1 in 100,000 live births. The prevalence of type 1 Gaucher disease is estimated as 1 in 200,000 in non-Ashkenazi Europeans, which equates to approximately 250 people in England and Wales. It is more common in people of Ashkenazi family origin, with a frequency of approximately 1 in 500 to 1 in 1000 live births. Clinical experts estimate that there are between 350 to 400 patients with Gaucher disease in England, and 50 to 100 patients will receive treatment with eliglustat.

1.3 The company submission states that the natural history of untreated disease prior to the availability of enzyme replacement therapy (ERT) is poorly documented and there is limited information on life expectancy for patients with Gaucher disease. People who present below the median age of approximately 14 years with massive splenomegaly and hypersplenism. This is generally followed by progression to bone disease and immobility in the third or fourth decade of life with a high early mortality.

1.4 Patient experts described how type 1 Gaucher disease can have a profound impact on health-related quality of life:

- Symptoms of the Gaucher disease are not easily recognised and diagnosis can take a long time
- Its rarity means that there little information for people with the condition leading to frustration and anxiety
- The disease however has an immediate impact on family life, social interactions and work
- There is a social stigma because of lack of understanding of the disease; there is an unmet need for mental health and psychosocial support
- Haematological, bone and visceral symptoms are key factors affecting the health-related quality of life of people with type 1 Gaucher disease. As disease progresses patients can experience anaemia and thrombocytopenia resulting in fatigue, joint pain and reduced mobility. Severe disease is associated with bone damage, with an increased incidence of fragility fractures, pain and loss of self-reliance.
- Current treatment options require regular IV infusions which is time consuming and burdensome for patients and caregivers.

1.5 A survey of people with the Gaucher syndrome identified that on average they saw 3-4 different healthcare professionals before being diagnosed. The showed that the mean time between symptoms and diagnosis was approximately 7 years. More recently, since the establishment of 8 specialist centres in England, many people report a shorter smoother diagnosis journey.

1.6 Patient groups reported that people with Gaucher disease face the challenge that they have an invisible disease and from the outside

they look normal since they do not have a visible disability, except for a handful of older patients that use a wheelchair or walking aids. This results in patients experiencing difficulties in accessing the care, support and services they need. For example benefits and employment support such as rest breaks, reduced working hours, time off for appointments and treatment.

1.7 Patient groups reported that even though treatment was made available on an individual patient basis in 1992, patients and their families faced significant challenges in accessing funding through local primary care trusts because of high cost of the treatment and the lack of knowledge of the disease. People with Gaucher disease still face challenges in being able to communicate with others about their disease and have to become experts in their own right. They know more about their disease than most GPs and other medical staff they come into contact with outside of the specialist centres.

1.8 Current management options include enzyme replacement therapy (such as imiglucerase or velaglucerase alfa) or substrate reduction therapy (miglustat) for people for whom enzyme replacement therapy is not suitable, alongside supportive therapy (which may include blood products, bisphosphonate therapy and/or analgesia). NHS England stated that current clinical practice in England is to titrate the dose of ERT and use the lowest effective dose. The company stated that miglustat is used in a very small number of people. Experts noted that people with type 1 Gaucher disease choose ERT whenever possible because miglustat is associated with tolerability and safety issues and modest efficacy. The company submission outlined that the management of Gaucher disease requires an individualised approach to treatment that takes into consideration the patient's disease manifestations and disease burden as well as quality-of-life needs.

1.9 The Lysosomal Storage Disorder Expert Advisory Group Standard Operating Procedures (SOP) recommends velaglucerase as the first choice for initiation of therapy, based on cost, but imiglucerase is also recommended as it is considered of equivalent efficacy. Miglustat is licensed only for patients with mild to moderate type 1 Gaucher disease in whom ERT is unsuitable. The company submission (page 48) contains more information on the dosing recommendations described in the SOP. The experts stated that the recommendations are followed consistently, resulting in minimal variation in practice.

1.10 Experts stated that enzyme replacement therapy is very effective, but is associated with a burden because it requires intravenous infusion every two weeks, causing an impact on physical and psychological well-being. Patient experts commented that eliglustat, being an oral treatment, will offer more freedom for patients and could potentially enhance quality of life compared with current treatments. There will also be no need to use a homecare service, wait for deliveries or store treatments in a refrigerator.

2 The technology

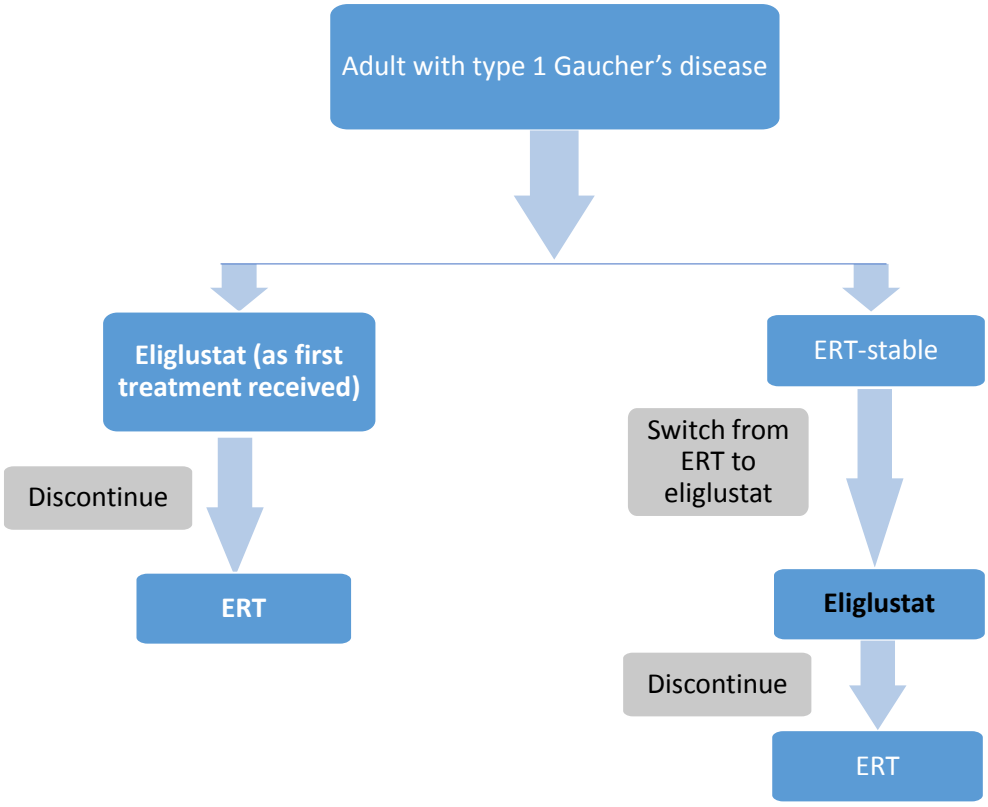
2.1 Eliglustat (Cerdelga, Genzyme Therapeutics) is a substrate reduction therapy that partially inhibits the enzyme glucosylceramide synthase, resulting in reduced production of glucosylceramide and Gaucher cells. It is given orally.

2.2 Eliglustat has a marketing authorisation in the UK for the long-term treatment of type 1 Gaucher disease in adults who are CYP2D6 poor metabolisers, intermediate metabolisers or extensive metabolisers. The recommended dose stated in the summary of product characteristics is 84 mg eliglustat twice daily in CYP2D6 intermediate metabolisers (IMs) and extensive metabolisers (EMs).

The recommended dose is 84 mg eliglustat once daily in CYP2D6 poor metabolisers (PMs).

2.3 The list price of eliglustat is £282.34 per capsule. People would be expected to have a total of 730.5 capsules over the course of the average year meaning that the total drug cost per person per year of treatment with eliglustat is £206,249.37 per year. For poor metabolisers, who will receive a total of 365.25 capsules per year, the total drug cost is £103,124.69 per year.

Figure 1. Expected positioning of eliglustat in clinical practice



2.4 Eliglustat is intended to be used in adults with type 1 Gaucher disease who are either stable on ERT who will be switched to eliglustat or people who have not had treatment.

2.5 The summary of product characteristics lists the following adverse reactions for eliglustat: headache, nausea, diarrhoea, abdominal pain, flatulence, arthralgia and fatigue. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this evaluation was: To evaluate the benefits and costs of eliglustat within its licensed indication for the treatment of type 1 Gaucher disease for national commissioning by NHS England.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults with type 1 Gaucher disease who are CYP2D6 poor metabolisers, intermediate metabolisers or extensive metabolisers	Adults with Gaucher disease type 1.
Intervention	Eliglustat	Eliglustat 84.4mg (as free base, equivalent to 100mg eliglustat tartrate) twice daily in intermediate metabolisers and extensive metabolisers, and once daily in poor metabolisers.
Comparators	• Imiglucerase • Velaglucerase alfa For people for whom enzyme replacement therapy is unsuitable: • miglustat	• Imiglucerase • Velaglucerase alfa The company stated that miglustat is not considered a relevant comparator as it is only used in a very small proportion of patients in England for whom ERT is unsuitable (<2% [4 patients] in 2015). The company stated that eliglustat would not be expected to be used in place of it
Outcomes	• type 1 Gaucher disease therapeutic goals • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).	As per scope. No data identified to allow the impact on carers to be assessed

4 Impact of the new technology

The premeeting briefing only presents an overview of the results for studies including treatment with eliglustat. For a more detailed presentation of the results, please see pages 60–165 of the company's submission.

4.1 The company conducted a systematic literature review and identified the following key phase 3 randomised controlled trials that studied eliglustat:

- ENCORE was an open label trial comparing eliglustat (n=106) with imiglucerase (n=54) in people who were stable on enzyme replacement therapy. People were given 50mg, 100mg or 150mg eliglustat twice daily, or 30 to 130 units per kilogram per month of imiglucerase. The statistical design of the ENCORE trial was to test non-inferiority.

- ENGAGE was a double blind, placebo-controlled trial, comparing eliglustat with placebo in 40 people (eliglustat n=20; placebo n=20) The company submission refers to the population as being treatment naïve, however, inclusion criteria allowed people who had previous treatment with ERT as long as they were not being treated at time of recruitment to the trial. People in the eliglustat arm were given 50mg on day 1; 50mg twice daily on day 2 to week 4; and 50mg or 100mg twice daily from week 4 to 39. See table 1 for further details.

4.2 The company submission also included supportive information from a phase 3 trial (EDGE) and a phase 2 trial (NCT00358150). EDGE was a double blind trial, comparing once daily (100mg or 200mg) with twice daily (50mg or 100mg) eliglustat dosing in 170 patients.

The trial started with a lead-in period of up to 18 months during which patients received eliglustat 50mg or 100mg twice daily for at least four months until therapeutic goals were achieved. Data was only provided for the open label lead in phase. The phase 2 trial (NCT00358150) included 26 people with type 1 Gaucher disease. Patients had not received ERT in the 12 months prior to the study. Eliglustat was administered at 50mg twice daily from day 1 to day 20 after which the dose could be increased to 100 mg if plasma levels were <5ng/ml. The primary outcome was improvement from baseline to week 52 in at least 2 of the 3 main efficacy parameters which were spleen volume, haemoglobin level and platelet count.

Table 1. List of RCTs presented in the company submission

Trial no. (Acronym) Phase	Interventions	Population	Primary outcome
NCT00943111 (ENCORE) Phase III, open-label, with an extension phase up to a minimum of week 104	• Eliglustat 50mg, 100mg, or 150mg, oral (twice daily) • Imiglucerase IV, varied dose, every 2 weeks • Duration: 52 weeks, with ongoing extension phase	160 adults with type 1 Gaucher disease, previously treated with ERT for ≥3 years.	Percentage of patients who remained stable for 52 weeks in all of the following parameters: • Haemoglobin levels ≤1.5g/dL from baseline • Platelet counts ≤25% from baseline Spleen volume ≤25% from baseline • Liver volume ≤20% from baseline
NCT00891202 (ENGAGE) Double blind Phase III, with open-label extension phase	• Eliglustat 50mg or 100mg, oral (twice daily) • Placebo • Duration: 39 weeks, with ongoing extension phase	40 adults with previously untreated type 1 Gaucher disease	• Percentage change from baseline in spleen volume after 39 weeks
NCT01074944 (EDGE) Double blind Phase III	• Eliglustat 50mg or 100mg twice daily, oral • Eliglustat 100mg or 200mg once daily, oral • Duration: up to 18 months lead-in, then 12 months double-blind treatment period	115 adults with type 1 Gaucher disease who demonstrated clinical stability on eliglustat twice daily	Percentage of randomised patients who remained stable for 52 weeks in all of the following parameters: • Haemoglobin levels ≤1.5g/dL from baseline • Platelet counts ≤25% from baseline • Spleen volume ≤25% from baseline • Liver volume ≤20% from baseline

ERG comments

4.3 The ERG commented that the company submission did not clearly explain how the pre-specified non-inferiority margin was derived for the ENCORE trial. The ERG commented that the non-inferiority margin of 25% was wider than would normally be accepted and suggest that a margin of 15% would have been more robust. The 25% non-inferiority margin assumes that a 10% reduction in efficacy is clinically insignificant, an assumption that was not justified clinically by the company. The ERG acknowledged that the EMA accepted the broader margin because of the rare nature of the disease and that conducting a larger trial (as would be necessary with a 15% margin) would not be feasible.

4.4 The ERG stated that the trials were of reasonable quality and well conducted, but highlighted that long term data for eliglustat was limited, especially in the context of a lifelong condition. Additionally, only 66 patients across the studies were untreated.

4.5 The ERG noted that the majority of patients in the trials were intermediate metabolisers and extensive metabolisers. Approximately 3% of patients were ultra-rapid metabolisers and not included in the marketing authorisation for eliglustat.

Clinical study results - ENCORE

4.6 The ENCORE study showed that 84.8% (95% CI: 76.2%, 91.3%) of people on eliglustat and 93.6% (95% CI: 82.5%, 98.7%) on imiglucerase met the non-inferiority criteria. Stability was maintained for 104 weeks with eliglustat in 87.8% of people (n=95). Further details of the primary outcome results are presented in

table 2. In both treatment groups, greater than 92% of patients were stable in each component of the composite endpoint.

Table 2. ENCORE study results (Per Protocol Set*)

Outcome	**Eliglustat (n=99)**	**Imiglucerase (n=47)**
Composite primary endpoint %	84.8 (76.2, 91.3)%	93.6 (82.5, 98.7)%
Difference in percentage stable for 52 weeks, % (95% CI)	-8.8% (95% CI: -17.6, 4.2)	
Patients who met stable criteria of primary endpoint % (exact 95% CI)		
Haemoglobin criteria	94.9 (0.89, 0.98)%	100%
Platelet criteria	92.9 (0.86, 0.97)%	100%
Spleen volume criteria	95.8 (0.88, 0.99)%	100%
Liver volume criteria	96 (0.90, 0.99)%	93.6 (0.83, 0.99)%
Percentage stable for 104 weeks % (95% CI)		
	Eliglustat (n=95)	
Composite endpoint	87.4% (0.79, 0.93)%	
Patients who met stable criteria of primary endpoint % (95% CI): Eliglustat (n=99)		
Haemoglobin criteria	96.8 (0.91, 0.99)%	
Platelet criteria	93.7 (0.87, 0.98)%	
Spleen volume criteria	95.8 (0.88, 0.99)%	
Liver volume criteria	96 (0.90, 0.99)%	
*Per protocol set: people in the full analysis set who were ≥80% compliant with treatment during the primary analysis period, had no major protocol deviations expected to interfere with the assessment of efficacy as defined in the statistical analysis plan, and did not exhibit haematological decline as a result of medically determined aetiologies other than Gaucher disease		

4.7 Of the secondary outcomes (absolute and percentage changes in haemoglobin, platelet count and organ volumes at Week 52 and Week 104), the difference was statistically significant between treatment groups only for absolute and percentage changes in haemoglobin (-0.28, 95% CI -0.52, -0.03, p value 0.03)). There were small or no differences in bone-related outcomes: spine BMD

(0.06), lumber spine T-score (0.01) and Z-score (0.0), total femur BMD (0.19), total femur T-score (0.03) and total femur Z-score (0.02)) (see table 17 of the company submission). Data on Gaucher Disease Type 1 Severity Scoring System (GD-DS3) was collected. This is the main measure used to score the severity of GD1 in clinical practice in England. The range of DS3 scoring is from 0 to 19. A score of between 0 and 3 indicates borderline to mild disease; 3 to 6 indicates moderate disease; 6 to 9 indicates marked disease; 9+ indicates severe disease. The DS3 scores showed no clinically important improvements with little change from baseline to week 52. Scores were all below 3 indicating mild disease.

4.8 The company also presented a post hoc subgroup analysis according to pre-treatment with either velagucerase alfa or imiglucerase. The company stated that the results of the post hoc analysis showed that:

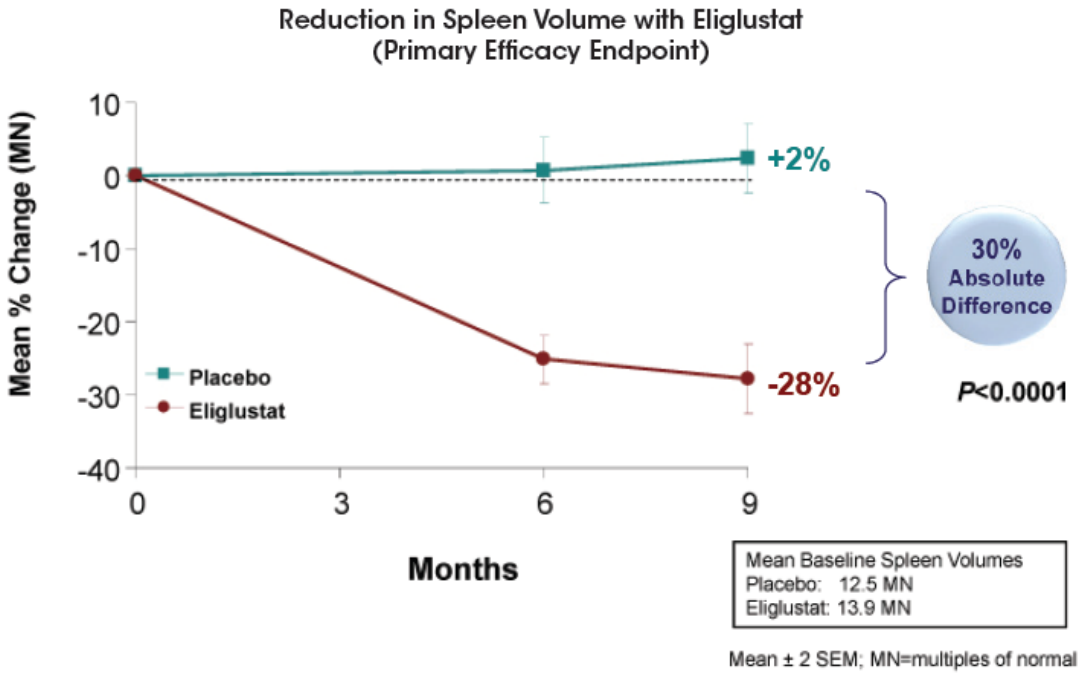
- Eliglustat has similar efficacy both post-imiglucerase and post-velaglucerase treatment, with continued stability
- Haemoglobin levels showed a similar change from baseline to Week 52 in the eliglustat arms both post-imiglucerase and post-velaglucerase treatment
- Spleen and liver volume outcomes also showed no significant change from baseline in both groups

Clinical study results - ENGAGE

4.9 The results for the primary endpoint of change in spleen volume were statistically significant, eliglustat was associated with a statistically significant mean difference of 30.03% compared with the placebo group ($p<0.0001$; figure 2). This reduction in spleen volume continued through to week 78 with a mean reduction of

44.6% in the eliglustat group. Additionally, by week 78 patients who started eliglustat at week 39 showed a similar response to that achieved at week 39 by patients randomised to eliglustat at week 0.

Figure 2. ENGAGE study results (ITT analysis) – primary outcome



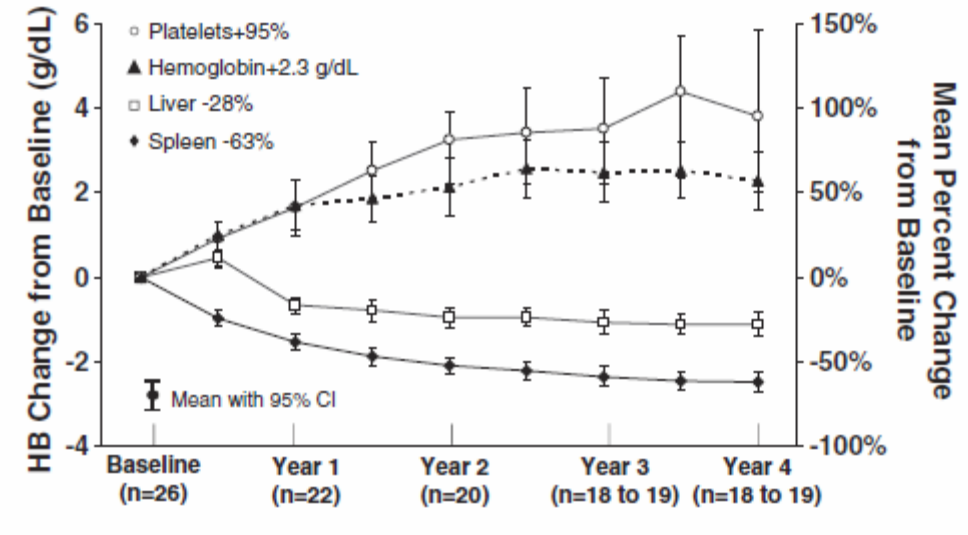
4.10 The company submission stated that eliglustat demonstrated efficacy compared with placebo on all secondary endpoints. At 39 weeks, the differences were liver volume (-6.64%; 95% -11.37% to -1.91%), haemoglobin level (1.22 g/dL; 95% CI 0.57 to 1.88), and platelet count (41.06%; 95% CI 23.95% to 58.17%). Data at week 78 demonstrated that these results were maintained.

4.11 The DS3 scores showed no clinically important improvements at 39 weeks. The company reported that there was a clincially significant decrease in bone marrow burden scores for 5 patients in the trial, with 3 shifting from the bone marrow burden category of marked/severe to moderate bone marrow infiltration.

Clinical study results - Phase II study (NCT00358150)

4.12 For the composite primary outcome, statistically significant improvements in haemoglobin, platelet counts, and liver and spleen volumes were maintained throughout 4 years of treatment demonstrating the long-term efficacy of eliglustat (see figure 3).

Figure 3. Phase II study (NCT00358150) results - Change in haemoglobin, platelet counts, liver and spleen volumes over 4 years



Clinical study results - EDGE

4.13 The company submission presented the interim analysis for the 18 month lead-in period only. The primary composite outcome of the lead-in period was the proportion of patients who maintained or achieved therapeutic goals and was based on measures of bone crisis, haemoglobin level, platelet counts, and spleen and liver volumes. A total of 137 (83%) patients achieved all five therapeutic goals during the lead-in period. The company stated the analysis of the randomised part of the study had not been completed at the time of submission. The company confirmed in response to a request from the ERG that the clinical study report for the EDGE study was not finalised. The company considers that data from the

lead-in period from this trial provides supporting evidence for the efficacy of eliglustat in type 1 Gaucher disease.

ERG comments

4.14 The ERG commented that because of the open label nature of the trial there was a high risk of bias for any subjective outcomes.

4.15 The ERG commented that the non-inferiority margins were wider than would normally be accepted and a margin of 15% would have been more robust (see section 4.3).

4.16 The ERG noted that long-term follow-up data from ENCORE demonstrated that for people who remain on eliglustat, stability on all four composite parameters was maintained over 4 years. The ERG noted that although few patients withdrew because of adverse events, the number of people in the analysis at 4 years was only 44 of 159 people who started the trial. The ERG highlighted that this unexplained loss of patients from follow-up brings uncertainty in interpreting the long term results.

4.17 The ERG highlighted that the sample size in the ENGAGE trial was very small (n=40), and the randomised phase of the trial was too short (39 weeks) to measure improvements in bone outcomes for people with type 1 Gaucher disease.

4.18 The ERG noted that the Phase II single arm trial that included people who were not being treated with ERT provided supporting data for 1, 2 and 4 years of treatment with eliglustat, although not all patients remained in the analysis beyond 1 year and, not all outcomes were reported at 4 years. The ERG noted the trial had a small sample size (n=26) and there was an unexplained loss of patients from later time points in the study. The ERG highlighted

that because of this, the treatment effects observed over the four year follow-up were uncertain.

4.19 The ERG highlighted that no data comparing eliglustat with imiglucerase or veleglucerase in untreated patients was presented, and a direct comparison of eliglustat with velaglucerase in ERT stable patients was also not available.

4.20 The ERG noted that the SPCs for imiglucerase and velaglucerase recommend higher starting doses of 60U/kg every two weeks however the SOP, developed by expert consensus in England reports that a maintenance dose of 15-30 U/kg is appropriate for most patients on either imiglucerase or velaglucerase, though this may be increased to 60 U/kg. Advice to the ERG suggested typical doses were around25 U/kg (range: 15-28 U/kg) and the expert submission reported doses of between 20-40 U/kg. The ERG highlighted that lower doses of ERT will affect the long-term costs in the model. NHS England commented that current clinical practice in England is to titrate the dose of ERT and use the lowest effective dose, stating that an economic evaluation should take account of this.

Adverse effects of treatment

4.21 The company presented a safety analysis that pooled data from 393 patients with type 1 Gaucher disease who received eliglustat in the clinical trial programme. The overall results of the pooled safety analysis demonstrate that eliglustat was generally well-tolerated, with few patients (3%) discontinuing treatment due to adverse events. Most patients reported treatment related adverse events as mild (78%) or moderate (44%), and in 79% of patients treatment related adverse events were considered not related to eliglustat treatment. The most common events were headache (17%),

arthralgia (14%), nasopharyngitis (13%), upper respiratory tract infection (11%), diarrhoea (10%), and dizziness (10%).

ERG comments

4.22 The ERG commented that the evidence from ENCORE showed a higher number of people experiencing treatment related adverse events with eliglustat. However, the ERG commented that this difference in tolerability may be because people were stable on ERT when recruited to the trial. The ERG noted that the evidence was mostly limited to the short-term data although some longer-term data up to 4 years demonstrated that eliglustat is generally well tolerated.

Health-related quality of life

4.23 The company stated that eliglustat maintained health-related quality of life in people stable on enzyme replacement therapy in the ENCORE study (table 17 of the company submission, page 96). The company also highlighted that because eliglustat is an oral therapy, it is easier to use compared to enzyme replacement infusions which take an average of 2 hours every 2 weeks and require some clinical oversight.

Table 3. Health-related quality of life outcomes - ENCORE

Health-related quality of life outcomes – ENCORE		
HRQL Measure	**Treatment group**	**Difference between treatment groups - Mean (SD)**
		% change
Fatigue Severity Score	Eliglustat (n=97)	14.73 (75.04)
	Imiglucerase (n=45)	8.78 (57.93)
Brief Pain Inventory,	Eliglustat (n=95)	-9.12 (103.05)

Average Pain	Imiglucerase (n=46)	-32.67 (79.13)
SF-36 – general health	Eliglustat (n=96)	4.75 (29.20)
	Imiglucerase (n=46)	9.16 (27.14)
SF-36 – physical component score	Eliglustat (n=95)	4·78 (16·26)
	Imiglucerase (n=46)	4·55 (14·19)
SF-36 – mental component score	Eliglustat (n=95)	0·00 (21·39)
	Imiglucerase (n=46)	-0·53 (17·88)

4.24 At screening for the ENCORE study, people completed a questionnaire showing their preference of treatment type (oral versus IV) which showed that 94% of patients in the eliglustat group and 94% in the imiglucerase group indicated a preference for oral treatment. After 12 months of treatment, 81% of 93 people who had switched from ERT to eliglustat said they preferred oral therapy because of the convenience it offers

4.25 In the ENGAGE trial, eliglustat was associated with an improvement in disease-specific quality of life outcome (fatigue severity score 0.7; 95% CI 0.02 to 1.33) compared with placebo at week 39. There was no statistically significant difference in brief pain inventory (BPI) (average pain) (-0.2; 95% CI -0.81 to 0.36) between the treatment and placebo groups. In terms of the SF-36 measures, no statistically significant differences between the two groups were observed for general health score, physical component score, and mental component score (table 4, and table 18 of the company submission).

Table 4. Health-related quality of life outcomes - ENGAGE

HRQL measure	**Treatment group**	**Difference between treatment groups [p-value]**

FSS	Eliglustat (n=20)	0.7 (0.02, 1.33) [p=0.04]
	Placebo (n=20)	
BPI, average pain	Eliglustat (n=19)	-0.2 (-0.81 to 0.36) [p=0.52]
	Placebo (n=20)	
SF-36 – general health	Eliglustat (n=20)	-2.4 (-9.84 to 4.94) [p=0.51]
	Placebo (n=20)	
SF-36 – physical component score	Eliglustat (n=20)	3.3 (-0.67 to 7.29) [p=0.12]
	Placebo (n=20)	
SF-36 – mental component score	Eliglustat (n=20/19[b])	-2.2 (-7.01 to 2.59) [p=0.36]
	Placebo (n=20)	

ERG comments

4.26 The ERG highlighted that the health-related quality of life data for eliglustat did not demonstrate a benefit compared with ERT, even though people expressed a preference for oral treatment in a patient survey. The ERG acknowledged that there may be some health-related quality of life benefits resulting from oral therapy compared with intravenous infusion, but the ERG considered that the magnitude of these benefits were unreasonably large when compared with QALY decrements from adverse events and QALY benefits of other oral therapies estimated in previous NICE submissions.

Indirect treatment comparison

4.27 In the absence of head-to-head trials of eliglustat, imiglucerase and velaglucerase, the company presented an indirect comparison focused on four outcomes; change from baseline in haemoglobin levels, platelet counts, spleen volume and liver volume the inputs.. The company highlighted that there were major limitations for the treatment comparisons because of heterogeneity between trials

and stated that the indirect comparisons should not be used as the base-case.

ERG comments

4.28 The ERG agreed with the company that because of the significant heterogeneity of population characteristics at baseline between the included trials, the outcomes cannot be compared and therefore the comparison lacked validity.

5 Cost to the NHS and personal social services and Value for money

Model structure, model inputs and assumptions

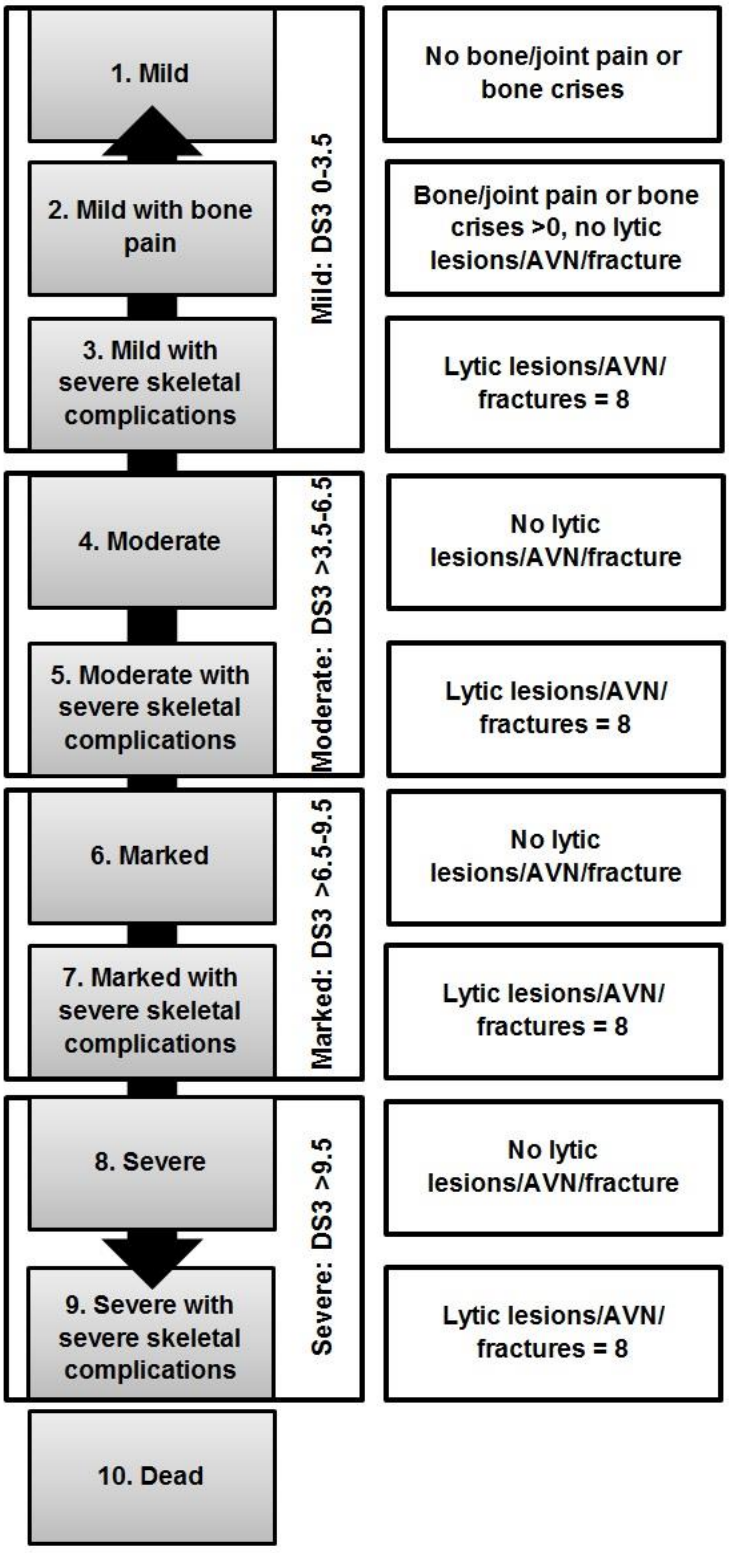
5.1 The company developed a cost consequence analysis using a 10 health state Semi-Markov model (that is, the transition probabilities used in the model depend on a patient's initial health state). The model, comparing eliglustat with imiglucerase and with velaglucerase, included two patient groups: those who were treatment-naïve and those who were taking enzyme replacement therapy and are considered clinically stable. Within each of these populations, the model also considered subgroups based on metaboliser status. The company did not present a comparison with miglustat, stating that is only used in less than 2% of patients, and is associated with issues around tolerability and efficacy. The company also stated that eliglustat is not expected to be used in place of miglustat in this small population.

5.2 The starting age of people in the treatment-naïve population was assumed to be 32 years based on the mean age in the ENGAGE trial. The starting age of people in the ERT stable population who switch to eliglustat was assumed to be 38 years. Health states

were defined by a patient's score on the DS3 severity scoring system, which is a validated measure of disease severity. In the model, people were grouped by: mild (DS3 = 0-3.5), moderate (DS3 = 3.5-6.5), marked (DS3 = 6.5-9.5), and severe (DS3 >9.5) disease. People could move between any of the living states per cycle, or remaining in their current state, or move to the absorbing death state. All people with moderate, marked and severe disease were assumed to have at least one instance of bone or joint pain or bone crisis, based on the contribution of this domain to the overall DS3 score

5.3 For people stable on enzyme replacement therapy, transition probabilities in the first year were based on the ENCORE trial and thereafter based on data from the DS3 score study, a registry validating the DS3 scoring system). The model assumed differential clinical effectiveness in the first year and then equal effectiveness in subsequent years. For the treatment naïve population, treatment effectiveness was assumed equal and based on the eliglustat arm of the ENGAGE study.

Figure 4. Model structure with description of health states



5.4 The model used a time horizon of 70 years and a cycle length of 1 year. The company stated that this was appropriate given the limited data available. The analysis was conducted from the perspective of the NHS and Personal Social Services, and costs and benefits were discounted at a rate of 3.5% per year.

5.5 Some of the assumptions used in the company's model were as follows:

- Treatment efficacy of eliglustat and the comparators was assumed to be equal in the treatment-naïve population.
- After the trial period, it was assumed that the state transitions derived from DS3 Score Study data were the same for eliglustat and all of the comparators
- People could discontinue treatment for up to three years following of initiation of therapy following which patients become stable on the selected treatment. A discontinuation rate of 1.9% was applied for treatment-naïve population for eliglustat and ERT. For the population stable on ERT, a 1.9% discontinuation rate was applied for eliglustat but it was assumed that patients on ERT would not discontinue treatment.
- Mortality was assumed to be the same for eliglustat and enzyme replacement therapies and across all health states (mortality rate does not increase with disease severity).
- The outcomes at 39 weeks from the ENGAGE trial were used for people at 1 year in the model.

ERG comments

5.6 The ERG highlighted 2 main concerns about the structure of the model developed by the company: the use of long-term transitions in the model and the use of the DS3 score system to define health state. The ERG considered the company's approach to generating long-term transition probabilities to be complicated and stated that it reduced the transparency of the model making validation of the company's model difficult. The ERG stated that it because the same transition probabilities were applied to both treatment and comparator groups it was unclear why a simpler approach was not used. Additionally, the ERG stated that the DS3 score appeared to be insensitive to changes in disease status, and therefore did not reflect differences between the treatments observed in the ENCORE trial. This means that differences between the treatment and comparators were not accounted for in the model, resulting in a bias in the model towards equivalence in clinical benefits, underestimating the differences between eliglustat and imiglucerase observed in the ENCORE study.

5.7 The ERG stated that assuming long-term equivalence of eliglustat and ERT underpins the calculation of long-term benefits and has a considerable impact on estimated incremental QALYs. The ERG considered that this assumption had not been adequately justified in the company's submission, stating that the non-inferiority results in the ENCORE trial were not the same as equivalence and non-inferiority in the short-term does not imply non-inferiority in the long term.

5.8 The ERG questioned whether the inclusion of a large number of heath states was necessary. The ERG acknowledged that more health states can improve the accuracy of the model however the

advantage of this approach is offset when the model has a greater complexity and reduced transparency as a result. The ERG commented that this was particularly important because data for type 1 Gaucher disease is limited.

5.9 The ERG questioned the company's assumption that eliglustat and ERT are equivalent in treatment naïve patients; it considered that the evidence from the ENCORE trial should have been incorporated instead.

5.10 The ERG considered that the company's assumptions regarding discontinuation were reasonable given the lack of data available but highlighted that the results from the model were very sensitive to discontinuation rates and the duration over which they are applied.

5.11 The ERG stated that mortality risk would increase with severity of disease and therefore disagreed with the company's assumption on mortality. The ERG explored this assumption in its analyses.

5.12 The ERG identified the Wyatt et al. study which indicated that the mean age at which treatment is initiated is 35.2 years in the treatment naïve population and 46.4 in the treatment stable population. The ERG considered that the starting age in the model was underestimated therefore overestimating lifetime differences; the ERG explored this in its analyses.

Utility values used in the company's model

5.13 Quality of life data were derived from the DS3 score study which collected SF-36 data. The SF-36 scores were mapped to EQ-5D utilities using a published algorithm. Utility decrements were applied to patients on treatment to reflect the impact of adverse events. Table 6 summarises the utility values used by the company

for its cost effectiveness analysis. The ERG agreed that the DS3 score study provided the most complete set of utility values. The model also incorporates preference for oral therapy over infusion therapy in the base-case analysis via a utility increment of 0.12, which is applied in every cycle. This value was taken from a vignette study which was commissioned by the company.

Table 6. Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Confidence interval	Reference in company submission	Company's Justification
Mild (1)	0.764	0.709–0.820	Section 10.1.3 of the company submission which describes the HRQL data derived from clinical trials	Registry data preferred because of smaller standard errors and confidence intervals
Mild + Bone Pain (2)	0.666	0.623–0.708		
Mild + SSC (3)	0.683	0.593–0.774		
Moderate (4)	0.686	0.648–0.725		
Moderate + SSC (5)	0.606	0.487–0.724		
Marked (6)	0.642	0.567–0.717		
Marked + SSC (7)	0.561	0.448–0.674		
Severe (8)	0.596	0.443–0.749		
Severe + SSC (9)	0.515	0.371–0.659		
AE: Back pain	-0.0187	-0.0121 to -0.0267	Section 10.1.8 of the company submission Published estimates of HRQL impact of adverse events	
AE: Abdominal pain	-0.0006	-0.0004 to -0.0008		
AE: Joint pain	-0.0012	-0.0008 to -0.0017		
AE: Infusion reaction	-0.0110	-0.0071 to -0.0157		
AE: URTI	-0.0001	-0.0001 to -0.0001		
AE: Dizziness	-0.0004	-0.0003 to -0.0006		

State	Utility value	Confidence interval	Reference in company submission	Company's Justification
Oral administration increment	0.12	0.146 to 0.326	Section 10.1.3	This utility benefit for an oral treatment compared with infusions was obtained from a vignette study commissioned by the company
Key: AE, adverse event; IV, intravenous; SC, subcutaneous; SSC, severe skeletal complications, URTI, upper respiratory tract infection.				

Costs

5.14 Costs for drug acquisition, administration, and monitoring and management were included in the model. Differential monitoring and management costs were applied to each health state, broadly increasing with severity of disease. No costs associated with adverse events were included in the model, and the company assumed that neither eliglustat nor the comparators required additional training of healthcare staff. No administration costs were included the model for eliglustat. Table 7 presents the costs included in the model. Additionally, direct medical and social service costs were included ranging from £2,583.05 per year for the mild heath state with no clinical symptoms of bone disease to £6,411.63 for the severe health state with severe skeletal complications.

5.15 Confidential discounts are available for imiglucerase and velaglucerase and results incorporating the confidential prices have been explored by the ERG for all analyses in a confidential appendix.

Table 7. Costs per treatment/patient per year based on the list prices

(see tables 59 and 60 of the company submission)

Items	Eliglustat	Imiglucerase	Velaglucerase
List price of the technology per treatment/patient	IM and EM metabolic status £206,249.95 PM metabolic status £103,124.97	£199,976	£263,303
Cost of infusing in hospital + cost of home with nurse support	-	£1751	£1751
Management cost (delivery, homecare services etc.)	£480	£12,587	£12,587
Training cost	£0.00	£0.00	£0.00
Other costs (monitoring, tests, etc.)	£0.00	£0.00	£0.00
Total cost per treatment/patient	IM and EM metabolic status £208,249.95 PM metabolic status £105,124.97	£214,314	£277,540
Key: EM, extensive metaboliser; IM, intermediate metaboliser; PM, poor metaboliser; ERT, enzyme replacement therapy; IV, intravenous.			

ERG comments

5.16 The ERG considered that the dose of eliglustat in the model was in line with practice. However, the ERG noted that the efficacy data was taken from ENCORE where 48% of patients received a higher dose of eliglustat of 150mg BID for the majority of the trial period. The ERG highlighted that this was a key driver in the model.

5.17 The ERG disagreed that there will be no administration costs associated with eliglustat because it is an oral therapy, and explored incorporating a minimum pharmacy dispensary cost. Additionally, the ERG considered that the company overestimated the administrative costs for ERT delivered at home because it was implausible that it would be higher than the cost of hospital administration.

5.18 The ERG noted concerns with the costs for ERT in the model. The ERG was concerned that the company did not include any vial wastage. The ERG reiterated that there was considerable evidence to suggest that substantially lower doses of ERT are used in practice (see section 4.19) and therefore the higher dose of ERT treatment assumed in the model overestimated the drug acquisition cost associated with ERT. The ERG also noted that treatment naive patients in the model are assumed to receive the same dose of ERT as stable patients. However, the clinical advisor to the ERG suggested that newly diagnosed patients are typically less severely affected than patients who initiate treatment in childhood and as such do not require such intensive dosing.

Model results

5.19 The company estimated that the lifetime benefit associated with using eliglustat in place of ERTs (driven almost entirely by the quality of life improvement associated with mode of administration) was 2.44 QALYs for people who are treatment naïve and 2.28 QALYs for people stable on enzyme replacement therapy.

5.20 The results of the incremental costs for eliglustat compared with imiglucerase and velaglucerase in people stable on ERT and those who were not on treatment at time of initiation on eliglustat are presented in table 8. The results are based on list prices. For an

analysis including confidential discounts of the comparators, see the confidential appendix provided for committee members only.

Table 8. Summary of incremental costs in company's base case cost effectiveness model (from table 84 of the company submission)

Comparison	Incremental cost
ERT stable population, IM and EM	
People switching from imiglucerase	-£147,394
People switching from velaglucerase	-£1,288,963
ERT stable population, PM	
People switching from imiglucerase	-£2,116,154
People switching from velaglucerase	-£3,323,218
Treatment naïve population, IM and EM	
People who would otherwise initiate on imiglucerase	-£212,299
People who would otherwise initiate on velaglucerase	-£1,352,367
Treatment naïve population, PM	
People who would otherwise initiate on imiglucerase	-£2,297,310
People who would otherwise initiate on velaglucerase	-£3,437,379
Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; PM, poor metaboliser.	

5.21 The company presented probabilistic sensitivity analyses for both the ERT stable and treatment naïve populations (see table 9).

Table 9. Summary of probabilistic sensitivity analyses cost and QALY results (adapted from tables 89 – 92 from the company submission)

Comparison	Mean Incremental Costs	Mean Incremental QALYs
ERT stable patients, IM and EM		
Patients switching from imiglucerase	-£162,006	2.30
Patients switching from velaglucerase	-£1,394,994	2.30
ERT stable patients, PM		
Patients switching from imiglucerase	-£2,168,860	2.29
Patients switching from velaglucerase	-£3,445,021	2.29
Treatment naïve patients, IM and EM		
Patients who would otherwise initiate on imiglucerase	-£93,499	2.48
Patients who would otherwise initiate on velaglucerase	-£1,295,291	2.50
Treatment naïve patients, PM		
Patients who would otherwise initiate on imiglucerase	-£2,377,114	2.43
Patients who would otherwise initiate on velaglucerase	-£3,512,064	2.45
Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; PM, poor metaboliser.		

5.22 The company presented one-way sensitivity analyses to explore uncertainty. Incremental costs were most heavily influenced by patient weight, as this determines the dosing and costs of the ERT comparators. Other influential parameters were those used to model overall survival of patients, the number of doses of ERT patients were assumed to receive per month and the duration over which patients can discontinue eliglustat. Varying the utility increment assigned to eliglustat for its more favourable

administration method was the biggest driver of the difference in QALYs

Budget impact analysis

5.23 The company presented a 5 year budget impact model to estimate the costs of eliglustat to the NHS. It was based on estimates of total costs generated by the cost consequence model. Some other key assumptions made by the company were:

- [redacted] patients are estimated to be eligible for treatment with eliglustat in England, and [redacted] new Gaucher patients will become eligible for treatment each year
- Newly diagnosed patients are assumed to start treatment on eliglustat rather than imiglucerase/velaglucerase
- Costs based on the licensed dose of eliglustat and the dosing of ERTs used in the ENCORE clinical trial
- Effects of mortality and discontinuation are included in the estimated total costs
- Model results for people who are intermediate or extensive metabolisers were used (majority of patients in the trials)

5.24 The company stated that there was uncertainty over uptake rates, which will be driven both by clinician and patient preference, and NHS purchasing decisions.

5.25 The company estimated that the cost of using eliglustat was estimated save £1,873,401 in Year 1 following launch, leading to a total saving of £4,846,357 in Year 5. This was based on an estimated [redacted] patients receiving eliglustat in Year 1, rising to [redacted] patients in Year 5. The company's budget impact analysis was

based on the list prices for the 2 comparators, and therefore the savings are expected to be less if the analyses were based on available discounts on the 2 comparators.

ERG comments

5.26 The ERG considered the company's base-case in its cost-consequence model to be too optimistic and likely to overestimate the benefits of eliglustat therapy and the costs of comparator therapies (see sections 4.25, 5.18 and 5.19).

5.27 The ERG stated the budget impact model was linked directly to the cost consequence model and therefore its concerns around the company's model were also applicable to the company's budget impact analysis. The ERG noted a number of issues with the budget impact analysis beyond those identified in the cost-consequence model. These related to:

- the size of the Gaucher population in England. The ERG suggests that the company estimate is uncertain and notes several inconsistencies in the company's estimate. Based on other sources of evidence, such as the submission from the UK Gaucher association, the ERG stated that the population size was likely to be higher.

- the integration of estimates of cost from the cost-consequence model into the budget impact model; this incorporates mortality such that total costs of treating patients represent the average cost of treating a patient over a life time rather the cost of treating one patient for a period of 5 years. The ERG stated that the latter was relevant to the budget impact analysis and the company's approach underestimates total costs. With regard to discontinuation,

the ERG stated that effects of switching are double counted because both the cost-consequence model and the budget impact analysis account for switching.

- the treatment received by the incidence population in the absence of eliglustat. The ERG suggests that it is plausible that all people are offered velaglucerase rather than some patients receiving imiglucerase.

- the composition of the Gaucher population (budget impact model excluded poor metabolisers). The ERG stated that this may overestimate the costs of treatment with eliglustat.

ERG exploratory analyses

5.28 The ERG conducted exploratory analyses to address the uncertainties it had identified. It presented its own base –case analysis with its preferred assumptions, including the following:

- Additional administration costs for eliglustat (£14.40 monthly dispensary cost);

- Revised administration costs for ERT treatments (Home therapy cost equal to hospital cost);

- Revised estimate of the QALY benefits of oral therapy (Estimate of ‘0.05’);

- Revised modelling of mortality to allow for increased mortality risk for marked and severe patients;

- Reduction in dose of ERT to bring it in-line with UK practice (25 units per kilogram);

- Using ENCORE effectiveness data in the treatment naïve population during the first cycle

5.29 The impact of the ERG's analyses, based on list prices for ERT treatments, is to reverse the company's results: eliglustat is no longer cost saving. Based on list prices of imiglucerase the impact of the ERG's assumptions is to increase incremental costs of implementing eliglustat from an estimated saving of £147,394 per patient in the company's model to an increase in total costs of £1,712,502 per patient in the ERG's base-case. With respect to velaglucerase, again based on list prices, the ERG's assumptions increase incremental costs from an estimated saving of £1,288,963 in the company's base-case to an increase in total cost of £923,621 in the ERG's base-case. The key driver of the change in results was the dose of ERT treatment used. Accounting for the confidential discounted costs of imiglucerase and velaglucerase would increase the incremental costs of eliglustat compared with imiglucerase and velaglucerase.

5.30 The ERG also highlighted that the QALY benefits of eligustat compared with imiglucerase and velaglucerase are reduced to around 1.05 driven by alternative assumptions about the size of the incremental benefit for oral therapy.

5.31 The ERG suggested that based on their analyses implementing eliglustat in the NHS would result in significantly increased costs with highly uncertain health benefits

Table 10. ERG base case analysis - Incremental QALYs and Costs (Eliglustat vs Imiglucerase) - based on list price of the comparator (See confidential ERG appendix for analyses with comparator discounts applied)

Patient Group	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Health states: 0.00	Drug acquisition: £ 1,869,333
	AE events: -0.01	Administration: -£ 157,025
	Oral therapy increment: 1.06	Management/ social service costs: £ 193
	Total: 1.05	Total: £ 1,712,502
ERT stable PM	Health states: 0.00	Drug acquisition: -£ 312,889
	AE events: -0.01	Administration: -£ 157,025
	Oral therapy increment: 1.06	Management/ social service costs: £ 193
	Total: 1.05	Total: -£ 469,721
ERT naïve IM/EM	Health states: -0.02	Drug acquisition: £ 1,833,454
	AE events: 0.00	Administration: -£ 157,635
	Oral therapy increment: 1.06	Management/ social service costs: £ 504
	Total: 1.04	Total: £ 1,676,323
ERT naïve PM	Health states: -0.02	Drug acquisition: -£ 357,252
	AE events: 0.00	Administration: -£ 157,635
	Oral therapy increment: 1.06	Management/ social service costs: £ 504
	Total: 1.04	Total: -£ 514,382

Table 11. ERG base case analysis - Incremental QALYs and Costs (Eliglustat vs Velaglucerase) – based on list price of the comparator (See confidential ERG appendix for analyses with comparator discounts applied)

Patient Group	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Health states: 0.00	Drug acquisition: £ 1,080,452
	AE events: -0.01	Administration: -£ 157,025
	Oral therapy increment: 1.06	Management/ social service costs: £ 193
	Total: 1.05	Total: £ 923,621
ERT stable PM	Health states: 0.00	Drug acquisition: -£ 1,101,770
	AE events: -0.01	Administration: -£ 157,025
	Oral therapy increment: 1.06	Management/ social service costs: £ 193
	Total: 1.05	Total: -£ 1,258,602
ERT naïve IM/EM	Health states: -0.02	Drug acquisition: £ 1,127,802
	AE events: 0.02	Administration: -£ 157,635
	Oral therapy increment: 1.06	Management/ social service costs: £ 504
	Total: 1.06	Total: £ 970,671
ERT naïve PM	Health states: -0.02	Drug acquisition: -£ 1,062,904
	AE events: 0.02	Administration: -£ 157,635
	Oral therapy increment: 1.06	Management/ social service costs: £ 504
	Total: 1.06	Total: -£ 1,220,035

5.32 The ERG presented an exploratory analysis for the budget impact analysis. This included the assumptions in section 5.28 but additionally assumed zero mortality, no treatment discontinuation and a UK Gaucher population of 293. The results are presented in table 12.

Table 12. ERG's exploratory analyses, Budget Impact - ERT Stable intermediate and extensive metabolisers based on list prices (see confidential ERG appendix for analyses with comparator discounts applied)

	2015	2016	2017	2018	2019
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**£2,961,673**	**£4,784,125**	**£5,928,950**	**£7,073,317**	**£8,219,694**
Cumulative Total	**£2,961,673**	**£7,745,798**	**£13,674,748**	**£20,748,065**	**£28,967,758**

6 Impact of the technology beyond direct health benefits and on the delivery of the specialised service

6.1 Eliglustat is not currently commissioned by NHS England. It would be used as an alternative to enzyme replacement therapy or substrate reduction therapy in patients with Gaucher disease eliglustat. It is an oral therapy but it will be important for patients to remain under the care of expert centres for initiation and monitoring of eliglustat therapy (if recommended). NHS England commented that current clinical practice in England is to titrate the dose of enzyme replacement therapy against the patient's clinical condition and use the lowest effective dose. The economic evaluation will need to take account of this

6.2 The company stated that the majority of the cost and health outcomes relevant to the decision problem are expected to be

captured within its model. The costs of the treatment and management of type 1 Gaucher disease are primarily borne by the NHS and PSS, and any additional costs incurred by patients and their families and carers are not expected to be substantial.

6.3 The company stated that it was assumed that eliglustat will require no additional development or staff training above what is already in place for the provision of care. Additionally, the availability of eliglustat would reduce the requirement of nurse support that is often required for home infusions of IV ERTs.

6.4 Prescription of eliglustat requires laboratory testing to determine rates of metabolism of eliglustat, in line with its licence in the treatment of poor, intermediate and extensive metabolisers only. Eliglustat is not licenced for use in patients who are ultra-rapid or indeterminate metabolisers. Metaboliser status is predominantly dependent on the activity of the enzyme CYP2D6, and the primary metaboliser of eliglustat. The test for CYP2D6 status can be conducted at laboratories in the UK with existing NHS contracts, and the cost of these tests will be covered by the company Genzyme.

7 Equalities issues

7.1 No potential equality issues were identified during the scoping process. No potential equality issues were identified that would need to be addressed by the Committee.

8 Innovation

8.1 The company highlighted that eliglustat is the first oral therapy available as first-line treatment, and may result in improvements in the management of the disease in England. Patient preference for oral therapy was clearly demonstrated in the ENCORE trial, in

which patients completed questionnaires indicating their preferred route of administration, citing the following reasons: convenience, the capsule form, taking the drug at home, and feeling better after treatment

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

There is no related NICE guidance for this technology

NHS England Policy Documents

- NHS England, Manual for prescribed specialised services, 2013/2014. Section 71: Lysosomal storage disorder service (adults and children). Available at: http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf
- National Specialised Commissioning Advisory Group, UK national guideline for adult Gaucher disease, 2012.

Appendix B: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003724/WC500182389.pdf

Summary of product characteristics can be found here:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003724/WC500182387.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

Final scope

Remit/evaluation objective

To evaluate the benefits and costs of eliglustat within its licensed indication for the treatment of type 1 Gaucher disease for national commissioning by NHS England.

Background

Gaucher disease is an inherited lysosomal storage disorder. It is caused by a deficiency of an enzyme (glucocerebrosidase) which leads to the storage of complex lipids in some types of blood cells. This creates Gaucher cells which occur throughout the liver, spleen, bone marrow and occasionally the lungs. There are 3 subtypes of Gaucher disease, of which type 1 (non-neuropathic) is the most prevalent. All types of Gaucher disease are associated with a variety of symptoms, including pain, fatigue, anaemia, thrombocytopenia, jaundice, bone damage, and enlargement of the liver and spleen.

There is limited data available on the epidemiology of Gaucher disease. Over 90% of people affected have type 1 Gaucher disease. The overall frequency of all types of Gaucher disease is approximately 1 in 50,000 to 1 in 100,000 live births. The prevalence of type 1 Gaucher disease is estimated as 1 in 200,000 in non-Ashkenazi Europeans, which equates to approximately 250 people in England and Wales. It is more common in people of Ashkenazi family origin, with a frequency of approximately 1 in 500 to 1 in 1000 live births.

Treatment of type 1 Gaucher disease requires an individualised approach that begins with a comprehensive multi-systemic assessment of all possible disease manifestations to accurately classify disease burden. Current management options include enzyme replacement therapy (such as imiglucerase or velaglucerase alfa) or substrate reduction therapy (miglustat) for people for whom enzyme replacement therapy is not suitable, alongside supportive therapy (which may include blood products, bisphosphonate therapy and/or analgesia).

The technology

Eliglustat (Cerdelga, Genzyme Therapeutics) is a substrate reduction therapy that partially inhibits the enzyme glucosylceramide synthase, resulting in reduced production of glucosylceramide and Gaucher cells. It is given orally.

Eliglustat has a marketing authorisation in the UK for the long-term treatment of type 1 Gaucher disease in adults who are CYP2D6 poor metabolisers, intermediate metabolisers or extensive metabolisers.

Intervention(s)	Eliglustat
Population(s)	Adults with type 1 Gaucher disease who are CYP2D6 poor metabolisers, intermediate metabolisers or extensive metabolisers
Comparators	• imiglucerase • velaglucerase alfa For people for whom enzyme replacement therapy is unsuitable: • miglustat
Outcomes	The outcome measures to be considered include: • type 1 Gaucher disease therapeutic goals • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Impact of the new technology	• clinical effectiveness of the technology • overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Cost to the NHS and Personal Social Services (PSS), and Value	• budget impact in the NHS and PSS, including patient access agreements (if applicable) • robustness of costing and budget impact

for Money	information • technical efficiency (the incremental benefit of the new technology compared to current treatment) • productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used) • allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)
Impact of the technology beyond direct health benefits, and on the delivery of the specialised services	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • staffing and infrastructure requirements, including training and planning for expertise.
Other considerations	If the evidence allows, the following subgroups will be considered: • people who have and have not been previously treated with enzyme replacement therapy • people with symptomatic type 1 Gaucher disease with and without pulmonary involvement Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. The availability of any nationally available price reductions, for example for medicines procured for use in secondary care through contracts negotiated by the NHS Commercial Medicines Unit, should be taken into account.
Related NICE recommendations and NICE pathways	None
Related national	NHS England, Manual for prescribed specialised

policy	services, 2013/2014. Section 71: Lysosomal storage disorder service (adults and children). Available at: http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf National Specialised Commissioning Advisory Group, UK national guideline for adult Gaucher disease, 2012.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Genzyme Therapeutics (eliglustat) Patient/carer groups • British Liver Trust • Gauchers Association Professional groups • Royal College of Nursing • Royal College of Physicians **Treatment Centres: Lysosomal Storage Disorders** • Addenbrooke's Lysosomal Disorders Unit • Charles Dent Metabolic Unit, UCLH • Department of Endocrinology, UHBFT • Royal Free Lysosomal storage disorders unit Others • Department of Health • NHS England	General • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland Comparator companies • Actelion Pharmaceuticals UK (miglustat) • Genzyme Therapeutics (imiglucerase) • Shire Human Genetic Therapies UK (velaglucerase alfa) Relevant research groups • MRC Clinical Trials Unit • National Institute for Health Research

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the evaluation; the manufacturer(s) or sponsor(s) of the technology; national professional organisations; national patient organisations; the Department of Health and relevant NHS organisations in England.

The manufacturer/sponsor of the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the recommendations.

All non-manufacturer/sponsor consultees are invited to make an evidence submission or submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the recommendations.

Commentators

Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the final evaluation documentation for information only, without right of appeal. These organisations are: manufacturers of comparator technologies; Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary).

All non-manufacturer/sponsor commentators are invited to nominate clinical specialists or patient experts.

[1] Non manufacturer consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Eliglustat for treating Gaucher disease type 1

INTERIM

Specification for manufacturer/sponsor submission of evidence

11th April 2016

Contents

Instructions for manufacturers and sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Highly Specialised Technologies Evaluation Programme. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. Use of the submission template is mandatory. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response.

The purpose of the submission is for the manufacturer or sponsor to collate, analyse and present all relevant evidence that supports the case for national commissioning of the technology by NHS England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Interim Process and Methods of the Highly Specialised Technologies Programme' available at: (http://www.nice.org.uk/media/188/49/HST_combined_Interim_Process_and_Methods_FINAL_31_May_2013.pdf). After submission to, and acceptance by NICE, the submission will be critically appraised by an independent Evidence Review Group appointed by NICE, before being evaluated by the Highly Specialised Technology Evaluation Committee.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the Highly Specialised Technology Evaluation Committee's decision-making. Appendices will not normally be presented to the Highly Specialised Technology Evaluation Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical evidence section with 'see appendix X'. Clinical trial reports and protocols should not form part of the submission, but must be made available on request.

All studies and data included in the submission must be referenced. Studies should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126], rather than 'one trial[126]').

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see Section 18 of this document 'Related procedures for evidence submission'.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked ‘Response’ or in the tables as appropriate. ‘Response’ text may be deleted.

List of tables and figures

Abbreviations

A&E	Accident and Emergency
AE	Adverse event
AIC	Akaike Information Criterion
ALT	Alanine transferase
ANCOVA	Analysis of covariance
ASHG	American Society of Human Genetics
AST	Aspartate aminotransferase
AWMSG	All Wales Medicines Strategy Group
AVN	Avascular necrosis
BIC	Bayesian Information Criterion
BID	Twice daily
BMB	Bone marrow burden
BMD	Bone mineral density
BNF	British National Formulary
BPI	Brief Pain Inventory
CCL18	Chemokine (CC motif) ligand 18
CENTRAL	Cochrane Central Register of Controlled Trials
CFB	Change from baseline
CGI-S	Clinical Global Impression – Severity scale
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMU	Commercial Medicines Unit
CPK	Creatine phosphokinase
CSR	Clinical study report
CT	Computed tomography
DS3	Disease severity scoring system
DSA	Deterministic sensitivity analysis
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
ECHO	Echocardiogram
EM	Extensive metaboliser
EMA	European Medicines Agency
EPAR	European public assessment report
ERT	Enzyme replacement therapy
FAS	Full analysis set

FDA	Food and Drug Administration
FSS	Fatigue Severity Score
GD	Gaucher disease
GD1	Gaucher disease type 1
GD2	Gaucher disease type 2
GD3	Gaucher disease type 3
GEE	Generalised estimating equation
GP	General practitioner
HSE	Health Service Executive
HRQL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICGG	International Collaborative Gaucher Group
IM	Intermediate metaboliser
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
KOL	Key opinion leader
LOCF	Last observation carried forward
LS	Least squares
LY	Life years
LYG	Life years gained
MedDRA	Medical Dictionary for Regulatory Activities
MIMS	Monthly Index of Medical Specialities
MN	Multiples of normal
MRI	Magnetic resonance imaging
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
PAP	Primary analysis period
PAS	Patient access scheme
PCS	Physical component summary
PD	Pharmacodynamics
PK	Pharmacokinetics
PM	Poor metaboliser

PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PRO	Patient reported outcome
Q2W	Every-other-week
QALY	Quality-adjusted life year
QD	Once daily
RCT	Randomised controlled trial
SAE	Serious adverse event
SSC	Severe skeletal complications
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SF-36	Short Form 36
SMC	Scottish Medicines Consortium
SOC	System organ class
SOP	Standard operating procedure
SPC	Summary of product characteristics
SRT	Substrate reduction therapy
SSI	Severity scale index
TEAE	Treatment-emergent adverse event
TTO	Time trade-off
URTI	Upper respiratory tract infection

Executive Summary

The technology

Eliglustat (Cerdelga™) has a UK marketing authorisation for the following indication: "Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1), who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs)." Authorisation was granted by the European Medicines Agency (EMA) on 19 January 2015.[1]

Eliglustat is a new substrate reduction therapy (SRT), which acts by mimicking the glucosylceramide synthase (i.e. the enzyme responsible for the synthesis of glucosylceramide), reducing synthesis of glucosylceramide and thereby preventing glucosylceramide accumulation. Eliglustat is an oral treatment administered twice daily over the course of a patients' lifetime.

The recommended dose is 100mg eliglustat twice daily in IMs and EMs. The recommended dose is 100mg eliglustat once daily in PMs.

The acquisition cost is £282.34 for one capsule, which is equivalent to £206,250 for 1 year of treatment for IMs and EMs and £103,125 for PMs.

Eliglustat will be used in those adult patients with GD1 in whom clinicians and patients decide that it is the most appropriate treatment. This will include patients switched from enzyme replacement therapy (ERT) or as the first treatment received by the patient.

Nature of the condition

Gaucher disease is a rare, autosomal recessive lysosomal glycolipid storage disorder, resulting from a deficiency in activity of the enzyme acid β-glucosidase. If left untreated, lipid-engorged macrophages (Gaucher cells) accumulate primarily in the liver, spleen, and bone marrow and secondarily in the lungs, kidneys, and intestines leading to debilitating visceral, haematological, and skeletal manifestations with a wide range of severity including extensive morbidity and a shortened life expectancy in many patients. Patients with GD1 present with a range of symptoms, including splenomegaly (85%); hepatomegaly (65%); anaemia (64%); thrombocytopenia (56%); significant growth retardation (34%); osteoporosis (49%); episodic bone pain (27%); avascular necrosis (15%); bone crises (9%) and pathological fractures (6%). The impact of GD1 on health-related quality of life (HRQL) is observed through haematological consequences (including anaemia and thrombocytopenia), fatigue, joint pain, and bone involvement, all of which can impact

patients' physical functioning and mobility, and cause a significant decrement in HRQL. Untreated patients with GD1 have a poor prognosis and shortened life expectancy, with an inevitable need for surgery (splenectomy), immobility in the third or fourth decade of life, bone disease/osteoporosis, and having a consequent high early mortality.

The introduction of ERT has had a substantial impact in reducing the incidence of haematological, visceral, bone manifestations associated with GD1, and consequently, in extending life expectancy and improving overall quality of life. Current treatment of GD1 requires intravenous (IV) administration of ERTs every two weeks, which is often burdensome and inconvenient for patients, families and caregivers. In addition, many patients experience infusion-related reactions on receiving ERT. Treatment options for GD1 patients in England are two ERTs, imiglucerase and velaglucerase alfa (velaglucerase) with a small proportion of patients (2%) receiving the SRT miglustat, which is licensed for those for whom ERT is unsuitable (because of patient inability to accept ERT or in the rare case of intolerance to ERT).

Impact of the new technology

The largest clinical trial programme in Gaucher disease to date has confirmed the substantial efficacy of eliglustat on all standard disease measures in ERT-stable patients, and treatment-naïve patients, as determined in two Phase III trials of 12 and 9 months duration, respectively. The Phase II four-year follow-up study shows further improvements in disease activity parameters and other markers including chitotriosidase, glycosphingolipids and bone parameters. These findings indicate that the novel mechanism of action of eliglustat has differentiated therapeutic effects that are central to the disease processes. These effects are also quite different from those seen with previous SRTs.

The key clinical evidence for eliglustat comes from the head-to-head, randomised controlled study ENCORE versus the ERT, imiglucerase in 160 GD1 patients, which is the largest trial of its kind conducted in Gaucher disease, with approximately four times as many patients and double the time horizon of previous trials. Additional evidence is available from a Phase III, randomised, placebo-controlled study of eliglustat in 40 GD1 patients, ENGAGE, and a Phase II, single-arm study of eliglustat treatment in 26 GD1 patients over 4 years.

- In the Phase III ENCORE study, eliglustat [50mg, 100mg or 150mg BID] (n=106) demonstrated non-inferiority to an ERT (imiglucerase) [30-130 U/kg/month] (n=54)

at 52 weeks. This was a randomised controlled study of patients previously treated and stabilised on ERT:

- The primary composite endpoint (percentage of patients stable at 52 weeks) was met by 84.8% (95% CI: 76.2%, 91.3%) of patients on eliglustat and 93.6% (95% CI: 82.5%, 98.7%) on imiglucerase and met the criteria set in this study to be declared non-inferior. In the extension phase, stability was maintained at 104 weeks on eliglustat in 87% of patients (n=95).
- In the Phase III ENGAGE study, eliglustat [Week 4 to 39, 50mg or 100mg BID] (n=20) versus placebo (n=20) demonstrated statistically significant and clinically meaningful improvements in spleen volume at 39 weeks. This was a randomised controlled clinical trial in treatment naïve patients:
- The primary endpoint of change in spleen volume was significant, with a decrease of -27.8% for the eliglustat treatment group compared with an increase of 2.3% for the placebo group ($p<0.0001$).
- Eliglustat also demonstrated statistically significant superior efficacy compared to placebo on all secondary efficacy endpoints.
- Eliglustat (50mg or 100mg BID) has demonstrated progressive improvements in parameters of bone disease over a 4-year follow-up of patients in the Phase II study (n=26). This was accompanied by a progressive decrease in circulating markers of overall disease activity (chitotriosidase and glycosphingolipids), suggesting a different time profile of response in comparison to ERT, which was not apparent in the 9-month randomised comparative phase of the studies.
- In Year 1, a majority of patients met the composite primary endpoint, with 77% (95% CI: 58, 89) of the intention-to treat (ITT) population showing specified improvements in at least two of the three main disease parameters (haemoglobin and platelet levels and spleen volume).
- Nearly all patients (18/19) had presence of some dark marrow (Gaucher cells) at baseline, and after 4 years of treatment with eliglustat, 10 (56%) of the 18 patients evaluable showed improvement, while the other eight patients (44%) remained stable.
- At Year 4, 15 patients had evaluable bone data. Lumbar spine T-score bone mineral density (BMD) increased by 9.9% ($0.8 g/cm^2$, $p=0.02$). This moved the T-

score from -1.6 (in the osteopenia range) to -0.9 (i.e. into the normal range of between -1.0 and 1.0).

- Over 4 years no bone crises were reported for the duration of the trial.

Eliglustat has shown positive effects on HRQL, with improvements in Short Form 36 (SF-36) scores in treatment-naïve patients in ENGAGE, and maintenance of HRQL in ERT-stable patients in ENCORE, adding to observed data from over 4 years in the Phase II study. In the ENCORE study, patients who received eliglustat for 12 months and were questioned regarding treatment preference all confirmed their preference for oral treatment.

A HRQL increment of 0.12 quality-adjusted life years (QALYs) per year was assumed to be encountered by patients that received eliglustat reflecting the patients' preference for oral therapy based upon a time trade-off (TTO) study of 100 members of the UK general public.[2]

No study exists comparing eliglustat to velaglucerase (which is the other ERT in addition to imiglucerase used in clinical practice in England). A systematic literature search identified one study comparing velaglucerase [60U/kg] (n=17) to imiglucerase [60U/kg] (n=17) in treatment naïve patients at 9 months. This was a randomised controlled trial. Non inferiority was demonstrated in this study based on the primary parameter of changes in haemoglobin concentration.

An indirect comparison of eliglustat with velaglucerase was conducted for the parameters of primary interest (spleen volume, liver volume, platelet count and haemoglobin level), despite the significant heterogeneity in the evidence base. The analysis reported relatively small differences that were not statistically or clinically significant, which support the position of eliglustat being at least as efficacious as current relevant treatment comparators, albeit within the limitations of the 9-month study period and subject to the limitations of the evidence base.

Eliglustat is a well-tolerated therapy, as determined from 535 patient-years of safety data collected among 393 patients over 4 years. The eliglustat clinical trials reported no deaths, a discontinuation rate of 3%, and rates of overall serious adverse events (SAEs) as 9%, with eliglustat-related SAEs as 1%. Most patients reported treatment-emergent adverse events (TEAEs) as mild (78%) or moderate (44%), and in 79% of patients, TEAEs were considered not related to eliglustat treatment.

The overall health benefit of using eliglustat in place of ERT results from the replacement of ERT treatment, which requires bi-weekly infusions each of approximately 2 hours with an orally administered tablet. The lifetime benefit associated with using eliglustat in place of ERTs (driven substantially by the quality of life improvement associated with mode of administration) has been estimated to be 2.44 QALYs for patients that are treatment naïve and 2.28 QALYs for ERT stable patients.

Cost to the NHS and Personal Social Services

A de novo cost-effectiveness model was built to estimate the cost and clinical outcomes associated with eliglustat compared to imiglucerase and velaglucerase, in two patient populations; those stable on ERT and those who are treatment naïve. The model adopts a Markov cohort state transition structure and an English NHS and Personal Social Services (PSS) perspective. Using eliglustat in place of imiglucerase for IM/EM ERT stable patients is estimated to lead to a cost saving of £147,394 in lifetime costs per patient to the healthcare and personal social services system (based on the list prices for the two comparators). Using eliglustat in place of velaglucerase for IM/EM treatment naïve patients is estimated to lead to a cost saving of £1,354,457 in lifetime costs per ERT stable patient to the healthcare and personal and social services system, based on the list price of velaglucerase. Genzyme are aware that velaglucerase has a confidential discount, for which different values from 0% to 80% are tested in scenario analysis within the economic model in 20% increments.

For the treatment naïve population, using eliglustat in place of imiglucerase and velaglucerase for IM/EM patients is estimated to lead to a cost saving of £212,299 and £1,352,367, respectively.

Using eliglustat in place of imiglucerase and velaglucerase for PM patients that are ERT stable is estimated to lead to a decrease of £2,116,154 and £3,323,218, respectively, in lifetime costs per patient to the healthcare and personal social services system (based on the list prices of the two comparators). Using eliglustat in place of imiglucerase and velaglucerase for PM patients that are treatment naive is estimated to lead to a decrease of £2,297,310 and £3,437,379, respectively, in lifetime costs per patient to the healthcare and personal social services system (based on the list prices of the two comparators).

The overall annual cost to the healthcare and personal social services of using eliglustat is estimated to bring a saving of £1,873,401 in Year 1 following launch, leading to a total saving of £4,846,357 in Year 5. This is based on an estimated XX patients receiving eliglustat in Year 1, rising to XXX patients in Year 5. These costs are based on the

ENCORE trial dosing of imiglucerase and velaglucerase and the SmPC recommended dose of eliglustat. It is recognised that such costs, as with all drugs, may be different in real life clinical practice.

Value for money

The annual cost of eliglustat is £206,250 (for IM/EM patients), which is higher than that for imiglucerase (£199,976) and lower than that for velaglucerase (£263,203) based on their respective list prices. This cost of eliglustat is justified as it has demonstrated similar efficacy to imiglucerase in its clinical trial programme (and by extension to velaglucerase), and in addition:

- It avoids the highly negative impact of infusion therapies every two weeks
- There is a high preference for eliglustat over ERT therapy based on results from ENCORE
- It demonstrates good efficacy in avoiding negative bone outcomes over 4 years. Skeletal problems have the highest impact on ERT treated GD1 patients

For PM patients, the estimated annual cost of eliglustat is £103,125, and for imiglucerase and velaglucerase it is £199,976 and £263,323, respectively, based on their list prices. PM patients are an estimated 7% of eliglustat's target population and IM/EM patients are 93%.

As part of the National Framework for supply of Treatments for Lysosomal Storage Disorders (June 2012) signed with the Secretary of State for Health which includes guidance on the use of drug treatments for Gaucher Disease in the UK, Genzyme can confirm that for imiglucerase no discount on its list price is operational. A discount was agreed with the Commercial Medicines Unit (CMU) for the use of the velaglucerase within the process that accompanied the production of this guidance which is being reviewed by the CMU in 2016. The level of this discount is commercial in confidence and is not known by Genzyme and hence has not been included as part of this analysis (except to consider alternative discount levels as part of a sensitivity analysis). Revisions to the price of velaglucerase and imiglucerase (e.g. based on commercially confidential discounts) have the potential to form part of the new tendering process. Genzyme notes the statement in the NHS Methodological Guidance that "analyses based on price reductions for the NHS will only be considered when the reduced prices are transparent and consistently available across the NHS, and if the period for which the specified price is available is guaranteed", and submits that discounts in the list price of velaglucerase should only be taken into account if they meet these criteria.

Impact of the technology beyond direct health benefits

Existing treatment with bi-weekly 2-hour infusions of ERTs may have a substantial negative impact on patients in terms of productivity within paid employment, employability and on domestic and child care responsibilities. Replacement with the oral treatment, eliglustat, will remove this negative impact associated with regular infusions.

The impact of the technology on the delivery of the specialised service

The costs and the infrastructure required to provide an ERT infusion service will be reduced with increasing use of the oral treatment, eliglustat, in place of ERTs. Most ERT infusion (over 90%) occurs in the patient's home with the remainder provided as a daycase service in hospitals. The ERT infusion service includes nursing support, the delivery of the treatment to the patient's home, the provision of pumps/drip stands and refrigeration/storage facilities and is estimated to be £12,567 (7.3% of the annual treatment cost based on a report estimating infusion ERT homecare costs from the Office of Fair Trading[3]).

Section A – Decision problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table 1: Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Intervention	Eliglustat	Eliglustat 84.4mg (as free base, equivalent to 100mg eliglustat tartrate) twice daily in CYP2D6 EMs and IMs, and once daily in CYP2D6 PMs.	Not applicable
Population	People with symptomatic Gaucher disease type 1 (GD1)	Adults with GD1	In line with SmPC
Comparator(s)	• Imiglucerase • Velaglucerase alfa For people for whom enzyme therapy is unsuitable: • Miglustat	• Imiglucerase • Velaglucerase alfa	Miglustat is not considered a relevant comparator as it is only used in a very small proportion of adult GD1 patients in England for whom ERT is unsuitable (<2% [X patients] in 2015).
Outcomes	The outcome measures to be considered include: • GD1 therapeutic goals • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers).	The outcome measures to be considered include: • GD1 therapeutic goals • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers).	No data identified to allow the impact on carers to be assessed
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of	• Disease morbidity and patient clinical	Not applicable

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
	care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	
Impact of the new technology	• Clinical effectiveness of the technology • Overall magnitude of health benefits to patients and, when relevant, carers • Heterogeneity of health benefits within the population • Robustness of the current evidence and the contribution the guidance might make to strengthen it • Treatment continuation rules (if relevant)	• Clinical effectiveness of the technology • Overall magnitude of health benefits to patients • Heterogeneity of health benefits within the population • Robustness of the current evidence and the contribution the guidance might make to strengthen it	Treatment discontinuation rule considered not relevant to the treatment under consideration. No data identified to allow the impact on carers to be assessed
Cost to the NHS and PSS, and value for money	• Budget impact in the NHS and PSS, including patient access agreements (if applicable) • Robustness of costing and budget impact information • Technical efficiency (the incremental benefit of the new technology compared to current treatment) • Productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used) • Allocative efficiency (the impact of the new technology on the budget	• Budget impact in the NHS and PSS, including patient access agreements (if applicable) • Robustness of costing and budget impact information • Technical efficiency (the incremental benefit of the new technology compared to current treatment) • Productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used) • Allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)	Not applicable

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
	available for specialised commissioning)		
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • Staffing and infrastructure requirements, including training and planning for expertise	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • Staffing and infrastructure requirements, including training and planning for expertise	Not applicable
Other considerations	If the evidence allows, the following subgroups will be considered: • People who have and have not been previously treated with enzyme replacement therapy • People with symptomatic GD1 with and without pulmonary involvement Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The following subgroups will be considered: • People who have and have not been previously treated with enzyme replacement therapy Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	No data are available for patients with pulmonary involvement in the eliglustat clinical trial programme, as confirmed at the Decision Problem Meeting. Subgroup based on type of ERT pre-treatment was conducted to assess the impact of type of pre-treatment on eliglustat efficacy.

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand name: Cerdelga™

Approved name: Eliglustat

Therapeutic class: Glucosylceramide synthase inhibitor; various alimentary tract and metabolism products: Anatomical Therapeutic Chemical (ATC) code: A16AX10[1]

2.2 Please complete the table below.

Table 2: Dosing Information of technology being evaluated

Pharmaceutical formulation	Hard capsule, containing 84.4mg eliglustat (equivalent to 100mg eliglustat tartrate)
Method of administration	Oral use
Doses	84.4mg eliglustat (equivalent to 100mg eliglustat tartrate)
Dosing frequency	84.4mg eliglustat (equivalent to 100mg eliglustat tartrate) twice daily (BID) in CYP2D6 EMs and IMs, and once daily in CYP2D6 PMs.
Average length of a course of treatment	Lifetime
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	None
Key: BID, twice daily; EM, extensive metaboliser; IM, intermediate metaboliser; PM, poor metaboliser.	

2.3 What is the principal mechanism of action of the technology?

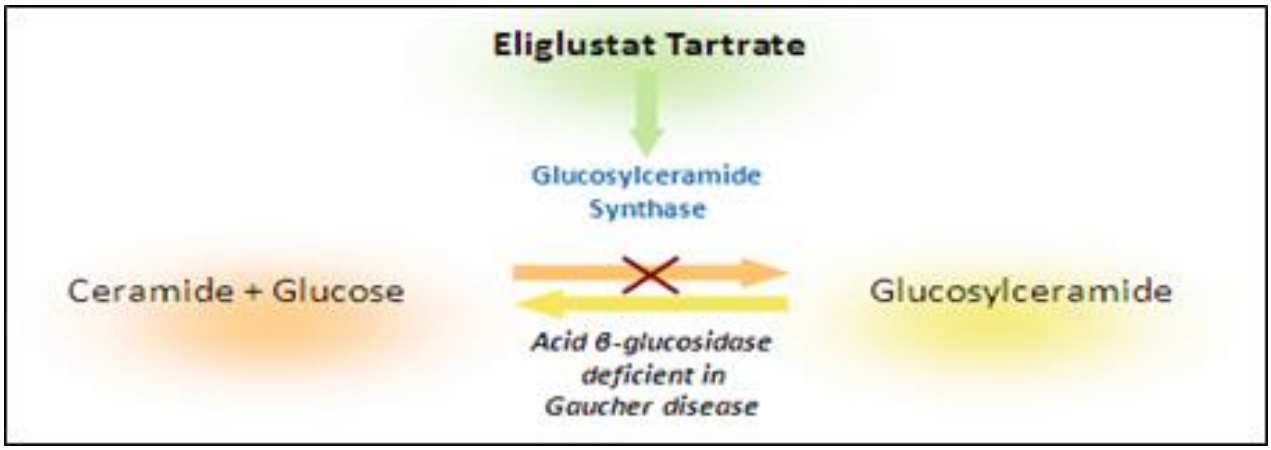
Eliglustat is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1), who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).

The major natural substrate (substance acted on by an enzyme) for acid β-glucosidase is glucosylceramide (also known as glucosylcerebroside). In patients with Gaucher disease, the liver, spleen, bone marrow and brain show increases in glucosylceramide concentrations due to acid β-glucosidase deficiency.[4] Glucosylceramide is an intermediate metabolite in the synthesis and catabolism of more complex glycosphingolipids. In Gaucher disease, the raised levels of glucosylceramide also result in raised levels of

glycosphingolipids in the liver, spleen, bone marrow and brain. Glucosylceramide synthesis is the first rate-limiting step in the biosynthesis of gangliosides and neutral glycosphingolipids. Glycosphingolipids are broken down by enzymes in lysosomes so that a low concentration of glycosphingolipids is maintained at all times in those without Gaucher disease. In those without Gaucher disease, glucosylceramide is distributed in many tissues, while glucosylsphingosine is usually not detected in visceral tissues in significant amounts.[4]

Eliglustat is a potent and specific inhibitor of glucosylceramide synthase (the enzyme responsible for the synthesis of glucosylceramide), and acts as a substrate reduction therapy (SRT) for GD1. SRT aims to reduce the rate of synthesis of glucosylceramide to match its impaired rate of breakdown in patients with GD1, thereby preventing glucosylceramide accumulation and alleviating clinical manifestations (Figure 1).[1, 5]

Figure 1: Mechanism of action of eliglustat



Source: Mankoski et al., 2013.[5]

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Eliglustat has a UK marketing authorisation for the following indication: “Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1), who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).” Authorisation was granted on 19 January 2015.[1]

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

The anticipated launch date of eliglustat in the UK is December 2016.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Eliglustat was approved by the US Food and Drug Administration (FDA) in the US on 19 August 2014[6]; by the Therapeutic Goods Administration in Australia on 17 February 2015[7]; and by the Ministry of Health, Labor and Welfare in Japan on 30th March 2015.[8]

3.4 If the technology has been launched in the UK provide information on the use in England.

Eliglustat has not yet been launched and is not currently used in the UK.

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

Table 3 presents the completed and currently ongoing trials of eliglustat in patients with GD1.

Table 3: List of completed and ongoing eliglustat trials

Trial no. (Acronym) Phase	Interventions	Population	Primary outcome	Status	Primary reference
NCT00891202 (ENGAGE) Phase III, with open-label extension phase	• Eliglustat 50mg BID or 100mg BID, oral • Placebo • Duration: 39 weeks, with ongoing extension phase	40 adult treatment-naïve patients with GD1	Percentage change from baseline in spleen volume (MN) after 39 weeks	Completed; extension phase is ongoing until Q1 2016 (study report expected Q3 2016)	Mistry et al., 2015[9]
NCT00943111 (ENCORE) Phase III, with open-label extension phase	• Eliglustat 50mg BID, 100mg BID, or 150mg BID, oral • Imiglucerase IV, varied dose, Q2W (bi-weekly) • Duration: 52 weeks, with ongoing extension phase	160 adult patients with GD1, who previously received treatment with ERT for ≥3 years.	Percentage of patients who remained stable for 52 weeks in all of the following parameters: • Haemoglobin levels ≤1.5g/dL from baseline • Platelet counts ≤25% from baseline • Spleen volume ≤25% from baseline • Liver volume ≤20% from baseline	Completed; extension phase completed (study report expected Q2 2016)	Cox et al., 2015[10]
NCT00358150 Phase II	• Eliglustat 50mg BID or 100mg BID, oral • Duration: 52 weeks, then extension period	26 adult patients with GD1, who had not received miglustat or	• Composite endpoint requiring improvement from baseline to Week 52 in ≥2 of the following 3 parameters: • Spleen volume (reduction of ≥15% from	Extension phase ongoing until Q1 2016	Lukina et al., 2010[11]; Lukina et al., 2014[12]

Trial no. (Acronym) Phase	Interventions	Population	Primary outcome	Status	Primary reference
	of further 3 years	imiglucerase during the previous 12 months	baseline) • Haemoglobin level (increase of ≥ 0.5g/dL from baseline) • Platelet count (increase of ≥15% from baseline)	(study report expected Q3 2016)	
NCT01074944 (EDGE) Phase III	• Eliglustat 50mg BID or 100mg BID, oral • Eliglustat 100mg QD or 200mg QD, oral • Duration: up to 18 months lead-in, then 12 months double-blind treatment period	115 adult patients with GD1 who demonstrated clinical stability on eliglustat BID	Percentage of randomised patients who remained stable for 52 weeks in all of the following parameters: • Haemoglobin levels ≤1.5g/dL from baseline • Platelet counts ≤25% from baseline • Spleen volume ≤25% from baseline • Liver volume ≤20% from baseline	Completed (study report expected Q2 2016)	Charrow et al., 2014[13]
Key: BID; twice daily; ERT, enzyme replacement therapy; MN, multiples of normal; Q2W, every other week; QD, once daily.					

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

In Wales, eliglustat has not been assessed by the All Wales Medicines Strategy Group (AWMSG), and as such, a notice of non-submission was released in March 2015. The AWMSG states “In the absence of a submission from the holder of the marketing authorisation, eliglustat tartrate (Cerdelga®) cannot be endorsed for use within NHS Wales for the long-term treatment of adult patients with Gaucher disease type 1 (GD1), who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).”[14]

Currently, eliglustat is not undergoing any other HTA process in the UK. However, a submission to the Scottish Medicines Consortium (SMC) is planned for 2016, after completion of the current NICE HST appraisal.

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

No equality issues are anticipated for the appraisal of eliglustat.

5.2 How will the submission address these issues and any equality issues raised in the scope?

Not applicable.

Section B – Nature of the condition

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

Gaucher disease is a rare, autosomal recessive lysosomal glycolipid storage disorder, resulting from a deficiency in activity of the lysosomal enzyme acid β-glucosidase. This enzyme deficiency leads to an accumulation of its substrate, glucosylceramide, an intermediate metabolite in the synthesis and catabolism of more complex glycosphingolipids, in cells derived from the monocyte/macrophage system.[15] Thus, Gaucher disease is an inherited metabolic disease that primarily affects organs where tissue macrophages are prevalent.

If Gaucher disease is left untreated, lipid-engorged macrophages (Gaucher cells) accumulate primarily in the liver, spleen and bone marrow, and secondarily in the lungs, kidneys, and intestines leading to debilitating visceral, haematological, and skeletal manifestations with a wide range of severity including extensive morbidity and a shortened life expectancy in many patients.[15]

Defects in acid β-glucosidase function are caused by mutations in the acid β-glucosidase gene, GBA, located on region q21 of chromosome 1. Almost 300 genetic defects (mutations) have been identified, with the four most common being N370S, L444P, 84GG and IVS2+1. These mutations account for 89% to 96% of the mutant alleles found in the Ashkenazi Jewish population.[16, 17]

There are three subtypes of Gaucher disease.[17] GD1 (non-neuropathic) is the most common subtype in the US, Canada, and Europe, representing approximately 94% of the Gaucher disease population.[18] GD1 is differentiated from GD2 (acute neuronopathic) and GD3 (subacute neuronopathic) by the absence of primary central nervous system involvement.[15, 17, 19] Eliglustat is indicated for GD1 only.

Patients with GD1 present with a range of symptoms[17, 18], including moderate/severe splenomegaly in 85% of patients; moderate/severe hepatomegaly in 65%; significant growth retardation (height below the 5th percentile) in 34%, with the majority below average height; osteoporosis in 49%; episodic bone pain in 27%; avascular necrosis in

15%; bone crises in 9% and pathological fractures in 6%.[20] Anaemia and thrombocytopenia are also present in a substantial proportion of patients (64%, and 56%), as reported in the Gaucher Registry.[18] A study at the Royal Free Hospital in London, UK, found a similar picture for those presenting with GD1 with splenomegaly in 87% of patients, hepatomegaly in 44%, bruising in 40%, bone pain in 36%, avascular necrosis in 11% and thrombocytopenia in 82%.[21] A comprehensive literature review of the burden of GD, which included 51 articles reporting clinical symptoms, comorbidities and/or natural history, reported the high prevalence of many clinical manifestations of the disease (Table 4).[22] These include haematologic and visceral symptoms, skeletal manifestations and common comorbidities such as Parkinson's disease and cancer.

Table 4: Clinical manifestations and comorbidities of Gaucher disease reported in a comprehensive literature review

Type of clinical manifestation	Prevalence (%)	Associated complications
Anaemia	11.0-75.0	Hypersplenism, iron or B12 deficiency, decreased erythropoiesis due to bone marrow failure
Thrombocytopenia	20.0-62.0	Easy bruising or bleeding, increased risk of bleeding due to clotting abnormalities
Splenomegaly	15.0-96.0	Increase risk of spleen rupture, infection, anaemia, leukopenia, and thrombocytopenia
Hepatomegaly	10.0-86.0	Possibly accompanied with abdominal pain, fatigue, nausea, vomiting, jaundice, and digestive problems
Bone pain	8.0-64.2	Progression to bone disease, spontaneous fractures, joint destruction, bone infarction, hip or shoulder replacement, osteoporosis, hospitalisation, and extended bed rest
Bone crises	3.4-24.2	
Parkinson's disease	1.3-8.6	Higher risk of parkinsonism and Parkinson's disease in GD patients due to GBA gene mutations
Cancer	4.0-21.0	Higher risk of myeloma, leukaemia, glioblastoma, lung cancer, and hepatocellular carcinoma, although relationship remains unclear
Source: Nalysnyk et al., 2015.[22]		

Symptom onset occurs in childhood or late into adulthood[15]; a review of registry data reported half of patients with Gaucher disease (94% were GD1) were diagnosed before 10 years of age.[18, 23]

In the absence of pharmacological treatment, patients would experience a number of debilitating manifestations often requiring difficult surgery as the disease progresses:

- Between 48% and 66% of patients would undergo splenectomy, which may subsequently accelerate bone disease[20, 24, 25] and has demonstrated a significant

link to severe bone involvement (odds ratio of 6.97; p<0.0001).[26] This has also been shown to lead to post-operative complications including infections and thrombotic events in 27% of patients.[24]

- Almost 100% of patients would suffer from bone disease, with the most common manifestation being osteoporosis.[20, 25, 27]
  - Serious bone complications would exist in 44% of patients, including bone crises (periods of painful bone inflammation and destruction) occurring approximately every four years.[28] Avascular necrosis occurs in the long bones, with the femoral and humeral head being particularly affected, resulting in pathological fractures and the need for arthroplasty.[27]
  - Small bone crises are also common in patients with GD1; these were found in 13% of a cohort of 100 patients with GD1.[29] However, because these are less severe than crises in the long bones, they may not be considered as important clinically. However, some patients have been reported to suffer multiple crises in small bones of the hands and feet, which can lead to reduced quality of life and reduced physical function, potentially impacting on ability to work and perform manual tasks.[29]
- Furthermore, life expectancy was substantially lower in the absence of drug treatment, although the natural history of untreated disease prior to the advent of enzyme replacement therapy (ERT) is poorly documented,[30] and there is limited reliable information on life expectancy for patients with Gaucher disease. Patients who present below the median age of ~14 years with massive splenomegaly, hypersplenism and bleeding episodes have a particularly poor prognosis. Without treatment, splenectomy would be inevitable in these patients, followed by progression to bone disease and immobility in the third or fourth decade of life with a high early mortality.[30-32] Meanwhile, untreated patients with milder disease may survive to the fifth and sixth decades of life, although have a greater risk of malignant neoplasia.[27]

The primary measure used to score the severity of GD1 in clinical practice in England is the Gaucher Disease Type 1 Severity Scoring System (GD-DS3). This is a validated measure established by an expert physician group using the nominal group technique of consensus formation. Items were selected by 36 GD1 physicians.[33] The expert group determined appropriate measurement techniques for each item. Measurements were

weighted considering contributions to GD1 morbidity and mortality. Patients are allocated a score between 0 and 19. Clinical Global Impression – Severity scale (CGI-S) scores for sample cases, as part of the validation process were compared with average GD-DS3 scores to estimate a minimal clinically important difference. The minimal clinically important difference was -3.2 for improvement and +3.9 for deterioration.[33] As shown in Figure 2 the domains within the measure are haematological (including items for anaemia and thrombocytopenia), visceral (including splenomegaly and hepatomegaly) and bone.

Figure 2: Gaucher disease type 1 severity scoring system (GD-DS3)

Gaucher Disease Type 1 Severity Scoring System (GD-DS3)

Patient ID

Assessment Date

DISEASE DOMAINS	ASSESSMENTS	DISEASE SEVERITY SCORE 0	1	2	3	4	5	6	7	8	9	10	Assessment Score	Average Domain Score
BONE	Lytic Lesions, AVN, or Pathological Fractures*	Absent								Present			8	8.0
	Bone / Joint Pain (past 30 days)	None to very mild pain		Mild pain			Moderate pain			Severe pain		Extreme pain	10	
	# Bone Crisis in Past 12 Months	0 to 1		≥ 2									2	
	Bone Marrow Infiltration**	0 to 4 (mild)								5 to 8 (moderate)		9 to 16 (marked to severe)	10	
	Bone Mineral Density Z-score†	> –1		> –2 to ≤ –1								≤ –2	10	
HEMATOLOGIC	Thrombocytopenia	≥ 120 x10^3/mm^3		21 to 119 x10^3/mm^3			< 20 x10^3/mm^3						5	6.0
	Bleeding	None to mild tendency; bruising		Moderate; no transfusions						Severe; transfusion needed			8	
	Anemia	> 12 g/dL (male), > 11 g/dL (female)		8 to 12 g/dL (male), 8 to 11 g/dL (female)			< 8 g/dL						5	
VISCERAL	Splenomegaly‡ (Volume as MN)	≤ 5		> 5 to ≤ 15			> 15 or Splenectomized						5	5.0
	Hepatomegaly‡ (Volume as MN)	≤ 2.5		> 2.5									2	
	Gaucher-related Pulmonary Disease	None								Any			8	
												Total Gaucher DS3 Score		19.0

AVN: avascular necrosis; MN: Multiples of Normal

*New within the past 12 months

**Bone marrow infiltration as measured by MRI using the Bone Marrow Burden score[24] or other quantitative or qualitative assessment of disease burden as mild, moderate, or marked to severe.

†Bone mineral density Z score to be measured by dual-energy X-ray absorptiometry (DXA) if available; computed tomography or other methods are acceptable as long as results are expressed as a Z score.

‡Splenomegaly and hepatomegaly to be measured by (1) MRI or CT, (2) ultrasound, or (3) physical exam, in this order of preference, depending on technology available.

The introduction of pharmacological treatments, primarily ERT, has had a substantial impact in reducing the haematological, visceral and bone manifestations associated with GD1, and consequently, in extending life expectancy. As stated in the guidance for England, the aim of ERT is to achieve therapeutic goals in the following areas: anaemia, thrombocytopenia, hepatomegaly, splenomegaly, skeletal pathology, pulmonary involvement, and functional health and well-being.[34] As such, the use of ERT enables all GD1 patients to live a life with fewer or no symptoms within a short period of starting appropriate management. As a result of these improvements in disease management, patient's quality of life and life expectancy has been dramatically improved compared since

the pre-ERT era. The International Collaborative Gaucher Group (ICGG) reported life expectancy in the treated patients in their registry as 68 years, compared with 77 years in a US reference population.[35] However, treatment for Gaucher disease has only been available since the late 1990s and young patients with severe disease are now predicted to survive through adulthood with further increasing life expectancy.

Although ERT has demonstrated substantial clinical effectiveness in its impact on haematologic abnormalities, visceral infiltration, and quality of life, the frequency of new bone complications is reduced but not eliminated, as reported in a study of treated Gaucher patients in a UK clinical setting.[23] Another UK cohort study assessed residual bone disease in 92 Gaucher patients who had been receiving ERT (imiglucerase or alglucerase), at a median dose of 30U/kg every 4 weeks for a mean of 8.5 years, and found that many reported bone manifestations including Erlenmeyer flask deformity (59%), osteonecrosis (43%), mobility problems (32%), fragility fractures (23%), and osteomyelitis (6%), despite ERT treatment.[23] Furthermore, a survey of members of the European Gaucher Alliance, conducted in 2012-2013, revealed that bone issues were an unmet need that UK patients were concerned about, according to the UK patient organisation, The Gauchers Association.[36] ERT is provided as an infusion therapy every 2 weeks. The availability of the oral therapy, eliglustat, will reduce the high negative impact on patients from the burden of infusion therapy. Several other issues exist with current treatments, including ERTs, as discussed in more detail in Section 8.3 and as a result, there is clear unmet need for a convenient, well-tolerated therapy with demonstrated efficacy in terms of patients reaching or maintaining therapeutic goals, with an ability to manage bone complications. Eliglustat provides an oral treatment that meets these needs both as a first-line treatment option and for stable patients switching from ERT.

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

There are limited data available on the epidemiology of Gaucher disease. Over 90% of affected individuals have GD1[37] with high frequencies reported in people of Eastern European (Ashkenazi) Jewish decent[38]; the incidence rate is 1 in 855 Ashkenazi Jewish births.[39]

The prevalence of GD1 has been estimated to be 1 in 200,000 (non-Ashkenazi Europeans)[40], equating to 214 adults in England, based on a 2014 adult population of

42.72 million.[41] This is also in line with estimates based on data from Connock et al.; the estimated number of diagnosed GD1 patients in the UK is XXX in 2015, of which 91% have GD1 and 86% are aged >18 years[42], resulting in XXX patients. This is then re-weighted for the 2014 England population (i.e., multiply by 54.32 million/64.60 million), resulting in XXX patients with GD1 in England who are ERT stable in 2015.

In order to estimate anticipated growth in the population until 2021, it is assumed that there will be a 0.4% growth in the diagnosis of GD1 between 2015 and 2017, and 0.4% growth each year between 2017 and 2021. This reflects improvements in the diagnosis of the disease, and the uptake of treatment in previously untreated prevalent patients.

The results of these calculations and assumptions as to the anticipated number of patients who will be covered by this indication and eligible for eliglustat, along with estimates up until 2021, are presented in Table 5.

Table 5: Number of patients anticipated to be eligible for eliglustat in England in 2017-2021

	2017	2018	2019	2020	2021
Estimated diagnosed GD1 patients aged >18 years	XXX	XXX	XXX	XXX	XXX
Estimated ERT stable patients with GD1 disease >18 years	XXX	XXX	XXX	XXX	XXX
Estimated ERT stable patients with GD1 disease >18 years, excluding ultra-rapid metabolisers (assume 1.5% [Samer et al., 2013][43])	XXX	XXX	XXX	XXX	XXX
Anticipated use of eliglustat in patients switched from ERT stable (newly initiated within year)	XX	XX	XX	XX	XX
Anticipated use of eliglustat in treatment-naïve patients (newly initiated within year)	X	X	X	X	X
Key: ERT, enzyme replacement therapy; GD1, Gaucher disease type 1.					

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

Gaucher disease is very rare and variable and the natural history of untreated disease prior to the advent of ERT is poorly documented as stated in the NIH Technology Assessment Conference[30]: “The Type 1 (adult) form is most common, especially variable and least well characterised.” There is no reliable information on life expectancy for

patients with Gaucher disease, especially those with severe disease presenting in childhood.

Without ERT, patients with Gaucher disease had a poor prognosis and shortened life expectancy. Those patients with a particularly poor prognosis are those who present below the median age of approximately 14 years with massive splenomegaly, hypersplenism and bleeding episodes. Without treatment, splenectomy would be inevitable in these patients, followed by progression to widespread destructive bone disease and immobility in the third or fourth decade of life with consequent high early mortality.[30-32] However, patients with milder disease may survive to the fifth and sixth decades although they are at greater risk from the development of malignant neoplasia.[27]

The advent of ERT has allowed treatment of all disease manifestations except where irreversible damage has already occurred. All severities of disease are treatable and life expectancy has improved remarkably; perhaps even towards normal, but this remains to be demonstrated. Data from the ICGG Gaucher registry in 2008 indicated life expectancy in treated patients with GD1 to be 68 years, compared with 77 years in a US reference population.[35] The main causes of death were malignancy, both solid and haematological (27%), cardiovascular disease (17%), and cerebrovascular disease (13%).[35]

7 Impact of the disease on quality of life

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

The health-related quality of life (HRQL) impacts of GD1 have been assessed in several published studies.

The literature indicates that although many of the symptoms of Gaucher disease in isolation do not cause substantial decrements in HRQL, the HRQL is reduced as patients progress into more severe disease, attributable to changes in haematological, bone and visceral symptoms. The haematological consequences of Gaucher disease include anaemia and thrombocytopenia, which impact patients' physical functioning and mobility. This is further impeded by fatigue and joint pain. For patients whose GD1 progresses to a severe disease, HRQL is further diminished by increasing bone damage and corresponding pain, and the incidence of fragility fractures, which can lead to joint replacements becoming necessary. Consequently, this may reduce the mobility and self-reliance of the patient, and lead to a potential need for a carer. Bone involvement is one of the most severe symptoms of Gaucher disease, and such health states have the largest detriments to patient utility.[37]

In an analysis of the impact of the different Gaucher disease symptoms (namely spleen volume, platelet count, liver volume, haemoglobin, bone pain, bone crisis and bone disease) on HRQL, the relationship between SF-6D and disease symptoms was statistically significant for bone pain only, suggesting that this symptom has the greatest impact on HRQL.[37] Indeed, mean SF-6D values for patients with bone pain was reported as 0.68 compared with 0.82 for those without, and was 0.59 in those with bone crises compared with 0.77 for those without.[37] In another analysis, haemoglobin level and platelet count showed a significant association with SF-6D, but the impact was negligible.[37] However, no statistically significant relationship was observed between spleen volume or liver volume and SF-6D.[37] As such, the haematological and visceral symptoms of GD1 are not associated with the same decrements in HRQL as bone involvement.

Current treatment of the condition requires IV administration of ERTs, which are often burdensome and inconvenient for patients, families and caregivers.[44, 45] In addition, many

patients experience infusion-related reactions on receiving ERT. The burden of current treatments has been described in more detail in Section 8.3. Furthermore, in some cases, having a nurse present during the home infusion may not be possible, and the caregiver may then be required to administer the ERT under a carefully regulated protocol.[46] Of the estimated 96% of infusions that are conducted at home, 50% are without nurse support, and would therefore require caregiver administration.[47]

Furthermore, a survey of members of the European Gaucher Alliance, conducted in 2012-2013, revealed that the areas of concern for the UK (i.e. the patient organisation, the Gauchers Association) were regarding unmet needs of current treatments.[36] In addition to bone issues, unmet needs were expressed for mental health services and psychosocial support for patients with GD, which suggests that the patient organisation recognises the impact of GD on patient quality of life.[36]

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

Eliglustat has also shown positive effects on HRQL, with significant improvements in the physical functioning domain of the SF-36 compared with placebo in the ENGAGE study.[48] Furthermore, eliglustat led to slight but consistent improvements in SF-36 scores in treatment-naïve patients in the ENGAGE study, and a maintenance of HRQL in ERT-stable patients in the ENCORE study.[49] These benefits of eliglustat have also been observed over the long term. After 4 years of treatment in the Phase II study, eliglustat showed small but consistent improvements in SF-36 scores and reductions in the Fatigue Severity Scale (FSS) score to levels similar to those of individuals without fatigue.

Furthermore, eliglustat is an oral therapy with the associated ease of use compared to ERT infusions for an average of 2 hours every 2 weeks that requires some clinical oversight. As such, eliglustat will reduce the burden on the patient in terms of travel to appointments, time commitment, disruption to usual activities, fear of the injection, the time burden of receiving the infusion and adverse effects such as pain at the infusion site, infection and rash.[50, 51] Indeed, patient preference for oral therapy over IV therapy with imiglucerase was reported in the ENCORE trial.[52] This is supported by results from a time

trade-off (TTO) study of 100 members of the UK general public commissioned by Genzyme, which reported a preference for an oral treatment compared with infusions, quantified as a utility benefit of XXX QALYs per year.[2]

In terms of the wider societal benefits on productivity or contribution, it is anticipated that the use of eliglustat would led to a reduced burden on patient's families and informal carers resulting from a reduction in the need for appointments for treatment administration, even if this impact cannot be quantified. Furthermore, introduction of the oral treatment would negate the need for caregiver administration and support of ERT in the home setting, in those 50% of cases where nurse support is not available.[46, 47]

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

There are no specific NICE guidance, protocols, or technology appraisals for Gaucher disease. However, two policy documents have been issued by the NHS:

- Deegan P; Lysosomal Storage Disorder Expert Advisory Group. Adult Gaucher Disease Standard Operating Procedures (2012).[34]
- NHS England, Manual for prescribed specialised services. November 2012. Available at: http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf [42]

The standard operating procedure (SOP) by the Lysosomal Storage Disorder Expert Advisory Group presents standard operating procedures to assist commissioning of services for Adult Gaucher Disease in England, as developed by a group of prescribing physicians, commissioners and patient group representatives working in designated treatment centres at the invitation of the National Specialist Commissioning team. The SOP was designed to regulate practice in England only and is not a clinical guideline for use elsewhere. The SOP recommends velaglucerase as the first choice for initiation of therapy, based on cost, but imiglucerase is also recommended as it is considered of equivalent efficacy. Miglustat is licensed only for patients with mild to moderate GD1 in whom ERT is unsuitable.

The document also provides dosing recommendations, which are also specified for particular patient subgroups. Initial dosing of 30-60 U/kg every 2 weeks is recommended for most patients, based on baseline disease severity. Lower starting doses may be considered for mild disease (e.g. platelet count 100-150 X109/L, or mild splenomegaly), while higher doses of up to 60 U/kg every two weeks should be considered for patients at higher risk, including patients with: severe or symptomatic thrombocytopenia, previous osteonecrosis (especially in the context of prior splenectomy), or Gaucher–related liver or pulmonary disease. After 12 months of treatment, dose should be reduced, once the patient is stabilised, with ongoing monitoring. A maintenance dose of 15-30 U/kg every 2 weeks is expected to be adequate in most cases although this may be increased

incrementally to 60 U/kg every 2 weeks if therapeutic goals are not met within the expected timeframe.

The dosing recommendations within the SOP need to be considered in the context of the relevant ERT SPCs. For example, in the SPC for imiglucerase the following is stated:

- "The rate and extent of response to Cerezyme treatment is dose-dependent. Generally, improvements in organ systems with a faster turnover rate, such as the haematological, can be noted far more rapidly than in those with a slower turnover, such as the bone."
- "In an ICGG Gaucher Registry analysis of a large cohort of patients (n=528) with GD1, a time- and dose-dependent effect for Cerezyme was observed for haematological and visceral parameters (platelet count, haemoglobin concentration, spleen and liver volume) within the dose range of 15, 30 and 60 U/kg body weight once every 2 weeks. Patients treated with 60 U/kg body weight every 2 weeks showed a faster improvement and a greater maximum treatment effect as compared with patients receiving the lower doses."

The NHS England manual lists Gaucher disease as one of seven lysosomal storage disorders for which the NHS Commissioning Board (NHS CB) commissions services. The NHS commissions services from Highly Specialist Lysosomal Storage Disorder Centres for adults and children with lysosomal storage disorders, including services delivered on an outreach basis as part of a provider network. The following drugs for Gaucher Disease are commissioned by NHS Commissioning Board:

- Imiglucerase (Cerezyme®)
- Velaglucerase alfa (Vpriv®)
- Miglustat (Zavesca®)

No subgroups were discussed in this document.

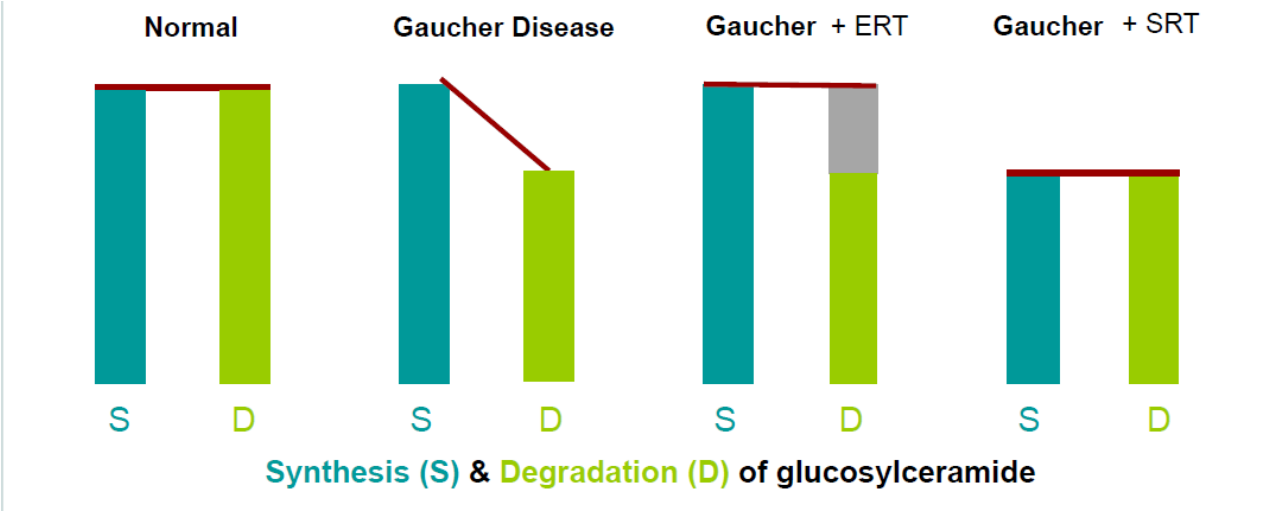
8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

Current management options for GD1 in Europe are the three treatments that have been approved for Gaucher disease by the European Medicines Agency (EMA); these are the two ERTs, imiglucerase licensed in 1997[50] and velaglucerase licensed in 2010[51], and the SRT, miglustat licensed in 2002.[53] The ERTs are indicated for both children and adults

with Gaucher disease, while miglustat is indicated for adults only in mild to moderate GD1 for whom ERT is unsuitable.

The ERT class works by replacing the defective acid β-glucosidase enzyme with a functioning version derived from recombinant technology. ERTs are very effective in reducing symptoms, controlling disease, and enhancing health-related quality of life (HRQL). SRTs inhibit the creation of the substrate for acid β-glucosidase, glucosylceramide, which accumulates in the organs of those affected by Gaucher disease. The different treatment approaches and the resulting balance between synthesis and degradation of glucosylceramide are summarised in Figure 3.

Figure 3: Treatment approaches in Gaucher disease



Key: ERT, enzyme replacement therapy; SRT, substrate reduction therapy.

Due to its heterogeneity, the management of Gaucher disease requires an individualised approach to treatment that takes into consideration the patient's disease manifestations and disease burden as well as quality-of-life needs.[54, 55]

UK guidance for treatment in these patients is not in the form of specific NICE guidance but exists as a recommended standard operating procedure for the treatment of Gaucher disease in adults.[34] In the UK, the usual treatment for GD1 is ERT, specifically velaglucerase on the basis of current cost, following a tender process.[34] ERT is indicated for both adults and children, the latter present with more severe disease and almost invariably require treatment. One cohort study has shown that 30% were diagnosed before 16 years of age, therefore suggesting that approximately 30% would be receiving treatment with ERT by the age of 16 years.[21]

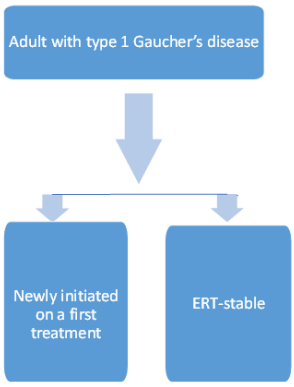
In line with its licence, miglustat may only be used in the treatment of patients with mild to moderate GD1 for whom ERT is unsuitable. Miglustat is not seen as a replacement for ERT given concerns over its efficacy and high discontinuation rates as a result of its substantial tolerability issues[56]; as a result, its use is very low in the UK, with less than 2% of Gaucher disease patients (X patients) receiving treatment.[57] The reason is that it is licensed only for mild to moderate patients for whom ERT is unsuitable.

Furthermore, supportive therapy alone is indicated for patients who decline or are unable to take ERT or miglustat because of adverse events (AEs) or difficulties with administration. For those patients who require ERT, discontinuation rates are very low in Gaucher disease; it is only patients with mild disease who may not require ERT, only supportive therapy. This is demonstrated in a study conducted at the Lysosomal Storage Disorder clinics in England in which 139 of the 146 adult patients with Gaucher disease were recruited. 139 had been initiated on treatment (100% on ERT), and all were still on treatment (94% on ERT and 6% on miglustat), at the time of being recruited to the study with a mean time on treatment of 10.8 years[42] (the number on miglustat at the time of the study was inflated out of necessity for treatment by a supply shortage of imiglucerase).

Symptomatic supportive interventions may include bisphosphonate therapy for osteopenia/osteoporosis, analgesics for bone pain, orthopaedic surgical intervention (e.g. joint replacement) or physical therapy for irreversible skeletal complications, transfusion for anaemia (rarely), splenectomy to ameliorate severe thrombocytopenia (rarely), and/or specific treatment to ameliorate portal and/or pulmonary hypertension.[17, 54, 55, 58, 59] Supportive therapy may also be necessary for those patients receiving ERT or miglustat who develop further complications. Monitoring is required for patients who have been identified with GD1 but who remain asymptomatic. These patients are monitored for disease progression, at which point treatment options will be reviewed.[60]

Figure 4 presents the types of patients with GD1 in which eliglustat is anticipated to be used.

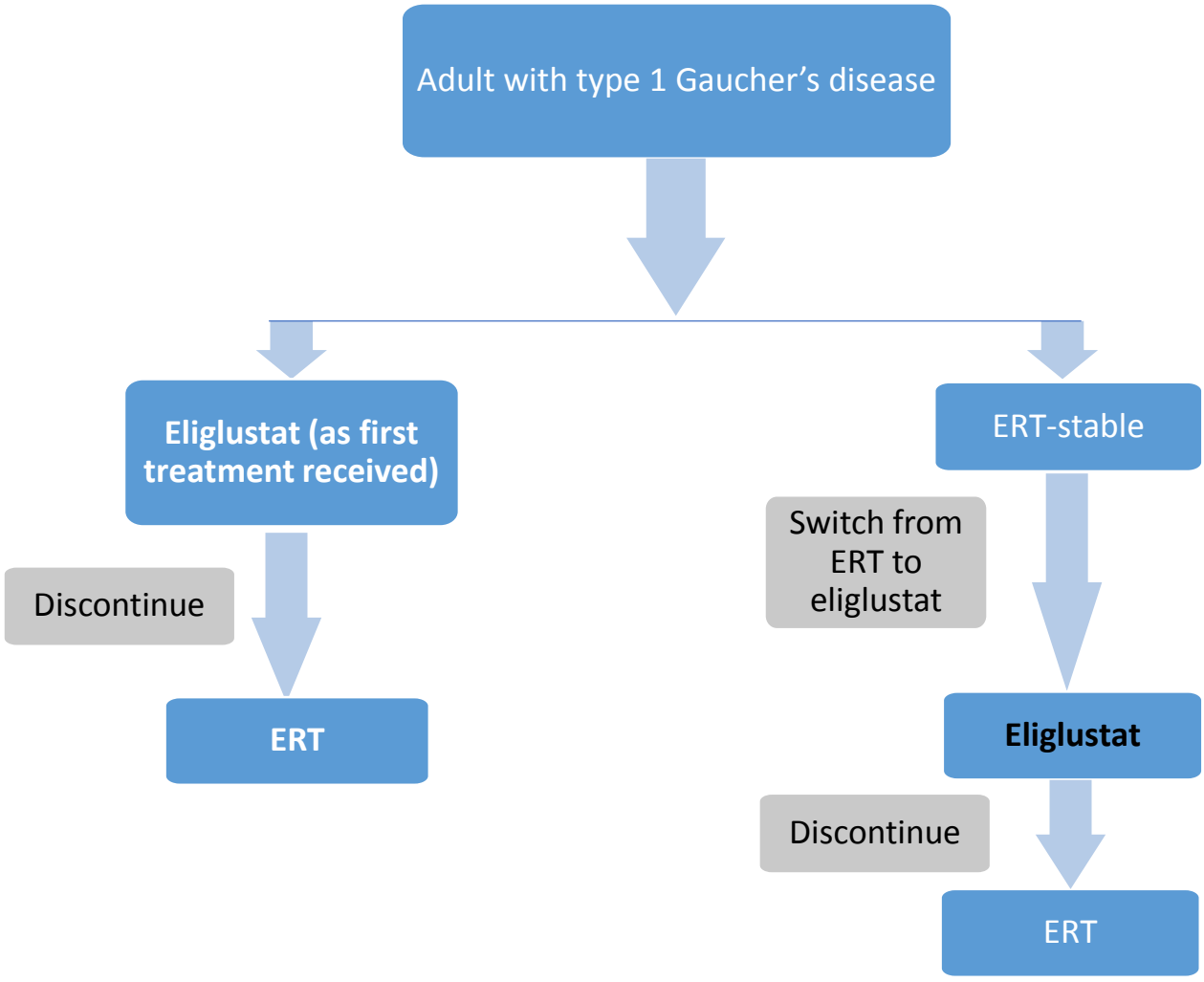
Figure 4: Types of patients in which eliglustat is anticipated to be used



Key: ERT, enzyme replacement therapy.

Figure 5 presents the expected place of eliglustat in the treatment pathway for Gaucher disease. Eliglustat will be used in those adult patients with GD1 in whom clinicians and patients decide that it is the most appropriate treatment. This will include patients who are either stable on ERT who will be switched to eliglustat or patients at first-line treatment. As stated in the SPC, treatment-naïve patients showing <20% spleen volume reduction after 9 months of treatment (i.e. sub-optimal results), should be monitored for further improvement or considered for an alternative treatment modality.[1] For patients who were stable on ERT and switched to eliglustat, disease progression should be monitored (e.g. after 6 months with regular monitoring thereafter) for all disease domains to evaluate disease stability. For patients who have a sub-optimal response, reinstitution of ERT or an alternative treatment should be considered.[1]

Figure 5: Anticipated positioning of eliglustat in clinical practice



Key: ERT, enzyme replacement therapy.

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

Despite the existence of ERT therapies and the SRT, miglustat, several unmet needs remain for patients with GD1. Firstly, current ERT treatments require IV infusions every two weeks for life, which require approximately 2 hours for the infusion time itself, in addition to the time taken for IV access, reconstitution, preparation and cleaning up, as well as any travel time if patient is not receiving a home infusion.[37] As such, these are burdensome and inconvenient for patients, families and caregivers.[44] IV infusions require scheduling appointments, taking time away from education, work and other responsibilities, in addition to receiving the infusions. Furthermore, 50% of home infusions are currently conducted without nurse support, and would therefore require caregiver administration, under a carefully regulated protocol.[46, 47] In addition, regular infusions can put limits on travel and independence, and can act as a reminder to patients that they have a serious disease. Furthermore, IV administration of ERT also carries a risk of infusion-related complications, particularly catheter-related infections. Although the risk of catheter-associated infections or events appears to be small, as reported in a systematic review of clinical effectiveness of ERT in Gaucher disease (one identified study reported two patients with catheter infections in 500 patient-months of therapy)[37], the oral administration of eliglustat provides an opportunity to avoid such complications altogether.

Secondly, approximately 10-15% of patients with GD1 treated with imiglucerase develop immunoglobulin G (IgG) antibodies to the enzyme protein. A few develop significant allergic reactions and these can be controlled with premedication with hydrocortisone, antihistamines or both.[61] A few patients with GD1 have developed antibodies that impair enzyme activity[61-63], although this has rarely required alternative treatment options.

Third, as a result of the manufacturing process for ERTs that is dependent on mammalian cell culture, the supply of ERTs may be affected by contamination, as previously reported.[60] In June 2009, a vesivirus infection (strain 2117) occurred in the dedicated bioreactor plant at the principal production facility of imiglucerase, which interfered with the growth of the Chinese hamster ovary cells used to produce recombinant imiglucerase. This led to a shortage of imiglucerase, which persisted into 2012. Eliglustat represents an alternative treatment that is not affected by such production issues.

Finally, while it is generally accepted that ERT improves parameters in all affected clinical domains, skeletal involvement requires longer treatment and higher doses.[64] This has

been demonstrated in a UK-based, longitudinal cohort study of 150 adults with GD1 which reported that a greater time on ERT was significantly associated (P<0.001) with reductions in liver volume and spleen volume, and improvements in platelet count and haemoglobin.[65] Risk of bone pain was reduced with time on ERT, but the relationship was not significant.[65] Furthermore, a cohort study of 133 adults in the US with GD1 reported that despite ERT, patients with severe disease (GD-DS3 >6) had a 58% chance at 10 years and a 70% chance at 15 years for a severe bone complication (avascular necrosis, fracture or lytic bone lesion).[66] Patients with moderate disease (GD-DS3 = 3-6) had a risk of a severe bone complication of 38% at 10 years, and 50% at 15 years, and for patients with mild disease (GD-DS3<3), this risk was 10% at 10 years and 40% at 15 years. The authors conclude that ERT alone is sometimes insufficient for achieving a complete remission of all GD1 manifestations.[66] A disease modelling study based on a cohort of Dutch patients supported the evidence that, while ERT substantially improves some disease manifestations, it is not optimal in treating bone complications.[67] After 10 years, 12% of patients receiving ERT were without bone complications for 10 years (defined as osteonecrosis/osteomyelitis/pathological fractures/vertebral collapse/bone crises).[67] Another study demonstrated that ERT treatment leads to reductions in the rate of crises in the long bones (from 2.1 to 0.5 events per patient), crises in the small bones were seen to increase (from 0.08 to 2.2 events per patient) during ERT therapy. The exact reason for this is unknown, although one hypothesis is the potential for reduced penetration of exogenous enzyme into the small bones of the extremities.[29]

Patients have been switched from the ERT imiglucerase to miglustat for several of these reasons, as demonstrated in a case series, where reasons for switching were: unwillingness to continue IV therapy, unavailability of imiglucerase, and the occurrence of immune reactions.[68] Only a very small minority of patients are deemed unsuitable for ERT, and were administered miglustat as an alternative (approximately X% of drug treatment in the UK). However, miglustat has a number of issues. Miglustat is frequently associated with adverse effects, including very common (≥10%) gastrointestinal symptoms (such as abdominal pain, diarrhoea and weight loss), and tremor (in many patients, this resolves spontaneously during treatment after 1-3 months, although dose reduction or discontinuation may sometimes be required).[53] Peripheral neuropathy is also commonly (1-10%) reported with miglustat treatment, as reported in several studies and a 5-year safety registry[69]; several cases of peripheral neuropathy have been described in the literature.[53, 70]

A survey of members of the European Gaucher Alliance, conducted in 2012-2013, revealed that the areas of concern for the UK (i.e. the patient organisation, The Gauchers Association) were regarding unmet needs of current treatments.[36] These unmet needs were listed as bone issues, and mental health services and psychosocial support for patients with GD, alluding to the recognition of the impact of GD on the patient quality of life.[36]

There is clearly a current need for a convenient, well-tolerated therapy with demonstrated efficacy similar to ERT in terms of patients reaching or maintaining therapeutic goals, and with an ability to manage bone complications. Eliglustat provides an oral treatment that meets these needs both as a first-line treatment option and for stable patients switching from ERT.

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

Please see Section 8.2 for details on the current pathway of care, and the proposed positioning of eliglustat and resulting care pathway if eliglustat is made available.

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Novel oral treatment

Eliglustat, is a novel, oral ceramide analogue, which represents a first-in-class treatment that acts as a specific inhibitor of glucosylceramide synthase, and differs from the oral imino-sugar, miglustat.[4] Specifically, eliglustat is approximately 1000-fold more potent for its target than miglustat.[71] Furthermore, eliglustat is rapidly absorbed, widely distributed across tissues, and extensively metabolised.[71] Eliglustat may lead to a significant shift in the management of GD1 as it is the first oral therapy that may be used as a first-line alternative treatment option to the intravenously administered ERTs. In addition, eliglustat would also offer an alternative treatment in patients who are stable on ERT but who have a preference for oral therapy. In the ENCORE trial, 94% of patients included in the ENCORE trial indicated a preference for oral treatment over IV treatment when questioned at screening.[72] Furthermore, after 12 months of treatment in ENCORE, all of the 93 patients who had switched from imiglucerase to eliglustat who responded to a treatment survey

said they preferred oral therapy to IV therapy, citing the reasons: convenience, the capsule form, taking the drug at home, and feeling better after treatment.[72]

In addition, oral administration will also alleviate the NHS burden associated with frequency of visits, and preparing and administering IV treatment, including staff time which can be reallocated elsewhere.

Efficacy in achieving Gaucher therapeutic goals and managing bone complications

Eliglustat has the potential to make a significant and substantial impact on health-related benefits, with demonstrated significant benefits in haematological, visceral, and skeletal manifestations of GD1 for treatment-naïve patients and in maintaining stability in adult patients previously treated with ERTs. In the ENCORE study, eliglustat demonstrated non-inferiority to imiglucerase in patients who had been previously treated with ERT for ≥3 years, in terms of maintaining patient stability (i.e. improvements in the composite endpoint of haemoglobin levels, platelet counts, and spleen and liver volume), based on the aggregate data from all doses tested in this study.[71] Eliglustat was also non-inferior to imiglucerase in terms of percentage change in spleen volume.[71] In the ENGAGE study, eliglustat showed statistically significant improvements in primary (spleen volume) and secondary (haemoglobin level, platelet counts, and live volume) efficacy endpoints compared with placebo in adult treatment-naïve patients. Eliglustat was associated with sustained and continuing improvements in bone mineral density (BMD), bone marrow burden (BMB) score, and biomarkers of bone disease in patients new to treatment. In patients switching from ERT, eliglustat maintained stable bone health seen after ≥3 years of ERT treatment.

Sustained efficacy over the long term

Eliglustat has also demonstrated long-term efficacy in a Phase II study of adult treatment-naïve patients, in which statistically significant improvements from baseline were seen and sustained over 4 years of treatment in terms of platelet count, haemoglobin level, and spleen and liver volumes.[12] Furthermore, eliglustat has also demonstrated long-term efficacy in the extension studies of ENCORE and ENGAGE.[6]

In ENCORE, the stability in terms of the primary composite endpoint of haematological and organ parameters was maintained over 104 weeks, while in ENGAGE, stability in terms of the primary endpoint of change in spleen volume was maintained over Week 78. In addition to efficacy benefits, eliglustat was a well-tolerated medication. In a safety analysis of pooled data from the Phase II and III clinical trial programme (representing

more than 535 patient years of data from 393 patients, the largest ever programme in GD1), there were very few discontinuations due to treatment-emergent adverse events (TEAEs) (3%), with most being mild to moderate in severity and few serious adverse events (SAEs) (1%) considered related to treatment.[73]

Improvements in health-related quality of life

Eliglustat has also shown positive effects on HRQL, with significant improvements in the physical functioning domain of the SF-36 compared with placebo, as well as slight but consistent improvements in the SF-36 physical component summary (PCS) and its other three scales, in treatment-naïve patients in the ENGAGE study.[48]

Furthermore, eliglustat resulted in a maintenance of HRQL in ERT-stable patients in the ENCORE study. These benefits of eliglustat have also been observed over the long term. After 4 years of treatment in the Phase II study, eliglustat showed small but consistent improvements in SF-36 scores and reductions in the FSS score to levels similar to those of individuals without fatigue.

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

Currently, it is estimated that 96% of infusions are done at home, of which 50% are with nurse support, and 50% are without nurse support. The remaining 4% are treated in hospital as day cases.[47] As such, the introduction of the oral treatment, eliglustat, will negate the need for nurse support in the home, or hospital visits in the 52% of patients who would have otherwise required this on ERT.

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

Patients are eligible for eliglustat if they have a diagnosis of GD1 confirmed by a documented deficiency of acid β-glucosidase activity by enzyme assay. In addition, since eliglustat is extensively metabolised by CYP2D6, eliglustat should be administered to patients with genetically confirmed CYP2D6 poor, intermediate or extensive metaboliser phenotypes. As such, all patients will need to undergo CYP2D6 genotyping before starting treatment with eliglustat. The cost of carrying out this genotyping will be met by Genzyme. Eliglustat is not indicated in patients who are CYP2D6 ultra-rapid, or indeterminate metabolisers. The service provided by Genzyme will be based on testing with a gene chip

based system. There are two such devices licenced for CYP2D6 genotyping by the EMA and the FDA. These are the Luminex xTAG® CYP2D6 kit v3 and the Roche AmpliChip™ CYP450 test. These systems have accuracies of 99.6% to 99.9% in CYP2D6 metaboliser status calls.[74, 75]

Eliglustat is an oral treatment, and therefore there are no specific administration requirements. Furthermore, patients receiving eliglustat will not require monitoring over and above usual clinical practice.

No other therapies are required to be administered with eliglustat.

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

Eliglustat does not require any additional facilities, technologies or infrastructure to be used. The test for CYP2D6 status can be conducted at laboratories in the UK with existing NHS contracts. The cost of carrying out the genotyping service will be borne by Genzyme.

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

As described in Section 8.6, the introduction of the oral treatment, eliglustat, will negate the need for home visits from nurses, or hospital visits, which are currently associated with administration of ERT.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' Section 5.2 available from www.nice.org.uk/guidance/ta.

The eliglustat clinical trial programme is the largest clinical trial programme in Gaucher disease to date, including 393 patients and 535 patient-years of safety data collected over 4 years. The programme comprised three Phase III RCTs (the two pivotal trials ENCORE and ENGAGE, and the EDGE trial) and one Phase II single-arm trial (NCT00358150).

Eliglustat is an effective, safe and convenient oral treatment that has demonstrated clinically relevant effects and HRQL improvements with benefits reported in both treatment-naïve patients and those who are switched from ERT.

In the Phase III, randomised controlled ENCORE study, eliglustat (50mg, 100mg or 150mg BID; n=106) demonstrated non-inferiority to the ERT imiglucerase (30-130 U/kg/month; n=54) in patients previously treated and stabilised on ERT.

- The primary composite endpoint (percentage of patients stable in all four therapeutic parameters at 52 weeks) was met by 84.8% (95% CI: 76.2%, 91.3%) of patients on eliglustat and 93.6% (95% CI: 82.5%, 98.7%) on imiglucerase met the criteria set in this study to be declared non-inferior. Stability was maintained for 104 weeks on eliglustat in 87.8% of patients (n=95)
- In the ENCORE study, patients who received eliglustat for 12 months and were questioned regarding treatment preference all confirmed their preference for oral treatment over IV treatment with imiglucerase

In the Phase III, randomised controlled ENGAGE study, eliglustat [Week 4 to 39, 50mg or 100mg BID] (n=20) versus placebo (n=20) demonstrated statistically significant and clinically meaningful improvements in spleen volume in treatment naïve patients:

- The primary endpoint of change in spleen volume was significant, with a decrease of -27.8% for the eliglustat treatment group compared with an increase of 2.3% for the placebo group ($p<0.0001$). This reduction in spleen volume continued through week 78 with a mean reduction of 44.6% in the eliglustat group

Eliglustat has demonstrated substantial improvements in bone outcomes, in addition to improvements in haemoglobin, platelet counts, liver and spleen volumes, in a 4-year follow-up of patients in the Phase II study (50mg or 100mg bid) (n=26)

- In Year 1, 77% (95% CI: 58, 89) of the ITT population met the composite primary endpoint, by showing specified improvements in at least two of the three main disease parameters (haemoglobin and platelet levels and spleen volume). At 4 years, 100% of patients met therapeutic goals for spleen volume and haemoglobin level, 94% met the goal for liver volume and 47% met the goal for platelet count
- Nearly all patients (18/19) had presence of some dark marrow (Gaucher cells) at baseline, and after 4 years of treatment with eliglustat, 10 (56%) of the 18 patients evaluable showed improvement, while the other eight patients (44%) remained stable
- At Year 4, 15 patients had evaluable bone data. Lumbar spine T-score BMD increased by 9.9% (0.8g/cm2, $p=0.02$). This moved the T-score from -1.6 (in the osteopenia range) to -0.9 (i.e., into the normal range of between -1.0 and 1.0)
- Over 4 years, no bone crises were reported for the duration of the trial

No studies exist comparing eliglustat to velaglucerase (the other ERT also used in clinical practice in England). A systematic literature search identified one randomised controlled trial comparing velaglucerase [60U/kg] (n=17) to imiglucerase [60U/kg] (n=17) in treatment naïve patients at 9 months. Non inferiority was demonstrated in this study based on the primary outcome of changes in haemoglobin concentration.

Eliglustat is well-tolerated, with the majority of AEs in the trials being mild (78%) and transient. No deaths were reported, only 9% of patients experienced SAEs, and only 3% of patients discontinued treatment due to AEs.

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

A systematic review was carried out to search for both trials of eliglustat and trials of relevant comparators, and conducted in two steps.

Original systematic review searches

The original systematic literature review was performed by searching MEDLINE (via PUBMED), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify articles on the efficacy and safety of ERT and SRT for the treatment of GD1. The literature search was not restricted by terms for specific treatments of interest; instead, studies in which the patient population did not receive a treatment of interest were subsequently excluded during level 1 (abstract and title) and level 2 (full-text article) screening.

The limits for this search included: humans, published since 1990, English language articles. The date limit was chosen as the first Gaucher disease therapy, imiglucerase, only became available in 1997 when it was approved by the EMA.[50] The search was conducted in two stages: originally on 6 February 2013, updated in January 2014 with a cut-off date of 5 January 2014. Full details of the search strategies used for each database are provided in Section 17.1 (Appendix 1).

Finally reference lists of all accepted studies, and all relevant systematic reviews, meta-analyses, and treatment guidelines were reviewed manually to supplement the above electronic searches and ensure that the most relevant studies were identified.

Additional searches of the Database of Abstracts of Reviews of Effects (DARE) and the Cochrane Database of Systematic Reviews (CDSR) were carried out after completion of the systematic review. However, these returned three results, of which no studies were deemed relevant.

Grey literature (material that can be referenced but it is not published in peer-reviewed or MEDLINE- or EMBASE-indexed medical journals) was also searched for relevant conference abstracts and posters reporting interventional or observational studies of GD1, which investigated the clinical efficacy, safety or patient-reported outcomes (PROs) of ERT

or SRT. Conference searches covered the period of 2012 onwards (since these may not yet have been published in MEDLINE-/Embase-indexed, peer-reviewed journals) for the following conferences:

- The 2012 annual meeting of the European Working Group on Gaucher Disease (EWGGD); there was no 2013 meeting
- The 2012 and 2013 meetings of the American Society of Human Genetics (ASHG)
- The 2012 meeting of the Society for the Study of Inborn Errors of Metabolism (SSIEM); there was no 2013 meeting
- The 2013 annual meeting of the Lysosomal Disease Network (LDN).

Updated systematic review searches

The 2015 update to the systematic review searches was then carried out on 14 August 2015, based on the original searches, and included the following databases:

- MEDLINE
- EMBASE
- The Cochrane Library
  - CDSR
  - CENTRAL
  - DARE

Database searches were limited by date from October 2013 to 14 August 2015 (date on which searches conducted). This was to allow for an overlap of the previous searches and ensure all potentially relevant articles would be identified. Full details of the search strategies used for each database are provided in Section 17.1 (Appendix 1). In addition, the following conferences were searched:

- The 2014 annual meeting of the European Working Group on Gaucher Disease (EWGGD); there was no 2015 meeting
- The 2014 and 2015 meeting of the American Society of Human Genetics (ASHG)
- The 2014 annual meeting of the Lysosomal Disease Network (LDN)

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Please see Section 9.1.1 which describes a literature review conducted in line with NICE STA guidance and therefore, describes retrieval of both published and unpublished evidence.

9.2 Study selection

Published studies

9.2.1 Complete table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table 6: Selection criteria used for published studies (Table C1 according to NICE HST template)

Inclusion criteria	
Population	Adult or mixed (adult and paediatric) patients with confirmed GD1
Interventions	• Alglucerase • Eliglustat • Imiglucerase • Miglustat • Taliglucerase alfa • Velaglucerase alfa • Unspecified ERT
Outcomes	• Clinical efficacy • Safety • PROs
Study design	*Level 1 screening (titles/abstracts)* • Interventional: – RCTs – Non-RCTs – Single-arm trials • Observational: – Prospective studies – Retrospective studies *Level 2 screening (full-text)* • Randomised controlled trials only

Language restrictions	English-language publications only
Search dates	6 February 2013, 5 January 2014, 14 August 2015
Exclusion criteria	
Population	• Subjects with no GD • Studies involving only paediatric patients • Studies involving only GD2 or GD3 patients • Studies of a mix of GD1 and GD2/3 patients whose outcomes were not reported separately • Pregnant women with GD • Studies in which outcomes were not reported separately by ERT or SRT treatment • Any clinical trial involving <5 GD1 patients or observational studies involving <10 GD1 patients*
Interventions	• Any treatment other than ERT or SRT
Outcomes	• In vitro, animal, foetal, molecular, genetic, PD/PK outcomes • Biopsy findings, plasma or serum levels of antibodies, lipids and proteins only
Study design	*Level 1 screening (titles/abstracts)* • Systematic reviews and meta analyses (references were checked for any additional relevant studies) • In vitro studies • Letters to the editor regarding a randomised trial • Case report • Expert opinion • Narrative review • Treatment guidelines (references were checked for any additional relevant studies) *Level 2 screening (full-text)* • As for level 1 screening listed above, and • Interventional: – RCTs where patients assigned to each treatment arm received the same treatment of interest, e.g. studies that evaluated interventions at different doses – Non-RCTs – Single-arm trials • Prospective, observational studies
Language restrictions	• Non-English studies
Search dates	Studies published prior to 1990; any observational studies published prior to 1 January 2000**

Key: ERT, enzyme replacement therapy; GD1, Gaucher Disease type 1; GD2, Gaucher Disease type 2; GD3, Gaucher Disease type 3; PRO, Patient reported outcome; RCT, randomised controlled trial; SRT, substrate reduction therapy; N/A, not applicable; PD/PK, pharmacodynamics/pharmacokinetic.

Notes: * Most of the rejected publications were case reports or case studies and were rejected at the abstract screening level. Also, almost two thirds of them are published before 2005, before any treatments for GD became available. In addition, a large proportion of them are studies of various genetic diseases, which appear to include only a few GD patients.

****** Observational studies published before 2000 were excluded as these only reported imiglucerase or alglucerase due to the availability of only these ERTs for GD1.

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

A PRISMA diagram showing the flow of studies through the systematic review is shown in Figure 6.

In the original search and the first search update, the MEDLINE, Embase and CENTRAL searches (including indexed meeting abstracts in MEDLINE and Embase) identified 3,669 publications with some overlap between the databases. A search of the grey literature sources identified an additional 196 abstracts. After removing duplicates, there were 2,430 unique publications. During abstract screening, 2,262 abstracts were rejected. The most common reasons for rejection at the abstract level were study design not of interest (740), no outcomes of interest (421), and fewer than five patients with GD1 (346). Full text articles were retrieved for the remaining 168 records and screened against the pre-defined inclusion/exclusion criteria. A manual review of reference lists of systematic reviews and all included publications did not identify any additional publications.

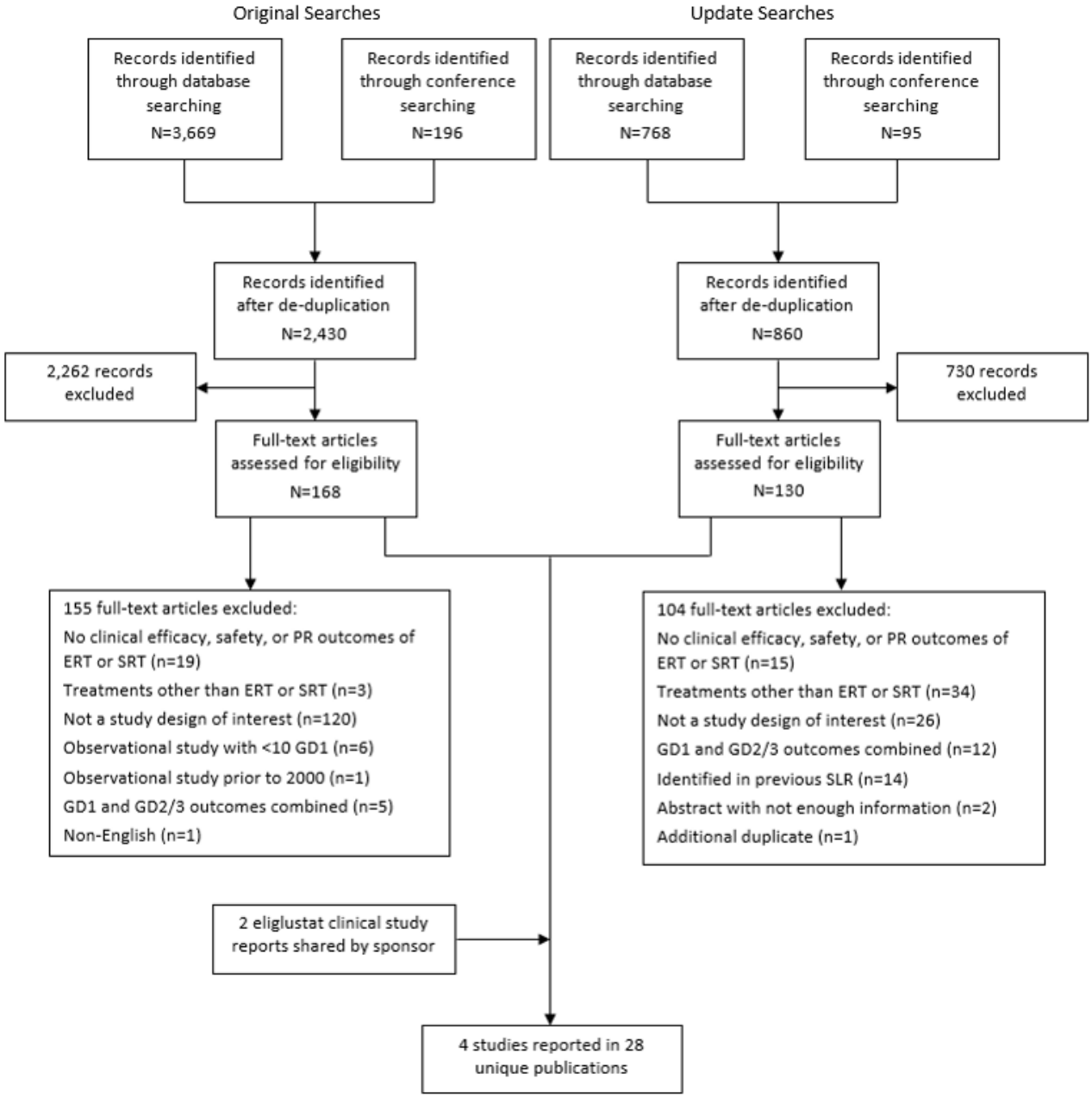
The search updates carried out in 2015 identified a total of 768 publications through database searches and a further 95 abstracts through conference searches. After removing duplicates, there were 860 unique publications. During primary screening of titles and abstracts, 730 citations were rejected. The most common reasons for rejection at primary screening were study design not of interest (339) and population not of interest (237). Full articles for the remaining 130 records were retrieved and screened against the pre-defined inclusion/exclusion criteria, as outlined in Table 6. A manual review of reference lists of systematic reviews did not identify any additional publications.

After cross-referencing between the three different searches to ensure no records were included twice, a total of 29 unique publications were identified reporting relevant RCTs of eliglustat or comparators in addition to two clinical study reports provided by Genzyme. Of these, two publications reported on taliglucerase alfa. Although this was included as a

comparator of interest in the systematic review, taliglucerase alfa was not listed in the scope for this submission as a relevant comparator, and as such, these two publications have been excluded from further discussion.

In total, 4 studies were reported in 28 unique publications. Of these, 21 sources reported trials of eliglustat including the ENCORE and ENGAGE RCTs, one source reported the EDGE trial, and the remaining 6 sources accounted for a comparator RCT[63, 76], as reported in Table 7.

Figure 6: PRISMA diagram for systematic literature review



Key: ERT, enzyme replacement therapy; GD, Gaucher disease; PR, patient-reported; SRT, substrate reduction therapy.

Table 7: Sources of published data

Study ID	Primary Reference	Additional References
ENCORE	Cox et al., 2015[10]	Balwani et al., 2013[49]; Burow et al., 2013[77]; Cox et al., 2013[78]; Cox et al., 2014[79]; Genzyme et al., 2014[72]; Peterschmitt et al., 2014[80]; Rosembloom et al., 2014[81]; Cox et al., 2015[82]
ENGAGE	Mistry et al., 2015[9]	Ben Turkia et al., 2013[83]; Dasouka et al., 2013[84]; Genzyme et al., 2013[52]; Lukina et al., 2013[85]; Mistry et al., 2013[86]; Packman et al., 2013[48]; Shankar et al., 2013[87]; Amato et al., 2014[88]; Barris et al., 2014[89]; Mistry et al., 2014[90]; Mistry et al., 2015[91]
EDGE	Charrow et al., 2014[13]	N/A
Ben Turkia	Ben Turkia et al., 2013[63]	Elstein et al., 2012[92]; Mehta et al., 2011[93]; Zimran et al., 2012[94]; Zimran et al., 2013[95]; Zimran et al., 2012[96]
Key: N/A, not applicable.		

Unpublished studies

9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Please see Section 9.2.1 which describes the inclusion/exclusion criteria for both published and unpublished evidence.

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

Please see Section 9.2.2 which describes the flow of studies included and excluded at each stage for both published and unpublished evidence.

9.3 Complete list of relevant studies

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

Three eliglustat RCTs were identified from the systematic review:

- ENCORE, which compares eliglustat to imiglucerase in 160 patients who are stable on ERT.

- ENGAGE, which compares eliglustat to placebo in 40 treatment-naïve patients.
- EDGE, which compares once daily to twice daily eliglustat dosing in 170 patients stable on eliglustat twice daily dosing

In addition, one published comparator study was identified from the systematic review, which has been included to inform the indirect comparison:

- Ben Turkia et al. (2013) compared imiglucerase with velaglucerase in 35 ERT-naïve patients.

This is described in further detail in Section 9.8.1 where the indirect comparison is discussed.

A Phase II, open-label, single-arm trial of eliglustat has also been conducted. While this was initially identified in the systematic review it was excluded at level 2 screening because the focus of the review was RCTs and this is a single-arm trial. However, this studies eliglustat in the relevant population and provides long-term safety and efficacy data. In addition the study has a large population and is meaningful in the context of the half-life of treatment responses. Therefore, the trial is directly relevant to the decision problem.

Table 8 provides an overview of the relevant eliglustat studies identified.

Table 8: List of relevant studies (combination of table C3 and C4 in NICE HST template)

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Cox et al., 2015[10]	NCT00943111 (ENCORE)	N: 160 100% adults, 25% splenectomised Previously treated and stabilised on ERT	Eliglustat [50mg, 100mg or 150mg BID]	Imiglucerase [30-130 U/kg/month]
Mistry et al., 2015[9]	NCT00891202 (ENGAGE)	N: 40 100% adults, 0% splenectomised Treatment-naïve	Eliglustat [Day 1, 50mg; Day 2 to Week 4, 50mg BID; Week 4 to 39, 50mg or 100mg BID]	Placebo
Charrow et al., 2014[13, 97]	NCT01074944 (EDGE)	N: 170 100% adults, 27% splenectomised 87% previous ERT	Eliglustat 50mg or 100mg BID vs eliglustat 100mg or 200mg QD. Lead in period: eliglustat 50mg or 100mg BID for at least 4 months until therapeutic goals achieved	N/A
Lukina et al., 2010a (1 year data)[11]; Lukina et al., 2010b (2-year data)[98]; Lukina et al., 2014 (4-year data)[12]	NCT00358150; Genzyme Phase II, 2013	N: 26 100% adults, None were splenectomised	Eliglustat [50mg or 100mg BID]	N/A
Key: BID, twice daily; ERT, enzyme replacement therapy; QD, once daily; RCT, randomised controlled trial.				

9.3.2 State the rationale behind excluding any of the published studies listed in tables C3 and C4.

No studies have been excluded from further discussion.

9.4 Summary of methodology of relevant studies

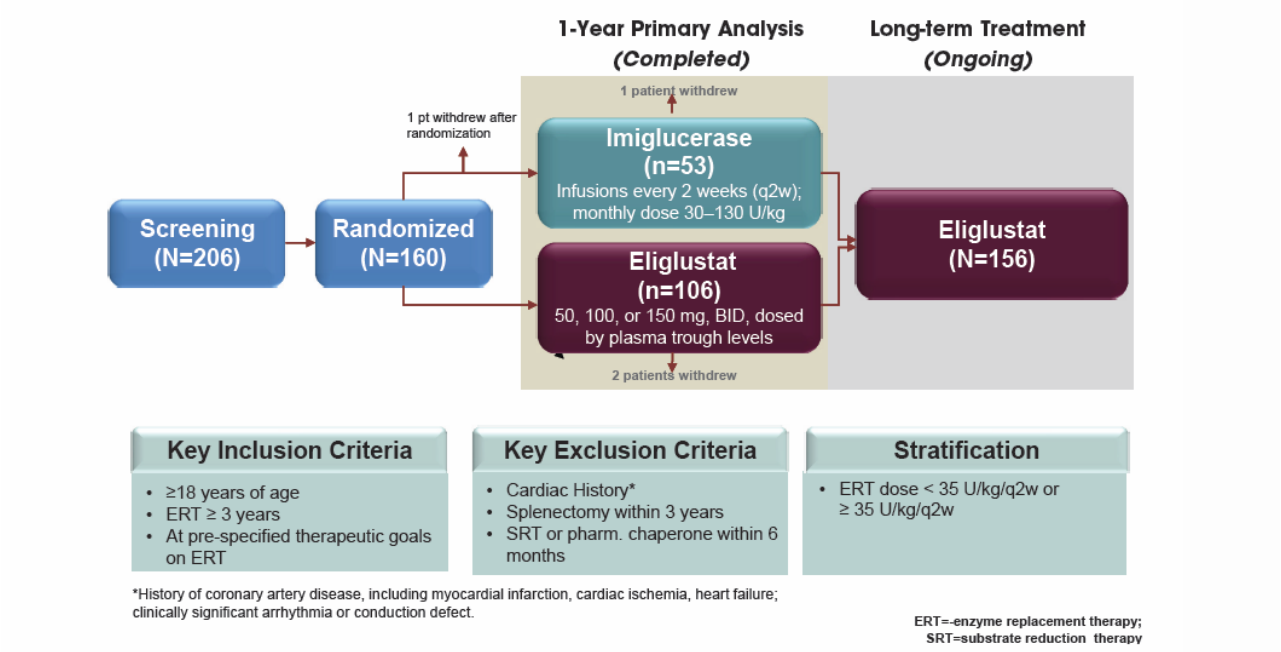
9.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables C5 and C6 as appropriate. A separate table should be completed for each study.

All of the RCTs identified to be of relevance to the decision problem were Phase III trials. These trials are described separately. Additional data on the statistical analysis and endpoints in each trial will be presented in Section 19.1 and **Error! Reference source not found.**.

ENCORE study

The design of the ENCORE study is presented in Figure 7.

Figure 7: Trial design diagram for the ENCORE study



Key: BID, twice daily; ERT, enzyme replacement therapy; SRT, substrate reduction therapy.
Source: Cox et al., 2013[78]

ENCORE was an open-label study for the following reasons:

- Because imiglucerase and eliglustat have different routes of administration, a double-blind design would have required patients to take two treatments for 52 weeks, thus placing an undue burden on study patients.
- All four components of the composite endpoint – spleen and liver volumes and haemoglobin and platelet levels – are objective measures.

- A double-blind design would not have permitted an important patient-reported assessment of treatment preference i.e. oral versus IV treatment.

The EMA concluded in the EPAR that "While an open-label design is considered to be less rigorous than a blinded design, the potential for patient and/or physician bias with respect to efficacy was considered to be low because all four components of the primary composite endpoint (spleen and liver volumes and haemoglobin level and platelet count), are objective measurements, and the organ volume assessments were centrally read by an independent organisation, blinded to treatment. Therefore the open label design is acceptable."[71]

In the ENCORE study, ERT-stable patients randomised to oral eliglustat received 50mg oral eliglustat capsules BID from Day 1 to Week 4. If patients had a plasma trough concentration of <5ng/mL at Week 2, dosage was increased to 100mg BID at Week 4. Patients with a trough concentration of ≥5ng/mL continued to receive 50mg BID. At Week 8, dosage was increased again if patients had trough concentration of <5ng/mL. For patients on 50mg, dosage was increased to 100mg, and for patients on 100mg dosage was increased to 150mg. Patients randomised to the control arm received imiglucerase until Week 52, at their usual doses (i.e., the doses received and stabilised upon before enrolment in the trial). During randomisation, patients were stratified by ERT dose level (<35U/kg/Q2W or ≥35U/kg/Q2W).

At the end of the protocol-defined titration period, the percentage of patients receiving the three possible eliglustat doses was: 20% (21/106) receiving 50mg BID, 32% (34/106) receiving 100mg BID and 48% (51/106) receiving 150mg BID.[6] The EPAR states that "Based on an analysis [using a population pharmacokinetic/pharmacodynamics model], the loss of efficacy is clinically negligible in most patients switching from 150mg BID to 100mg BID. This conclusion is justified by the actual data that do not show a difference in response between EM patients treated with 100 or 150 mg/ BID."[71, 99]

After Week 52 (the end of the randomised study period) assessments were completed, patients receiving imiglucerase switched to a 50mg BID dose of eliglustat, while those on eliglustat remained on the same dosage as they had been receiving at Week 52. Dose-adjustments took place on Weeks 54 and 56 for the newly switched patients dependent on the patient's plasma levels and patients remained in the study for a minimum of 104 weeks.

The primary endpoint in the ENCORE study was the percentage of patients who were deemed to be stable at Week 52, measured as a composite endpoint including liver and spleen volume, haemoglobin levels and platelet count. In order to be classed as stable and meet the primary composite endpoint, patients needed to meet goals on all four parameters of the endpoint at 52 weeks.

These outcomes represent the common clinical manifestations of Gaucher disease and have been investigated in previous trials of GD1. In addition, these endpoints are representative of GD1 therapeutic goals, which include increasing haemoglobin levels, increasing platelet counts and reducing and maintaining the liver and spleen volumes to 1.0-1.5 and ≤2-8 times normal volume, respectively.[54] Therapeutic goals for Gaucher disease also look at skeletal pathology and pulmonary involvement along with functional health and wellbeing and biomarkers.[54] These are represented in the secondary and tertiary outcomes of this study. A summary of the methodology of the ENCORE study is presented in Table 9.

Table 9: Summary of methodology for randomised controlled trials: ENCORE (in line with table C5 in NICE HST template)

Study name	**ENCORE**
Objectives	To assess the efficacy and safety of eliglustat compared with imiglucerase after 52 weeks of treatment in patients with GD1 who have reached therapeutic goals with ERT
Location	39 centres in Latin America, US, Canada, Australia, Middle East and Europe participated in the study.
Design	A Phase III, randomised, multi-centre, open-label, active comparator study to evaluate the efficacy and safety of eliglustat in patients with GD1 who have reached therapeutic goals with ERT. A long-term extension study was carried out from Week 52 to a minimum of 104 weeks with patients being able to receive treatment for up to 5.5 years
Duration of study	52 weeks then entered a long-term extension period up to a minimum of Week 104.
Sample size	One hundred sixty (160) patients were randomised in a 2:1 ratio to treatment with eliglustat (n=106) or imiglucerase (n=54).
Inclusion criteria	• Willing and able to provide signed informed consent • ≥18 years • Tanner stage ≥4 prior to randomisation • Diagnosis of GD1 confirmed by a documented deficiency of acid β-glucosidase activity • Consent to provide a blood sample for genotyping • Received treatment with ERT (including velaglucerase or imiglucerase) for at least 3 years. For at least 6 of the 9 months before randomisation, the patient has received a total monthly dose of 30 U/kg to 130 U/kg of ERT • Reached Gaucher disease therapeutic goals prior to randomisation

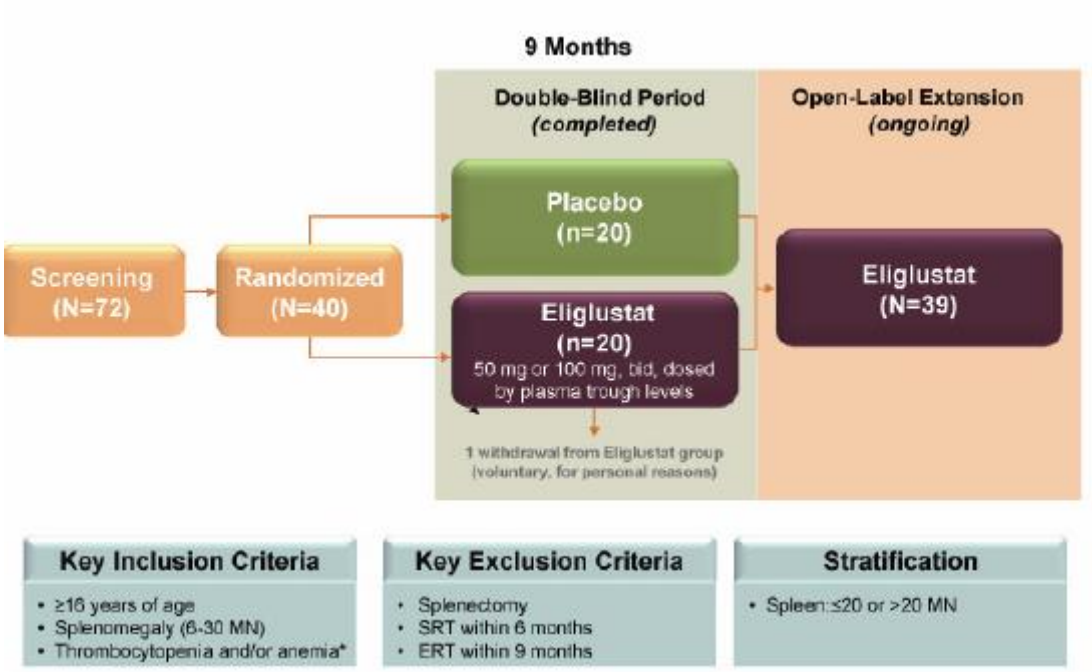
Study name	ENCORE
	– Spleen volume <10 times normal or total splenectomy (if occurred >3 years prior to randomisation) – Liver volume <1.5 times normal • Negative pregnancy test • Medically accepted form of contraception • Willing to abstain from grapefruit, grapefruit juice or grapefruit products for 72 hours prior to the first dose of study medication
Exclusion criteria	• Received substrate reduction therapies for Gaucher disease within 6 months prior to randomisation • Partial or total splenectomy within 3 years prior to randomisation • Any evidence of neurological or pulmonary involvement as related to Gaucher disease • Transfusion-dependent • Prior oesophageal varices or liver infarction or current liver enzymes or total bilirubin >2 times upper limit of normal (unless patient has Gilbert Syndrome) • Any clinically significant disease other than Gaucher disease • Clinically significant coronary artery disease, arrhythmias or conduction defect, complete bundle block, prolonged QTc interval or sustained ventricular tachycardia • Tested positive for HIV antibody, hepatitis C antibody or hepatitis B surface antigen • Received investigational product within 30 days prior to randomisation • Scheduled for in-patient hospitalisation • History of cancer within 5 years of randomisation • Pregnant or lactating • Received medication that may prolong QTc interval or induce CYP3A4 • Not a CYP2D6 poor metaboliser or an intermediate metaboliser with one allele identified as active or neither allele known to be active • Use of strong inhibitors of CYP3A4, if the patient was a CYP2D6 poor or indeterminate metaboliser • Use of strong inhibitors of CYP3A4 or CYP2D6, if the patient was not a CYP2D6 poor/indeterminate metaboliser, except where a patient had chronically received either medication (but not both) for at least 30 days prior to randomisation and was continuing the same dosing regimen during the primary analysis period of this study. • Unable to receive imiglucerase due to known hypersensitivity
Method of randomisation	Randomisation was stratified based on Q2W equivalent of the patients ERT dose prior to any unanticipated treatment interruption, dose reduction, or regimen change. Patients were then randomised in a 2:1 ratio to receive eliglustat or imiglucerase.
Method of blinding	Open-label study. Efficacy and safety evaluations performed by external central readers blinded to treatment assignment.
Intervention(s) and comparator(s)	Eliglustat (n=106): 50mg, 100mg, or 150mg, orally, twice daily (depending on plasma levels) Imiglucerase (n=54): infusions every 2 weeks (Q2W); monthly dose 30–130 U/kg

Study name	ENCORE
Baseline differences	See full details of baseline data in Section 9.4.3
Duration of follow-up, lost to follow-up information	The extension study is completed and key results are already available. Full study results will be available in Q2 2016. No patients were lost to follow-up by Week 104.
Statistical tests	All statistical analyses were conducted using SAS version 9 or higher. The percentage of patients remaining stable, as well as exact 95% confidence interval (CI) for that percentage, was computed at 52 weeks for both the eliglustat and imiglucerase treatment groups. A difference in the percentage of patients remaining stable in the two treatment groups along with a 95% CI for the difference between the eliglustat and imiglucerase treatment groups was calculated. If the lower-bound of the 95% CI for the difference was within the pre-specified non-inferiority margin of 25%, then eliglustat treatment was declared non-inferior to imiglucerase treatment. The non-inferiority margin was on a 95% imiglucerase response rate and an 85% eliglustat response rate (as established by results from the Phase II study[11]). This margin is less than half the expected difference of 51% between imiglucerase treatment and discontinued treatment after 1 year with data from a matched population from the International Collaborative Gaucher Group Gaucher Registry.[10] The secondary efficacy endpoints were analysed using ANCOVA, natural logarithm differences were used for the parameters that were analysed using percentage changes. Statistical tests were conducted at the 5% level of significance. Additional information on statistical analyses is presented in Section 19.1.
Primary outcomes (including scoring methods and timings of assessments)	Percentage of patients who remained stable for 52 weeks on the composite endpoint defined as: • Haemoglobin level does not decrease >1.5g/dl from baseline; • platelet count does not decrease >25% from baseline; • spleen volume does not increase >25% from baseline; • liver volume does not increase >20% from baseline Additional information is presented in Section 19.1.
Secondary outcomes (including scoring methods and timings of assessments)	• Total T- and Z-scores for BMD (DXA) of femur and lumbar spine, • haemoglobin level • platelet count • spleen volume • liver volume Additional information is presented in Section 19.1.
Key: ANCOVA, analysis of covariance; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; ERT, enzyme replacement therapy; GD, Gaucher disease. **Source:** Cox et al., 2015[10]	

ENGAGE study

The design of the ENGAGE study is presented in Figure 8.

Figure 8: Trial design diagram for the ENGAGE study



Source: Packman et al., 2013[48]

In the double-blind ENGAGE study, treatment-naïve patients in the eliglustat arm received a single 50mg dose of eliglustat on Day 1 and repeat doses of 50mg twice daily from the morning of Day 2 through the evening prior to the Week 4 visit. From Week 4 to Week 39 patients could receive an increased dose of 100mg twice daily dependent on plasma levels (patients with a trough concentration of <5ng/mL received the increased dose). Patients randomised to placebo received capsules on the morning of Day 1 and then twice daily to Week 39.

After Week 39 (the end of the randomised study period) all patients received open label dosing in an extension period up to Week 78. This was preplanned in the protocol. From Week 39 through to Week 43 all patients received 50mg eliglustat twice daily. Dose adjustments were made at Week 43 and Week 47 and patients with a trough concentration of <5ng/mL received 100mg (for patients who had been receiving 50mg) or 150mg (for patients who had been receiving 100mg) doses twice a day.

The primary outcome in the ENGAGE study was percentage change in spleen volume from baseline to Week 39. In both trials the endpoints were chosen because they are the clinically important measures representing the 'goals of treatment' in Gaucher disease and have been investigated in previous studies of ERT in patients with GD1. A summary of the methodology of the ENGAGE study is presented in Table 10.

Table 10: Summary of methodology for randomised controlled trials: ENGAGE (in line with table C5 in NICE HST template)

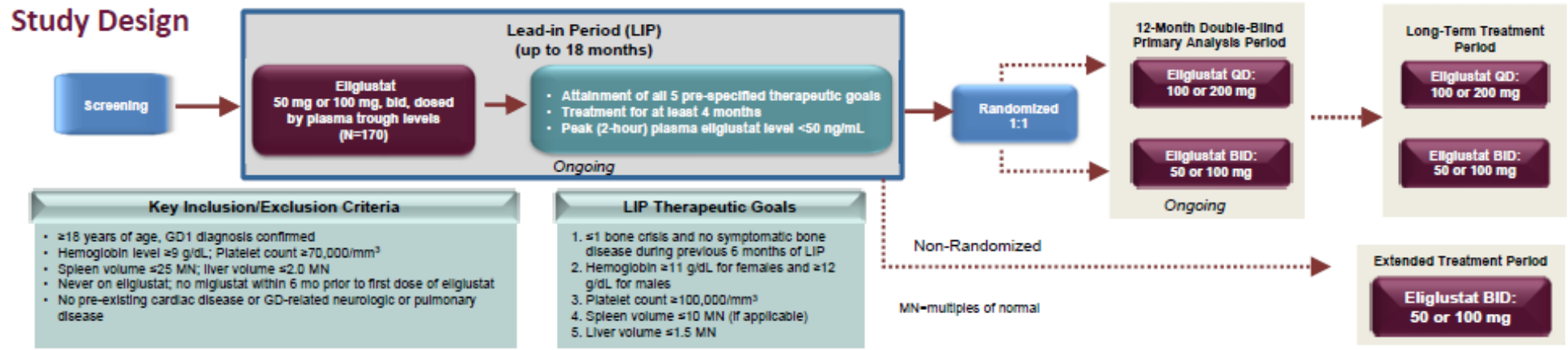
Study name	**ENGAGE**
Objectives	To confirm the efficacy and safety of eliglustat after 39 weeks of treatment in patients with type 1 Gaucher disease (GD1).
Location	26 centres in Latin America, the United States, Canada, Middle East and Northern Africa, India and Europe participated in the study.
Design	A Phase III, randomised, double-blind, placebo-controlled, multi-centre study confirming the efficacy and safety of eliglustat in patients with GD1. A long-term extension study was carried out from Week 39 to a minimum of 78 weeks, with patients being able to receive treatment for a total duration of up to 6 years.
Duration of study	39 weeks then entered a long-term extension period for a minimum of 78 weeks.
Sample size	A total of 40 patients were randomised and treated with eliglustat (n=20) or placebo (n=20).
Inclusion criteria	• ≥16 years • Tanner stage ≥4 prior to randomisation • Diagnosis of GD1 confirmed by documented deficiency of acid β-glucosidase activity • Haemoglobin level 8.0 to 11.0g/dL (females) or 8.0 to 12.0g/dL (males) and/or platelet count 50,000 to 130,000/mm^3 • Spleen volume 6-30MN • Liver volume <2.5MN • Consent to provide blood sample for genotyping
Exclusion criteria	• Treatment with substrate reduction therapy within 6 months prior to randomisation • Enzyme replacement therapy within 9 months prior to randomisation • Transfusion-dependent • Anaemic • History of splenectomy • Evidence of neurological or pulmonary involvement due to Gaucher disease • Bone crisis within 12 months • Prior oesophageal varices or liver infarction, ALT, AST and total bilirubin >2 times the upper limit or normal (unless patient had Gilbert syndrome) within 30 days prior to randomisation treatment with investigational products, medication that cause QTc interval prolongation, inducers of CYP3A4, strong inhibitors of CYP3A4 if patient was CYP2D6 poor metaboliser or indeterminate metaboliser with neither allele known to be active
Method of randomisation	Randomisation was stratified based on the patient's baseline spleen volume (≤20 MN or >20 MN) and within each stratum patients were randomised in a 1:1 ratio to each treatment group. Randomisation was via an IVRS/IWRS. Patient identification numbers were assigned through this system with each ID number corresponding to an allocated randomisation number.

Study name	ENGAGE
Method of blinding	Patients, investigators, and sponsors investigational team were blinded to study treatment until all patients completed the double-blind primary analysis period. Blinding was maintained due to both intervention and placebo capsules being identical in appearance.
Intervention(s) and comparator(s)	Eliglustat (n=20): 50mg or 100mg capsule twice daily Placebo (n=20): 50mg or 100mg capsule containing 50% Avicel PH101 and 50% lactose monohydrate USP/Ph-Eur twice daily
Baseline differences	See full details of baseline data in Section 9.4.3
Duration of follow-up, lost to follow-up information	The extension study is currently ongoing and is expected to report in mid-2016. 78-week results are already available. No patients were lost to follow-up by Week 78.
Statistical tests	The primary efficacy endpoint was analysed using an ANCOVA model, normal distribution was confirmed using the Shapiro-Wilk test at a 5% level of significance. Secondary endpoints were analysed using a closed-testing procedure. For within-patient analyses, a paired t-test was used for analysis of endpoints with normally distributed data, and a Wilcoxon signed-ranks test was used for analysis of endpoints with normally distributed data. Additional information on statistical analyses is presented in Section 19.1.
Primary outcomes (including scoring methods and timings of assessments)	Percentage change in spleen volume from baseline to 39 weeks in MN with eliglustat as compared with placebo. Additional information is presented in Section 19.1.
Secondary outcomes (including scoring methods and timings of assessments)	• Absolute change from baseline in haemoglobin level (in g/dL), • percentage change from baseline in liver volume (in MN) • percentage change from baseline in platelet count (in/mm^3) within patient changes from baseline to 39 weeks of eliglustat treatment for percentage changes in spleen volume, liver volume, and platelet count Additional information is presented in Section 19.1.
Key: ALT, alanine transferase; ANCOVA, analysis of covariance; AST, aspartate aminotransferase; IVRS, interactive voice response system; IWRS, interactive web response system; MN, multiples of normal. **Source:** Mistry et al., 2015[9]	

EDGE study

The EDGE study is a multicentre, randomised, double-blind study to evaluate maintenance of therapeutic goals with once-daily versus twice-daily dosing of eliglustat in stabilised adults with GD1. A summary of the EDGE study design is presented in Figure 9.

Figure 9: Trial design for the EDGE study



Key: BID, twice daily; GD, Gaucher Disease; MN, multiples of normal; QD, once daily.
Source: Charrow et al., 2014[13].

The EDGE study consists of a lead-in period of up to 18 months where patients receive eliglustat 50mg or 100mg BID, dosed by plasma trough levels. Patients who demonstrate clinical stability through attainment of all 5 pre-specified therapeutic goals and a peak (2-hour) plasma eliglustat level of <50 ng/ml will then be randomised 1:1 to eliglustat 100 or 200mg QD versus eliglustat 50 or 100mg BID. This randomised, 12-month primary analysis period has recently been completed with the clinical study report (CSR), expected in Q2 2016, as such, these data can be available to NICE shortly after dossier submission, if requested. As such, the publication identified through the systematic review reports only interim results from the lead-in period, and encompasses all available data as of 31 January 2013.

A total of 219 patients were screened, of which 170 were treated in the lead-in period. As of January 2013, 131 patients had completed the lead-in period while 27 patients were still in the lead-in period. A total of 12 patients withdrew during the lead-in period due to AEs (n=2), pregnancy (n=4) and non complaint (n=1) while 5 patients withdrew due to their own wishes.

Efficacy was assessed by number of patients who sustained or achieved individual therapeutic goals while safety was assessed by AEs and changes from baseline in vital signs, physical exams, bone disease assessments, electrocardiography and routine laboratory tests. A summary of the methodology of the ENGAGE study is presented in Table 11.

Table 11: Summary of methodology for randomised controlled trials: EDGE (in line with table C5 in NICE HST template)

Study name	**EDGE**
Objectives	To evaluate maintenance of therapeutic goals with twice-daily versus once-daily dosing of eliglustat
Location	46 study sites in 17 countries the US, Australia, Austria. Brazil, Canada, China, Croatia, France, Greece, India, Japan, Netherlands, Portugal, Romania, Russian Federation, Serbia and Sweden
Design	A Phase III, multicentre, randomised, double-blind study to evaluate different doses of eliglustat in stabilised adults with GD1. The study consisted of a lead-in period of up to 18 months during which time patients were treated with eliglustat 50 or 100mg BID. The patients entering the lead in period were both treatment naïve and treatment experienced. As soon as patients achieved all randomisation criteria they were randomised to the primary analysis period for 12 months of treatment. Following this, patients can enter a long-term treatment period
Duration of study	12 month primary analysis period

Study name	EDGE
Sample size	170 patients were treated in the lead-in period of which 131 have completed the lead-in period and 27 are still in the lead-in period. A total of 12 patients withdrew The randomised, 12-month primary analysis period has recently been completed with the CSR expected to be available Q2 2016.
Inclusion criteria	• Willing and able to provide signed informed consent prior to any study-related procedures • Diagnosis of GD1 confirmed by a documented deficiency of acid β-glucosidase activity by enzyme assay • ≥18 years of age • Haemoglobin level ≥9 g/dL • Platelet count ≥70,000/mm^3 • Spleen volume ≤25 MN • Liver volume ≤2.0 MN • Females of childbearing potential must have a documented negative pregnancy test prior to administration of the first dose of eliglustat, and use a medically accepted form of contraception throughout the study (i.e., a barrier method or hormonal contraceptive with norethindrone and ethinyl estradiol or similar active components).
Exclusion criteria	• Partial or total splenectomy within 3 years prior to randomisation • Received pharmacological chaperones or miglustat within 6 months prior to administration of the first dose of eliglustat tartrate • Any clinically significant disease, other than Gaucher disease, including cardiovascular, renal, hepatic, gastrointestinal, pulmonary, neurologic, endocrine, metabolic (including hypokalaemia or hypomagnesemia), or psychiatric disease, other medical conditions, or serious intercurrent illnesses that, in the opinion of the Investigator, may preclude participation in the study. • Tested positive for human immunodeficiency virus antibody, hepatitis C antibody or hepatitis B surface antigen • Received an investigational product (other than eliglustat) within 30 days prior to administration of first dose of eliglustat • Pregnant or lactating
Method of randomisation	Patients were randomised in a 1:1 ratio
Method of blinding	The primary analysis period was double-blind
Intervention(s) and comparator(s)	Eliglustat: 50mg or 100mg BID Eliglustat: 100mg or 200mg QD
Baseline differences	See full details of baseline data in Section 9.4.3
Duration of follow-up, lost to follow-up information	The study is now completed with data analysis ongoing. The CSR is expected in Q2 2016. Only interim results from the lead in period are available at this time.
Statistical tests	Not reported

Study name	EDGE
Primary outcomes (including scoring methods and timings of assessments)	Primary efficacy endpoint is the number of patients who remain stable over 52 weeks of the blinded regimen of eliglustat treatment for both dosing regimens separately, and a difference between the two dosing regimens.
Secondary outcomes (including scoring methods and timings of assessments)	• Haemoglobin levels • Platelet counts • Spleen volume • Liver volume • Biomarkers • Bone disease assessments • Gaucher assessments: mobility, bone crises and bone pain
Key: BID, twice daily; CSR, clinical study report; GD1, type 1 Gaucher disease; MN, multiples of normal; QD, once daily. **Source:** Charrow et al., 2014[13]; www.clinicaltrials.gov.[100]	

Phase II study (NCT 00358150)

A summary of the Phase II, single-arm, eliglustat trial is provided in Table 12. The inclusion and exclusion criteria along with the outcomes for this trial are similar to those in the eliglustat RCTs.

A total of 50 patients underwent screening and 26 were enrolled and received at least one dose of eliglustat. The other 24 patients failed screening as a result of at least one of the following: small spleen size (n=10), cardiac findings (n=5), recent miglustat, bisphosphonate, or vitamin B12 treatment (n=5), high or low platelet counts (n=3), nonmedical withdrawals (n=3), and neurologic involvement (n =2).[11] Of the 26 enrolled patients, 22 (85%) patients completed the Week 52 assessment.[101] Two patients were withdrawn after the discovery of asymptomatic non-sustained ventricular tachycardia, and a further two patients ended the study due to pregnancy.[11]

Table 12: Summary of methodology for phase II single-arm trial (in line with table C5 in NICE HST template)

Study name	**NCT 00358150**[11, 12, 98, 102]
Objective	The primary objective of this study is to evaluate the efficacy, safety, and pharmacokinetics (PK) of eliglustat administered as an oral dose of either 50 mg twice daily (BID) or 100 mg BID, to patients with GD1 for 52 weeks. The secondary objective of the study is to determine the long-term efficacy, safety, and PK effects of eliglustat, at doses of 50, 100, or 150 mg BID, administered to the same patients from approximately Week 54 through study completion.
Location	7 sites in 5 countries (Russia, Argentina, the United States, Israel and Mexico)
Design	A Phase II, open-label, single-arm trial to evaluate the efficacy, safety and pharmacokinetics of eliglustat in GD1 patients.
Duration of study	52-week primary analysis period, and additional 3-year extension period
Sample size	50 patients were screened to enter the study, resulting in 26 patients being treated with at least 1 dose of eliglustat in this open-label study
Inclusion criteria	• Willingness and ability to provide written informed consent • Diagnosis of GD1 and documented deficiency of acid β-glucosidase activity • Consent to provide a blood sample for genotyping for Gaucher disease, chitotriosidase and for genetic assessment of cytochrome P450
Exclusion criteria	• Patients with partial or total splenectomy; those with evidence of any neurologic or pulmonary involvement; those with new pathological bone involvement or bone crisis in 12 months prior to enrolment • Haemoglobin level <8.0g/dL or platelet level <45,000/mm^3 • Patients who received miglustat, ERT or corticosteroids within 12 months prior to enrolment, or received bisphosphates within 3 months prior to enrolment • Patients with other serious co-morbidities • Patients with cardiac functional and/or anatomical abnormalities or clinically significant ECG or ECHO findings at time of screening • Those who received any medication within 30 days prior to enrolment that may induce or inhibit CTP2D6, or cause QT interval prolongation
Intervention(s) and comparator(s)	Eliglustat supplied as 50mg and 100mg hard capsules. Eliglustat was administered at 50mg twice daily from Day 1 to Day 20. Dose could be adjusted to 100mg at Day 20 if plasma levels were <5ng/mL
Baseline differences	Not applicable
Statistical tests	Based on an assumed efficacy response rate of 75% with a 90% CI of 55% to 95%, a sample size of 25 was proposed to achieve at least 12 evaluable patients at 52 weeks. Efficacy analyses are reported for all patients who received at least one dose of eliglustat tartrate (ITT) and for patients who completed 52 weeks of treatment (completer population). Changes from baseline to Week 52 were compared with a change of 0 using a 2-tailed t test (for normally distributed data) or Wilcoxon signed-rank test (for non-normally distributed data) at $p<0.05$

Study name	NCT 00358150[11, 12, 98, 102]
Primary outcomes (including scoring methods and timings of assessments)	• A composite endpoint requiring improvement from baseline to Week 52 in at least 2 of the 3 main efficacy parameters: – Spleen volume – Haemoglobin level – Platelet count
Secondary outcomes (including scoring methods and timings of assessments)	• Changes over time in the main efficacy parameters (Hb, platelets, spleen) • Liver volume in MN • Disease-related plasma biomarkers – Chitotriosidase – CCL18 – Angiotensin-converting enzyme – Tartrate-resistant acid phosphatase • Exploratory biomarkers – Plasma glucosylceramide – Ganglioside GM3 • Bone-related outcomes – Bone pain – Bone crises – Mobility – Skeletal changes – Bone mineral density • HRQL – SF-36 – Fatigue Severity Scale • Safety outcomes • Pharmacokinetic outcomes
Key: CI, confidence interval; ECG, electrocardiogram; ECHO, echocardiogram; ERT, enzyme replacement therapy; GD, Gaucher disease; Hb, haemoglobin; HRQL, health-related quality of life; ITT, intention-to-treat; MN, multiples of normal; SF-36, Short-Form 36. **Source:** Lukina et al., 2010.[11]	

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Table 7, in Section 9.2.2, presents all studies and sources identified in the systematic literature review.

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

A key difference in the methodology between the trials is that both ENCORE and ENGAGE are Phase III RCTs while the third study is a Phase II, single-arm trial. Additionally differences can be seen when comparing ENCORE and ENGAGE. While ENCORE is an open-label study, ENGAGE is a double-blind trial. Also, ENCORE has an active comparator and compares eliglustat with imiglucerase, a key comparator, while ENGAGE compares eliglustat to placebo.

ENGAGE evaluated treatment-naïve patients (patients could not have received ERT within 9 months of randomisation or SRT within 6 months). In contrast, ENCORE enrolled patients previously treated (for at least 3 years) and stabilised on ERT; for at least 6 of the 9 months prior to randomisation, the patient had to have received a total monthly dose of 30-130U/kg of ERT. Additionally patients had to have reached Gaucher therapeutic goals prior to randomisation.

Another key difference was that ENGAGE excluded patients who had undergone splenectomy (partial or total), whereas splenectomised patients were allowed to participate in ENCORE, provided splenectomy had been carried out more than 3 years before randomisation.

ENCORE has a much larger patient population of 160 patients randomised in a 2:1 ratio while ENGAGE randomised 40 patients in a 1:1 ratio with 20 patients in each arm. Furthermore, ENGAGE is a 9-month study and ENCORE is a 12-month study. The full population eligibility criteria for the RCTs are presented in Table 9 and Table 10.

In contrast to the ENCORE and ENGAGE studies, the EDGE study was designed to evaluate efficacy and safety of once-daily compared to twice-daily dosing of eliglustat. Furthermore, the EDGE study enrolled more patients than the ENCORE and ENGAGE studies; 170 patients were randomised in a 1:1 ratio to each treatment arm.

The ENCORE study

Demographic and other baseline characteristics of participants, including ERT dose at study entry, were well balanced within treatment groups for ENCORE (Table 13).

Table 13: Characteristics of participants (randomised population) in ENCORE across randomised groups

	Eliglustat (n=106)	Imiglucerase (n=53)
Age, mean (SD), years	37.6 (14.2)	37.5 (14.9)
Male, n (%)	47 (44)	25 (47)
White, n (%)	98 (92)	48 (91)
Jewish descent, yes, n (%)	29 (27)	14 (26)
Spleen volume, MN, mean (SD) (normal size: ≤5MN)	3.17 (1.35)	2.74 (1.15)
Liver volume, MN, mean (SD) (normal size: ≤2.5MN)	0.94 (0.19)	0.92 (0.16)
Haemoglobin levels, g/L, mean (SD) (normal values: >120g/L for males, >110g/L for females)	136 (13)	139 (13)
Platelet count, 10^9/L, mean (SD) (normal: >120 x 10^9/L)	203 (79)	188 (57)
ERT <35U/kg/Q2W, n (%)	43 (41)	22 (42)
ERT ≥35U/kg/Q2W, n (%)	63 (59)	31 (58)
Splenectomised, n (%)	No: 76 (72) Partial: 1 (1) Total: 29 (27)	No: 44 (83) Partial: 1 (2) Total: 8 (15)
Acid β-glucosidase, nmol/hr/mg, mean (SD)	1.15 (1.31)	1.12 (0.95)
Total BMB score, mean (SD)	8.22 (2.66)	8.12 (2.63)
Lumbar spine BMD T score, mean (SD) (normal T-score: ≥-1; osteopenia defined by T-scores <-1 to >-2.5; osteoporosis defined by T-scores ≤-2.5)	-0.54 (1.38)	-0.34 (1.15)
Femur BMD T score, mean (SD) (normal T-score: ≥-1; osteopenia defined by T-scores <-1 to >-2.5; osteoporosis defined by T-scores ≤-2.5)	-0.15 (1.09)	-0.41 (1.28)
Chitotriosidase activity (nmol/h per mL), mean (SD) (normal: <15 to 181 nmol/h per mL)	1159 (1465)	1105 (1059)
CYP2D6 metaboliser status, n (%)	Poor: 4 (4) Intermediate: 12 (11) Extensive: 84 (79) Ultra-rapid: 4 (4) Indeterminate: 2 (2)	Poor: 2 (4) Intermediate: 9 (17) Extensive: 39 (74) Ultra-rapid: 1 (2) Indeterminate: 2 (4)
Age at Gaucher disease diagnosis, years, mean (SD)	17.8 (13.6)	20.3 (14.3)
Age at first Gaucher symptom onset, year, mean (SD):	12.7 (12.0)	15.9 (14.2)

	Eliglustat (n=106)	Imiglucerase (n=53)
Gaucher disease genotype, n (%)	N370S/Other: 34 (32) N370S/N370S: 23 (22) N370S/L444P: 38 (36) L444P/Other: 2 (2) Other/Other: 9 (8)	N370S/Other: 14 (26) N370S/N370S: 12 (23) N370S/L444P: 18 (34) L444P/Other: 0 (0) Other/Other: 9 (17)
Years on imiglucerase, mean (SD)	9.8 (4.0)	10.0 (3.6)
Current ERT, n (%)	Imiglucerase: 84 (79) Velaglucerase: 22 (21)	Imiglucerase: 45 (85) Velaglucerase: 8 (15)
Key: BMB, bone marrow burden; BMD, bone mineral density; ERT, enzyme replacement therapy; GD, Gaucher disease; MN, multiples of normal; SD, standard deviation. **Source:** Cox et al. 2015[10]		

In the eliglustat and imiglucerase arms 44% and 47% of patients were male, respectively. Approximately a quarter of patients in each arm were of Jewish descent (including Ashkenazi and Sephardic Jews) reflecting the increased prevalence of Gaucher disease in this population. Furthermore, patients of Jewish descent often have mild disease and the relatively small proportion of this particular population shows it was not over-represented in this trial. The mean age of Gaucher disease symptom onset was 12.7 years in the eliglustat arm and 15.7 years in the imiglucerase arm with Gaucher disease diagnosis at 17.8 and 20.3 years, respectively. One or both of the common allelic mutations of the acid β-glucosidase gene (N370S, L444P) were present in 92% of patients on eliglustat and 83% of patients on imiglucerase. Splenectomies, which represent severe disease complications prior to diagnosis, were performed in 28% of patients in the eliglustat arm compared with 17% in the control arm. Overall baseline disease characteristics were well balanced between treatment arms in this study (Table 13). However, there are some key differences. In particular, age at first symptom onset and age at Gaucher diagnosis is much later in the imiglucerase arm. In addition, rate of splenectomy in the imiglucerase arm is almost a half of the rate in the eliglustat arm. This suggests that the patients in the ERT group were of milder severity and that patient randomisation was unfavourable for eliglustat. This is a reflection of the small number of patients in the trial due to the rarity of the condition.

The ENGAGE Study

Demographic characteristics were generally similar between treatment groups (Table 14), although the eliglustat group had slightly lower proportions of male patients (40%) and patients of Jewish descent (15%, including Ashkenazi and Sephardic Jews) compared with

placebo (60% and 40%, respectively).[71] The mean age at first Gaucher symptom onset was 16.7 and 15.2 years, for eliglustat and placebo groups, respectively; with Gaucher disease diagnosis at 22.3 and 20.1 years, respectively. In the eliglustat group 90% of patients had one of the N370S and/or L444P mutations compared with 95% in the placebo group.

All patients had splenomegaly at baseline as this was a requirement for study entry. Four patients (three in the eliglustat group and one in the placebo group) had moderate or severe bone disease at baseline, as defined by the investigator, and two patients (one in each group) had growth retardation.

Table 14: Characteristics of participants in ENGAGE across randomised groups

	Eliglustat (n=20)	**Placebo (n=20)**
Age, mean (SD), years	31.6 (11.6)	32.1 (11.3)
Weight, mean (SD), kg	64.8 (11.7)	68.6 (17.2)
Male, n (%)	8 (40)	12 (60)
White, n (%)	19 (95)	20 (100)
Jewish descent, yes, n (%)	3 (15)	8 (40)
Spleen volume, MN, mean (SD) (normal size: ≤5MN)	13.9 (5.9)	12.5 (6.0)
Liver volume, MN, mean (SD) (normal size: ≤2.5MN)	1.4 (0.4)	1.4 (0.3)
Haemoglobin levels, g/dL, mean (SD) (normal values: >12g/dL for males, >11g/dL for females)	12.1 (1.8)	12.8 (1.6)
Platelet count, 10^9/L, mean (SD) (normal: >120 x 10^9/L)	75.1 (14.1)	78.5 (22.6)
CYP2D6 metaboliser status, n (%)	Poor: 0 (0) Intermediate: 1 (5) Extensive: 18 (90) Ultra-rapid: 1 (5)	Poor: 0 (0) Intermediate: 2 (10) Extensive: 18 (90) Ultra-rapid: 0 (0)
Acid β-glucosidase activity, nmol/hour/mg, mean (SD)	2.29 (3.38)	2.04 (3.79)
Spine BMB Score, mean (SD)	5.33 (1.503)	5.93 (1.346)
BMD, g/cm^2, mean (SD)	1.04 (0.152)	0.99 (0.162)
Chitotriosoidase genotype, n (%)	Normal: 13 (65) Heterozygous: 6 (30) Homozygous mutation: 1 (5)	Normal: 16 (80) Heterozygous: 4 (20) Homozygous mutation: 0 (0)
Age at Gaucher disease diagnosis, years, mean (SD)	22.3 (9.6)	20.1 (13.2)

	Eliglustat (n=20)	Placebo (n=20)
Age at first Gaucher symptom onset, year, mean (SD):	16.7 (10.5)	15.2 (12.4)
Gaucher disease genotype, n (%)	N370S/Other: 8 (40) N370S/N370S: 5 (25) N370S/L444P: 2 (10) L444P/Other: 3 (15) Other/Other: 2 (10)	N370S/Other: 8 (40) N370S/N370S: 6 (30) N370S/L444P: 4 (20) L444P/Other: 1 (5) Other/Other: 1 (5)
Key: BMB, bone marrow burden; BMD, bone mineral density; MN, multiples of normal; SD, standard deviation. **Source:** Mistry et al., 2015[9]Genzyme et al., 2013[52]; EMA, 2014[71]		

EDGE

A total of 170 patients were treated in the lead-in period and baseline characteristics of these patients are presented in Table 15.

Table 15: Baseline characteristics for patients in the lead-in period of the EDGE study

Characteristic	Population (n=170)
Male, n (%)	88 (52)
White, n (%)	124 (73)
Age, years, median (range)	33.5 (18, 75)
Gaucher disease genotype, n (%)	At least one L444P: 68 (40) At least one N3703: 118 (69)
Age at Gaucher disease diagnosis, years, median (range)	19.0 (0.3, 63.4)
Age at first Gaucher symptom onset, year, median (range)	10.0 (0.0, 63.3)
Splenomegaly, MN, n (%)	Mild (≤5): 82 (48) Moderate (>5 to ≤15): 42 (25)
Hepatomegaly, MN, n (%)	Mild: (<1.25): 139 (82) Moderate (≥1.25 to ≤2.50): 31 (18)
Haemoglobin levels, g/dL, mean (SD)	No anaemia (≥12 male, ≥11 female): 159 (94) Mild (≥11 to <12 male; ≥10 to < 11 female): 7 (4) Moderate (≥9 to <11 male; ≥9 to < 10 female): 4 (2)
Platelet count, 10^9/L, mean (SD)	>400:3 (2) No thrombocytopenia (≥130 -≤400): 102 (60) Mild to moderate (≥60-<130): 65 (39)
Bone disease, n (%)	None: 55 (32) Mild to Moderate: 88 (52) Severe: 21 (12)

Characteristic	Population (n=170)
	Unknown: 6 (4)
Key: MN, multiples of normal; SD, standard deviation. **Source:** Charrow et al., 2014[13]	

Phase II study

Demographic and other baseline characteristics of the Phase II study are shown in Table 16.

Table 16: Baseline characteristics for patients in the Phase II study

Characteristic	Population (n=26)
Male, n (%)	10 (38)
Ashkenazi Jew, n (%)	7 (27)
Age, years, mean (SD)	34 (13)
Acid β-glucosidase, nmol/h/mg, mean (SD)	0.47 (0.77)
Gaucher genotype, n (%)	N370S/N370S: 3 (12) N370S/ L444P: 8 (31) N370S/ other: 11 (42) L444P/ other: 3 (12) Other: 1 (4)
Haemoglobin level, g/dL, mean (SD) (normal values: >12g/dL for males, >11g/dL for females)	11.1 (1.7)
Platelet count, n/mm^3, mean (SD) (normal: >120,000/mm^3)	66,442 (20,118)
Spleen volume, MN, mean (SD) (normal size: ≤5MN)	20.0 (12.8)
Liver volume, MN, mean (SD) (normal size: ≤2.5MN)	1.8 (0.6)
Chitotriosidase, nmol/h per mL (n=24), mean (SD) (normal: <15 to 181 nmol/h per mL)	9,168 (5,395)
Key: MN, multiples of normal; SD, standard deviation. **Source:** Lukina et al., 2010[11]	

Mean age at diagnosis was 24 years and at symptom onset was 11 years. A small percentage were of Ashkenazi Jewish ethnicity reflecting the higher prevalence of Gaucher disease in this population. In general, patients had moderate to severe GD1 manifestations.[11]

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in Section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

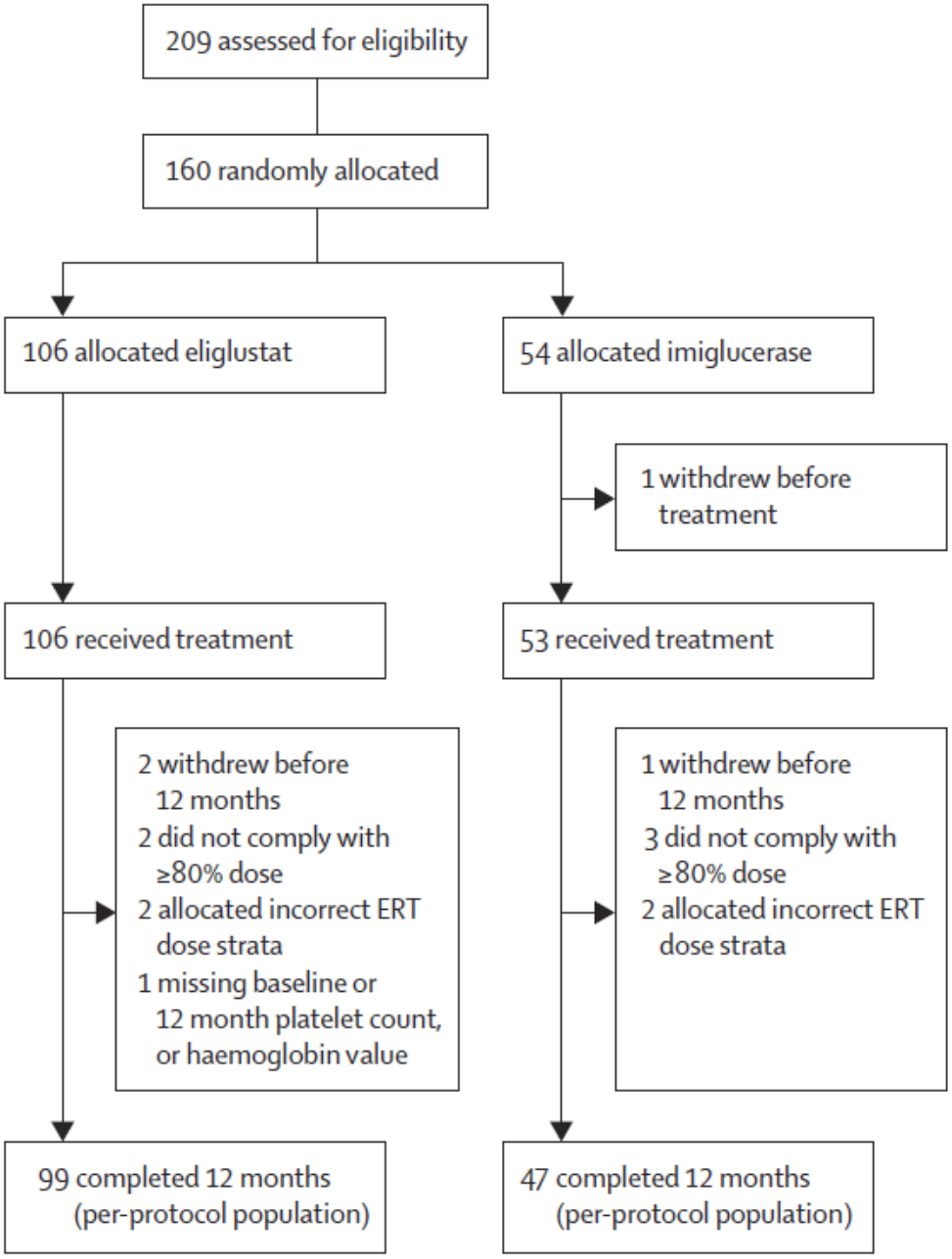
Within the ENCORE trial, patients may have been pre treated with either velaglucerase or imiglucerase. A post hoc subgroup analysis is presented for patients in ENCORE pre-treated on velagucerase alfa and switching to either eliglustat or imiglucerase in the trial. It is thought that evidence of patients remaining well controlled on eliglustat after switching from velaglucerase is useful supporting evidence with regard to the use of eliglustat in velaglucerase stable patients.

Similarly, a post hoc subgroup analysis is presented for patients in ENCORE pre-treated on imiglucerase and switching to either eliglustat or imiglucerase in the trial. This also may provide some aditional supporting evidence in imiglucerase stable patients switched to eliglustat remaining well controlled. Full methodology of the ENCORE trial is presented in Section 9.4.1.

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Figure 10 shows a flow diagram of patient disposition for the ENCORE study. In total, 160 patients were randomised into two treatment arms. The eliglustat arm had 106 patients and the imiglucerase arm had 54 patients. The full analysis set (all patients who signed informed consent and received at least 1 dose of study drug) comprised 106 and 53 patients in each arm, respectively. A total of 104 (98%) and 52 (96%) of the randomised patients within the eliglustat and imiglucerase arms, respectively, completed 52 weeks of the study (primary analysis period). The per protocol set (patients in the full analysis set who were ≥80% compliant with treatment during the primary analysis period, had no major protocol deviations expected to interfere with the assessment of efficacy as defined in the statistical analysis plan, and did not exhibit haematological decline as a result of medically determined aetiologies other than Gaucher disease) included 99 patients in the eliglustat arm and 47 in the imiglucerase arm. A total of 99 (93%) and 46 (85%) of patients completed the study extension through Week 104 in the eliglustat and imiglucerase arms, respectively.

Figure 10: A CONSORT diagram of participant flow in the ENCORE study

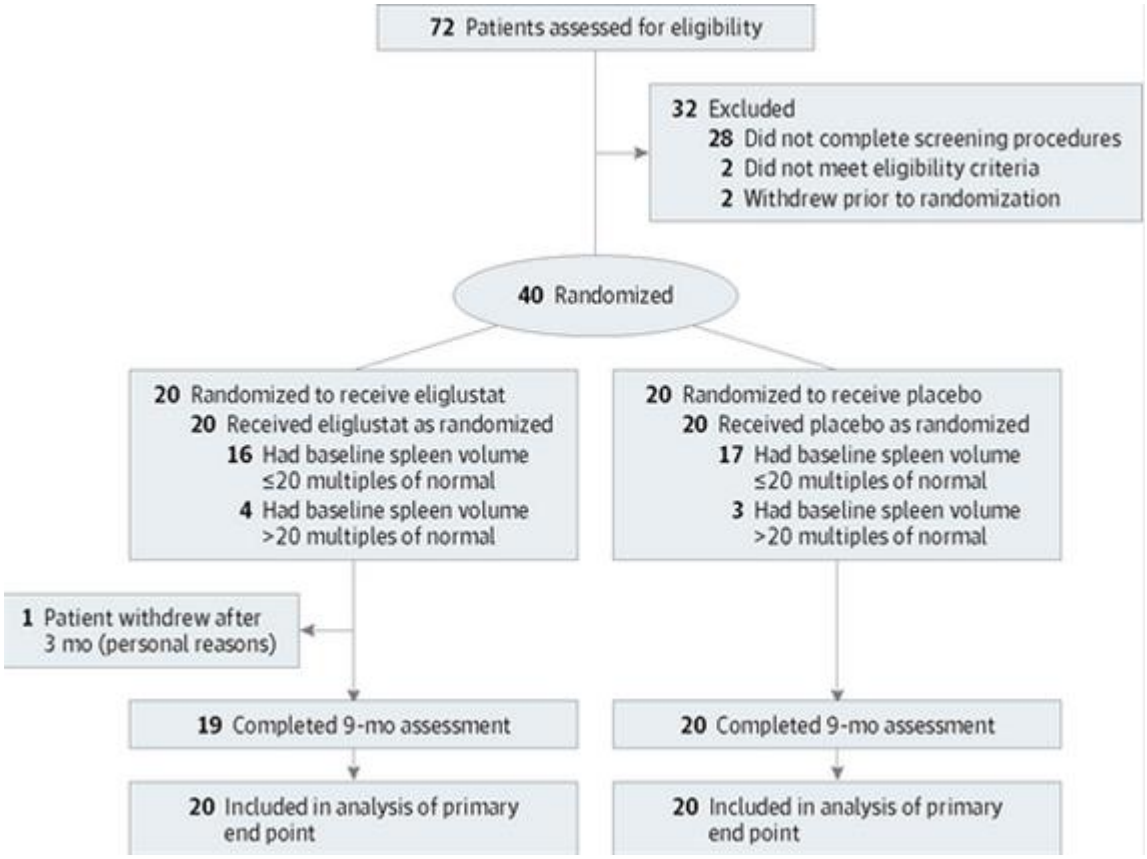


Key: ERT, enzyme replacement therapy.
Source: Cox et al., 2015[10]

Figure 11 shows a flow diagram of patient disposition for the ENGAGE study. Of 72 patients screened, 32 were excluded before randomisation, and 20 patients were randomised to each group. The mean time on study treatment was 274.5 days (SD=19.94) overall and was similar in the two treatment groups.[52, 71] Patients receiving eliglustat received 50mg QD on day 1 and proceeded to 50mg BID and/or 100mg BID. The majority of patients (17 [85%]) received a dose escalation to 100mg BID at Week 4, and three patients (15%) continued to receive 50mg BID for the duration of the study.[52] All patients

completed the primary study period (39 weeks) in the placebo group and one patient in the eliglustat group did not; this was a voluntary withdrawal for personal reasons, not because of an AE. 19 (95%) patients in the eliglustat arm and 20 (100%) patients in the placebo arm completed 78 weeks of the study.

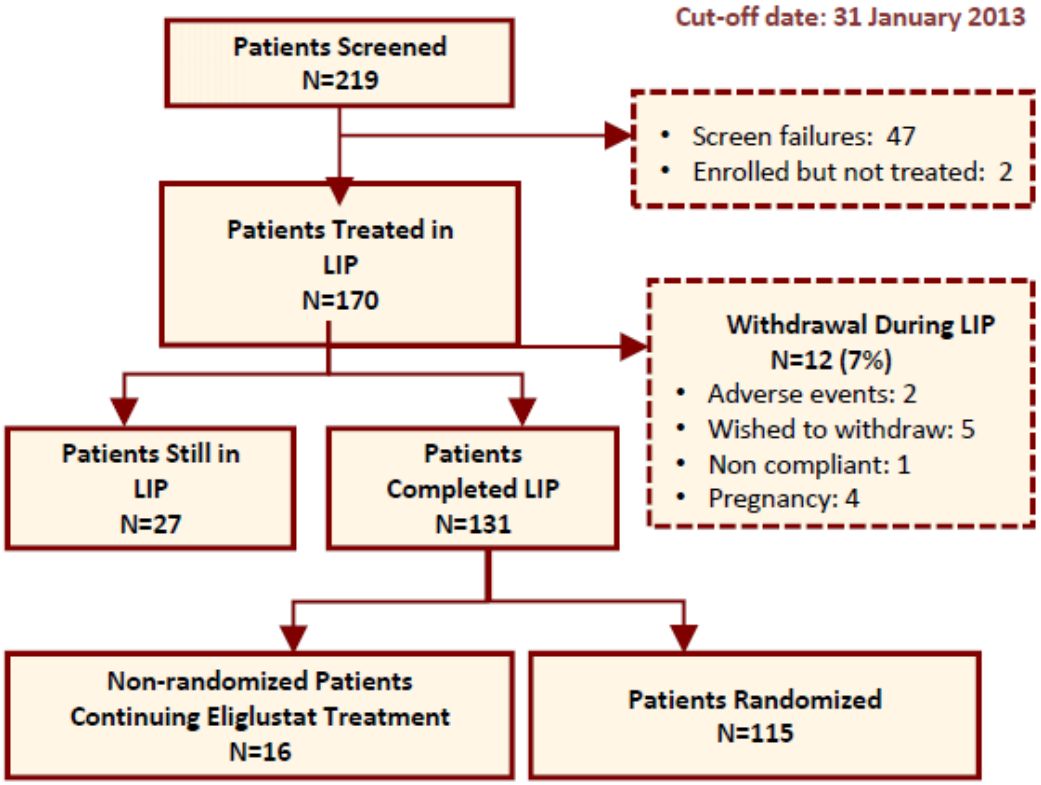
Figure 11: A CONSORT diagram of participant flow in the ENGAGE study



Source: Mistry et al., 2015[9]

In the EDGE study, a total of 170 patients were treated with eliglustat BID in the lead-in period. A flow diagram of patient disposition is presented in Figure 12.

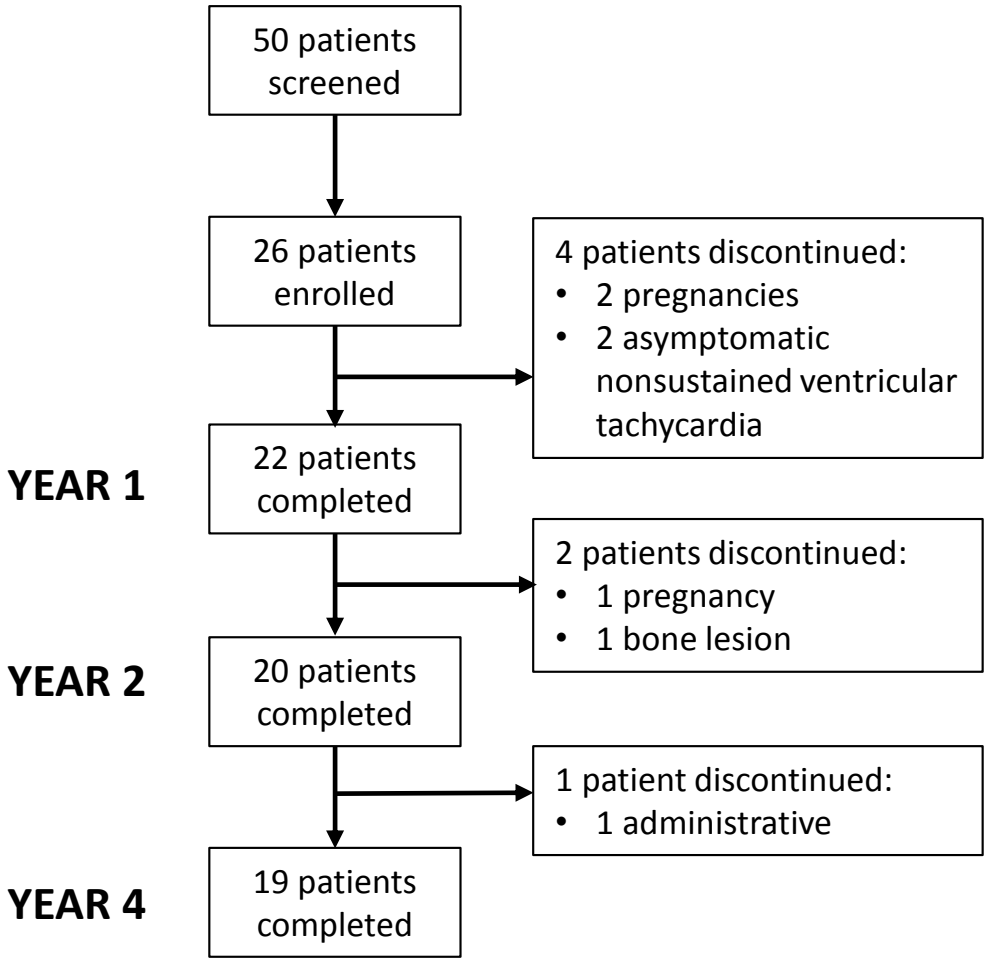
Figure 12: Patient disposition in the lead-in period of the EDGE study



Key: LIP, lead-in period
Source: Charrow et al., 2014[13]

In the Phase II study a total of 22 (85%) of patients completed Year 1, 20 patients (76.9%) completed Year 2 and 19 patients (73%) completed Year 4 (Figure 13).[12]

Figure 13: A CONSORT diagram for participant flow in the Phase II study



Source: Lukina et al., 2014[12]

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

Detail provided in Section 9.4.5 and the figures therein.

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables C7 and C8.

Critical appraisals for the ENCORE and ENGAGE RCTs are presented in Section 19.3. For the single-arm Phase II study, the Downs and Black checklist for non-randomised studies has been used for critical appraisal, also presented in Section 19.3.

As the publication identified for the EDGE study reported only interim results of the lead-in period, no critical appraisal has been carried out as analysis of the randomised part of the study has not been completed. The CSR is expected to be available in April 2016.

9.6 Results of the relevant studies

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table C9.

The results of each trial are presented below in a tabulated format, and supplemented with text and figures, where appropriate.

ENCORE

The results of the ENCORE study are summarised in Table 17. Information on the hypotheses under consideration and the statistical analysis used for testing these hypotheses in each trial is presented in Section 19.1. In addition, the outcomes of each trial and their relevance to the decision problem can also be found in Section 19.1.

Table 17: ENCORE study results (Per Protocol Set)

Study name	**ENCORE**	
Size of randomised study groups (per protocol population)	**Treatment (eliglustat)**	N=99
	Control (imiglucerase)	N=47
Study duration	**Time unit**	52 weeks with extension phase to 104 weeks
Primary outcome – proportion of patients stable in the composite endpoint		
	Percentage stable for 52 weeks, n (%), [95% CI]	
	Eliglustat (n=99)	**Imiglucerase (n=47)**
Composite endpoint	84 (84.8) [76.2, 91.3]	44 (93.6) [82.5, 98.7]
Difference in percentage stable, %	-8.8 (95% CI: -17.6, 4.2) [Eliglustat met the criteria for non-inferiority because the lower 95% CI (-17.6%) was within the pre-specified threshold of -25%]	
Patients who met stable criteria of primary endpoint, n (%), [exact 95% CI]		
Haemoglobin criteria	94 (94.9) [0.89, 0.98]	47 (100.0), [NR]
Platelet criteria	92 (92.9) [0.86, 0.97]	47 (100.0), [NR]
Spleen volume criteria	68 (95.8) [0.88, 0.99]*	39 (100.0)*, [NR]
Liver volume criteria	95 (96.0) [0.90, 0.99]	44 (93.6) [0.83, 0.99]
Percentage stable for 104 weeks, n (%), [95% CI]		
	Eliglustat (n=95)	
Composite endpoint	83 (87.4) [0.79, 0.93]	
Patients who met stable criteria of primary endpoint, n (%), [95% CI] Eliglustat (n=99)		
Haemoglobin criteria	92 (96.8) [0.91, 0.99]	

Platelet criteria	89 (93.7) [0.87, 0.98]			
Spleen volume criteria	68 (95.8) [0.88, 0.99]*			
Liver volume criteria	91 (96.0) [0.90, 0.99]			
Secondary outcomes – absolute and percentage changes in haemoglobin, platelet count and organ volumes at Week 52 and Week 104				
	Haemoglobin levels (g/dL)		**Platelet count (10^9/L)**	
	Eliglustat (n=98)	**Imiglucerase (n=47)**	**Eliglustat (n=98)**	**Imiglucerase (n=47)**
Baseline, mean (SD)	13.59 (1.25)	13.80 (1.22)	206.75 (80.74)	192.30 (57.34)
Week 52, mean (SD)	13.38 (1.28)	13.84 (1.29)	216.28 (83.96)	198.34 (61.16)
Percentage change from baseline to Week 52, mean (SD)	-0.21 (0.71)	0.04 (0.66)	3.79 (18.85)	2.93 (11.89)
Treatment difference: *LS Mean (SEM)* *95% CI* *p-value*		-0.28 (0.12) -0.52, -0.03 0.03		1.30 (3.01) -4.65, 7.24 0.67
Week 104, mean (SD) Eliglustat (n=94)	13.49 (1.18)	---	203.40 (76.78)	---
Percentage change from baseline to Week 104, mean (SD)	-0.10 (0.77)	---	2.27 (17.64)	---
	Liver volume (MN)		**Spleen volume (MN)**	
	Eliglustat (n=98)	**Imiglucerase (n=47)**	**Eliglustat (n=70)**	**Imiglucerase (n=39)**
Baseline, mean (SD)	0.95 (0.19)	0.91 (0.16)	3.23 (1.37)	2.62 (1.08)
Week 52, mean (SD)	0.96 (0.19)	0.94 (0.17)	3.07 (1.38)	2.53 (0.99)
Percentage change from baseline to Week 52, mean (SD)	1.78 (9.64)	3.57 (10.24)	-6.17 (14.14)	-3.01 (10.50)
Treatment difference: *LS Mean (SEM)* *95% CI* *p-value*		-1.14 (1.66) -4.42, 2.15 0.49		-2.83 (2.68) -8.14, 2.47 0.29
Week 104, mean (SD)		N=94 0.96 (0.18)		N=70 2.97 (1.36)
Percentage change from baseline to Week 104, mean (SD)	2.07 (9.71)	-	-7.75 (15.11)	-
Secondary outcomes – changes in bone-related endpoints at Weeks 52 and 104				
	Eliglustat (n=99)		**Imiglucerase (n=47)**	
Total spine BMD (g/cm^2)				

Baseline, mean (SD)	n=94 1.09 (0.16)	n=45 1.11 (0.16)
% change to Week 52, LS Mean (SEM)	0.50 (0.33)	0.55 (0.48)
Treatment difference (eliglustat-imiglucerase), LS Mean (SEM) [95% CI] p-value		-0.06 (0.58) [-1.21, 1.09] P=0.9203
Absolute change to Week 52, mean (SD)	n=93 0.01 (0.036)	n=40 0.00 (0.031
% change to Week 104, mean (SD)	n=87 0.94 (3.66)	N/A
Absolute change to Week 104, mean (SD)	N=87 0.01 (0.039)	N/A
Total lumbar spine T-score		
Baseline, mean (SD)	n=81 -0.56 (1.31)	n=38 -0.33 (1.17)
% change to Week 52, mean (SD)	N=76 1.54 (72.45)	N=36 -3.47 (63.37)
Treatment difference (eliglustat-imiglucerase), LS Mean (SEM) [95% CI] p-value		0.01 (0.06) [-0.10, 0.13] P=0.8345
Absolute change to Week 52, LS Mean (SEM)	0.04 (0.03)	0.03 (0.05)
% change to Week 104, mean (SD)	N=70 7.16 (106.12)	N/A
Absolute change to Week 104, mean (SD)	n=74 0.07 (0.31)	N/A
Total lumbar spine Z-score		
Baseline, mean (SD)	n=94 -0.35 (1.26)	n=45 -0.14 (1.11)
% change to Week 52, mean (SD)	N=92 5.17 (79.09)	N=39 12.56 (61.62)
Treatment difference (eliglustat-imiglucerase), LS Mean (SEM) [95% CI] p-value		0.0 (0.05) [-0.11, 0.10) P=0.9553

Absolute change to Week 52, LS Mean (SEM)	0.06 (0.03)	0.06 (0.04)
% change to Week 104, mean (SD)	N=86 -8.75 (128.99)	N/A
Absolute change to Week 104, mean (SD)	n=87 0.11 (0.32)	N/A
Total femur BMD (g/cm^2)		
Baseline, mean (SD)	n=93 1.01 (0.16)	n=44 0.98 (0.18)
% change to Week 52, LS Mean (SEM)	0.18 (0.22)	0.00 (0.31)
Treatment difference (eliglustat-imiglucerase), LS Mean (SEM) [95% CI] p-value		0.19 (0.38) [-0.57, 0.94] P=0.63
Absolute change to week 52, mean (SD)	N=92 0.00 (0.02)	N=38 0.00 (0.028)
% change to Week 104, mean (SD)	n=85 0.13 (3.21)	N/A
Absolute change to week 104, mean (SD)	N=85 0.00 (0.032)	N/A
Total femur T-score		
Baseline, mean (SD)	n=80 -0.11 (1.08)	n=37 -0.47 (1.29)
% change to Week 52, LS Mean (SEM)	N=77 -3.69 (57.58)	N=32 -4.71 (23.23)
Treatment difference (eliglustat-imiglucerase), LS Mean (SEM) [95% CI] p-value		0.03 (0.03) [-0.57, 0.94] P=0.3519)
Absolute change to Week 52, LS Mean (SEM)	0.00 (0.02)	-0.03 (0.03)
% change to Week 104, mean (SD)	N=71 -19.21 (94.82)	N/A
Absolute change to Week 104, mean (SD)	n=73 -0.02 (0.23)	N/A
Total femur Z-score		
Baseline, mean (SD)	n=93 0.09 (1.02)	n=44 -0.18 (1.12)
% change to Week 52, LS Mean (SEM)	N=89 -1.16 (73.41)	N=35 -8.75 (32.34)

Treatment difference (eliglustat-imiglucerase), LS Mean (SEM) [95% CI] p-value		0.02 (0.03) [-0.04, 0.07] P=0.5847
Absolute change to Week 52, LS Mean (SEM)	0.03 (0.02)	0.02 (0.02)
% change to Week 104, mean (SD)	N=82 -13.30 (91.05)	N/A
Absolute change to Week 104, mean (SD)	n=85 0.04 (0.26)	N/A
Spine BMB score		
Baseline, mean (SD)	n=98 3.79 (1.62)	n=46 3.65 (1.62)
% change to Week 52, mean (SD)	n=98 -1.71 (23.92)	n=42 1.22 (49.02)
Absolute change to Week 52, mean (SD)	N=98 -0.12 (0.71)	N=42 -0.24 (1.16)
% change to Week 104, mean (SD)	n=94 2.95 (36.38)	N/A
Absolute change to Week 104, mean (SD)	N=94 -0.08 (1.03)	N/A
Femur BMB score		
Baseline, mean (SD)	n=99 4.44 (1.82)	n=46 4.42 (1.73)
% change to Week 52, mean (SD)	n=96 -0.34 (19.81)	n=42 0.70 (39.04)
Absolute change to Week 52, mean (SD)	N=96 -0.04 (0.41)	N=42 -0.08 (0.9)
% change to Week 104, mean (SD)	n=95 5.23 (43.20)	N/A
Absolute change to Week 104, mean (SD)	N=95 5.23 (43.20)	N/A
Total BMB score		
Baseline, mean (SD)	n=98 8.25 (2.62)	n=45 8.28 (2.70)
% change to Week 52, mean (SD)	n=95 -1.79 (14.58)	n=42 -2.75 (23.34)
Absolute change to Week 52, mean (SD)	N=95 -0.14 (0.88)	N=42 -0.31 (1.32)

% change to Week 104, mean (SD)	n=94 1.22 (23.05)	N/A
Absolute change to Week 104, mean (SD)	N=94 1.22 (23.05)	N/A

Tertiary outcomes – change in biomarker values to Week 52				
Biomarker	**Treatment group**	**Median (min, max)**		
		Baseline	**Week 52**	**% change**
Normalised chitotriosidase (nmol/hr/mL)	Eliglustat (n=89)	730.0 (0, 10761)	667.5 (0, 11898)	-26.45 (-92.2, 269.8)
	Imiglucerase (n=47)	773.0 (16, 4342)	569.5 (20, 3249)	-15.88 (-85.4, 55.1)
Plasma glucosylceramide (µg/mL)	Eliglustat (n=96)	5·20 (2·7, 10·5)	2·00 (2·0, 4·9)	-60·8 (-80·8, -11·8)
	Imiglucerase (n=47)	5·50 (2·9, 11·5)	5·0 (2·2, 12·0)	-12·7 (-54·9, 58·1)
Plasma GM3 (µg/mL)	Eliglustat (n=86)	13·0 (7, 30)	5·0 (4, 16)	-56·3 (-83, -8)
	Imiglucerase (n=44)	13·0 (6, 22)	13·0 (7, 24)	0·0 (-38, 50)
Plasma macrophage inflammatory protein 1β (pg/mL)	Eliglustat (n=95)	59·4 (9·3, 433·8)	46·1 (15·2, 349·4)	-18·9 (-83·2, 375·5)
	Imiglucerase (n=47)	57·1 (25·7, 792·7)	42·4 (22·8, 399·9)	-17·1 (-78·7, 84·5)
Plasma ceramide (µg/L)	Eliglustat (n=95)	3·90 (2·2, 8·3)	3·70 (1·0, 6·6)	-8·57 (-75·0, 85·2)
	Imiglucerase (n=47)	4·00 (2·4, 6·9)	3·80 (2·2, 7·0)	-8·3 (-63·1, 132·0)
Plasma sphingomyelin (µg/mL)	Eliglustat (n=95)	314·0 (200, 596)	354·0 (200, 512)	7·2 (-30, 124)
	Imiglucerase (n=47)	328·0 (200, 589)	326·0 (200, 474)	3·0 (-33, 71)

Health-related quality of life outcomes				
HRQL Measure	**Treatment group**	**Mean (SD)**		
		Baseline	**Week 52**	**% change**
FSS	Eliglustat (n=97)	3.06 (1.55)	3.13 (1.63)	14.73 (75.04)
	Imiglucerase (n=45)	3.01 (1.54)	2.92(1.54)	8.78 (57.93)
BPI, Average Pain	Eliglustat (n=95)	1.67 (2.05)	1.55 (1.97)	-9.12 (103.05)
	Imiglucerase (n=46)	1.17 (1.44)	0.85 (1.19)	-32.67 (79.13)
SF-36 – general health	Eliglustat (n=96)	70.5 (19.56)	71.21 (19.03)	4.75 (29.20)
	Imiglucerase (n=46)	75.15 (18.67)	78.91 (15.28)	9.16 (27.14)

SF-36 – physical component score	Eliglustat (n=95)	49·59 (9·16)	51·22 (8·37)	4·78 (16·26)
	Imiglucerase (n=46)	53·38 (7·17)	55·07 (5·20)	4·55 (14·19)
SF-36 – mental component score	Eliglustat (n=95)	51·97 (9·85)	50·97 (10·30)	0·00 (21·39)
	Imiglucerase (n=46)	51·99 (8·87)	51·34 (10·09)	-0·53 (17·88)
DS3 score				
DS3 score	**Treatment group**	**Mean (SD)**		
		Baseline	**Week 52**	**Change from baseline to Week 52**
Total	Eliglustat (n=68)	2.37 (0.90)	2.40 (1.06)	0.03 (0.81)
	Imiglucerase (n=38)	2.08 (0.93)	2.10 (0.87)	0.03 (0.69)
Bone domain	Eliglustat (n=93)	2.16 (0.74)	2.22 (0.92)	0.06 (0.85)
	Imiglucerase (n=45)	1.92 (0.77)	2.14 (0.89)	0.21 (0.67)
Haematologic domain	Eliglustat (n=93)	0.10 (0.24)	0.15 (0.38)	0.05 (0.41)
	Imiglucerase (n=45)	0.12 (0.33)	0.03 (0.15)	-0.08 (0.34)
Visceral domain	Eliglustat (n=68)	0.13 (0.36)	0.14 (0.46)	0.01 (0.36)
	Imiglucerase (n=38)	0.08 (0.31)	0.04 (0.28)	-0.04 (0.16)

Key: BMB, bone marrow burden; BMD, bone mineral density; BPI, Brief Pain Inventory; CI, confidence interval; DS3, disease severity scoring system; FSS, Fatigue Severity Score; HRQL, health-related quality of life; LS, least squares; MN, multiples of normal; NR, not reported; SD, standard deviation; SEM, standard error of the mean; SF-36, Short Form 36.

Source: Cox et al. 2015[10]; Genzyme 2014[72]; Genzyme, 2014[103]

As well as HRQL outcomes, treated patients also completed a questionnaire showing their preference of treatment type (oral versus IV) which showed that 94% of patients in the eliglustat group and 94% in the imiglucerase group indicated a preference for oral treatment at screening. After 12 months of treatment, all of the 93 patients who had switched from ERT to eliglustat and responded to the preference survey said they preferred oral therapy to the ERT infusion therapy they had previously received primarily due to convenience (81%).

Eliglustat met the criteria to be declared non-inferior to imiglucerase in maintaining stability. Stability in the composite endpoint, including haemoglobin and platelet levels, and spleen and liver volumes, was maintained after 52 weeks of treatment in 85% of patients in the eliglustat group and 94% in the imiglucerase group. The lower bound of the 95% CI

in the difference in percentage (-17.6%) was within the pre-specified threshold of -25%. In both treatment groups, greater than 92% of patients were stable in each component of the composite endpoint.

A post-hoc analysis was conducted in the ENCORE trial for the subgroups of patients pre-treated on velaglucerase.[104] Overall this analysis showed that:

- Eliglustat has similar efficacy both post-imiglucerase and post-velaglucerase treatment, with continued stability
- Haemoglobin levels and platelet counts showed no significant change from baseline to Week 52 post-velaglucerase treatment (mean change of -0.42g/dL ± 0.62 and 1% ± 25.9% for platelets)
- Spleen and liver volume outcomes also showed no significant change from baseline (mean change of -1% ± 8.7 and 1.6% ± 7.9, respectively.

ENGAGE

The results of the ENGAGE study are summarised in Table 18. Information on the hypotheses under consideration and the statistical analysis used for testing these hypotheses in each trial is presented in Section 19.1. In addition, the outcomes of each trial and their relevance to the decision problem can also be found in Section 19.1.

Table 18: ENGAGE study results (intention to treat analysis)

Study name	**ENGAGE**	
Size of study groups (ITT population)	Treatment (eliglustat)	N=20
	Control (placebo)	N=20
Study duration	Time unit	39 weeks with extension phase to 78 weeks
Primary outcome – mean percentage change in spleen volume		
	Eliglustat (n=20)	**Placebo (n=20)**
Baseline, mean MN (SD)	13.89 (5.93)	12.50 (5.96)
Percentage change to Week	-27.77% (2.37)	2.26% (2.37)

39, LS Mean (SEM)		
Treatment difference,		
LS Mean (SEM)		-30.03% (3.35)
95% CI		-36.82, -23.24
P-value		<0.001
Percentage change to Week 78, mean (SD) [95% CI]	-44.6% (10.1) [-49.6, -39.6][a]	-31.3% (10.1) [-36.0, -26.6]
Secondary outcomes – absolute and percentage changes in haemoglobin, platelet count and liver volume to Weeks 39 and 78		
	Eliglustat (n=20)	**Placebo (n=20)**
Haemoglobin (g/dL)		
Baseline, mean (SD)	12.05 (1.82)	12.75 (1.63)
Absolute change from baseline to Week 39, LS Mean (SEM)	0.69 (0.23)	-0.54 (0.23)
Treatment difference,		
LS Mean (SEM)		1. 22 (0.32)
95% CI		0.57, 1.88
P-value		P=0.0006
Change from baseline to Week 78 (SD)	n=18 1.02 (0.84)	n=20 0.79 (0.82)
Liver volume (MN)		
Baseline, mean (SD)	1.44 (0.35)	1.36 (0.28)
% change from baseline to week 39, LS Mean (SEM)	-5.20 (1.64)	1.44 (1.64)
Treatment difference,		
LS Mean (SEM)		-6.64% (2.33)
95% CI		(-11.37, -1.91)
P-value		P=0.0072
% change from baseline to Week 78 (SD)	n=18 -11.18 (9.35)	n=20 -7.31 (9.97)
Platelet count (10^9/L)		
Baseline, mean (SD)	75.05 (14.10)	78.48 (22.61)
% change from baseline to Week 39, LS Mean (SEM)	32.00 (5.95)	-9.06 (5.95)
Treatment difference,		
LS Mean (SEM)		41.06% (8.44)
95% CI		23.95, 58.17
P-value		P<0.0001
% change from baseline to	n=18	n=20

Week 78 (SD)	58.16 (41.07)	39.82 (37.37)

Tertiary outcomes – changes in bone-related endpoints at Weeks 39 and 78			
	Eliglustat (n=20)	**Placebo (n=20)**	**Treatment Difference, LS Mean, (95% CI)**
Lumbar spine BMD (g/cm^2)			
Baseline, mean (SD)	N=19 0.99 (0.17)	N=20 1.04 (0.15)	
% change to Week 39, LS mean (95% CI)	N=19 0.4 (-1.17 to 2.0)	N=20 -0.8 (-2.38 to 0.71)	1.2 (-0.97, 3.47)
Absolute change to Week 39, mean (SD)	n=19 0.00 (0.03)	n=20 -0.01 (0.04)	NR
% change to Week 78, mean (SD)	n=17 3.47 (5.43)	n=20 0.26 (2.75)	NR
Absolute change to Week 78, mean (SD)	N=17 0.03 (0.05)	N=20 0.00 (0.03)	NR
Total spine T-score			
Baseline, mean (SD)	n=17 -1.1 (0.8)	n=18 -1.1 (1.2)	NR
% change to Week 39, mean (SD)	N=14 -2.64 (23.83)	N=18 4.83 (53.05)	NR
Absolute change to Week 39, LS mean (95% CI)	N=17 0.0 (-0.1 to 0.2)	N=18 -0.1 (-0.2 to 0.03)	0.1 (-0.1, 0.3)
% change to Week 78, mean (SD)	n=13 -7.3 (31.9)	n=17 5.2 (21.9)	NR
Absolute change to Week 78, mean (SD)	N=15 0.19 (0.35)	N=18 0.03 (0.25)	NR
Total spine Z-score			
Baseline, mean (SD)	n=19 -1.1 (0.9)	n=20 -1.2 (1.2)	
% change to Week 39, mean (SD)	N=15 -4.59 (24.55)	n=20 1.68 (40.47)	NR
Absolute change to Week 39, LS mean (95% CI)	n=19 0.1 (-0.1 to 0.2)	n=20 -0.1 (-0.2 to 0.02)	0.2 (-0.01 to 0.4)
% change to Week 78, mean (SD)	n=15 -12.34 (31.21)	n=19 3.38 (19.53)	NR
Absolute change to Week 78, mean (SD)	N=17 0.26 (0.36)	N=20 0.03 (0.23)	NR
Total femur BMD (g/cm^2)			
Baseline, mean (SD)	n=19 0.97 (0.15)	n=20 0.98 (0.16)	NR

% change to 39 weeks, LS mean (95% CI)	N=19 -0.7 (-2.19 to 0.76)	N=20 0.1 (-1.29 to 1.57)	-0.9 (-0.01 to 0.36)
Absolute change to 39 weeks, mean (SD)	n=19 -0.006 (0.02)	n=20 0.001 (0.03)	
% change to Week 78, mean (SD)	N=17 -0.36 (4.37)	N=20 -0.64 (2.37)	NR
Absolute change to Week 78, mean (SD)	N=17 -0.01 (0.04)	N=20 -0.01 (0.02)	NR
Total femur T-score			
Baseline, mean (SD)	n=17 -0.26 (0.77)	n=18 -0.45 (1.21)	NR
% change to Week 39, mean (SD)	N=16 4.43 (73.21)	N=17 -10.24 (33.75)	NR
Absolute change to Week 39, LS Mean (95% CI)	N=17 -0.1 (-0.2 to 0.04)	N=18 0.0 (-0.1 to 0.1)	-0.1 (-0.3 to 0.04)
% change to Week 78, mean (SD)	N=15 32.63 (98.52)	N=16 17.64 (30.78)	NR
Absolute change to Week 78, mean (SD)	N=15 -0.09 (0.23)	N=18 -0.06 (0.19)	NR
Total femur Z-score			
Baseline, mean (SD)	-0.1 (0.7)	-0.4 (1.2)	NR
% change to Week 39, mean (SD)	N=15 -10.42 (84.82)	N=19 -7.68 (59.89)	NR
Absolute change to Week 39 , LS mean (95% CI)	n=18 0.0 (-0.1 to 0.1)	n=20 0.0 (-0.1 to 0.1)	0.0 (-0.2 to 0.1)
% change to Week 78, mean (SD)	N=14 48 .45 (103.34)	N=19 32.82 (77.14)	NR
Absolute change to Week 78, mean (SD)	N=16 -0.06 (0.23)	N=20 -0.01 (0.18)	NR
Absolute change in spine BMB, LS Mean (SEM)	Week 39, LS Mean (SEM): -0.6 (0.20)	Week 39, LS Mean (SEM): 0.1 (0.20)	-0.6 (0.29) P=0.002
	Week 78 (n=18), mean (SD): -1.43 (1.12)	Week 78, mean (SD): -0.57 (0.89)	NR
Absolute change in femur BMB, LS Mean (SEM)	Week 39, LS Mean (SEM): -0.5 (0.10)	Week 39, LS Mean (SEM): 0.0 (0.10)	-0.4 (0.15) P=0.026
	Week 78 (n=18), mean (SD): -0.72 (1.31)	Week 78, mean (SD): -0.37 (0.83)	NR

Absolute change in total BMB, LS Mean (SEM)	Week 39, LS Mean (SEM): -1.1 (0.23)	Week 39, LS Mean (SEM): 0.0 (0.23)	-1.1 (0.33) P=0.0021
	Week 78 (n=18), mean (SD): -2.15 (2.05)	Week 78, mean (SD): -0.94 (1.47)	NR

Tertiary outcomes – change in biomarker values to Week 39

Biomarker	Treatment group	Mean, (SD)		
		Baseline	Week 39	% change LS mean (95% CI) [p-value between groups]
Normalised chitotriosidase (nmol/h/mL)	Eliglustat (n=19)	12,648 (8,473)	8,204 (6,340)	-39.0 (-53.0 to -25.0) [p<0.001 vs. placebo]
	Placebo (n=20)	11,118 (8,313)	10,950 (7,345)	5.4 (-8.3 to 19.0)
Plasma glucosylceramide (µg/mL)	Eliglustat (n=20)	12.7 (4.8)	3.5 (2.2)	-71.7 (-79.5, -64.0) [p<0.001 vs. placebo]
	Placebo (n=20)	9.6 (3.8)	8.9 (3.5)	-4.9 (-12.6, 2.9)
Plasma GM3 ganglioside (µg/mL)	Eliglustat (n=14)	27.7 (5.3)	12.0 (6.4)	-54.0 (-64.4, -43.7) [p<0.001 vs. placebo]
	Placebo (n=14)	22.6 (7.0)	20.7 (4.6)	-7.7 (-18.1, 2.7)
Plasma macrophage inflammatory protein 1β (pg/mL)	Eliglustat (n=20)	277 (101)	134 (76)	-51.6 (-60.3, -42.9) [p<0.001 vs. placebo]
	Placebo (n=20)	287 (143)	255 (120)	-8.0 (-16.7, 0.6)
Plasma ceramide (µg/L)	Eliglustat (n=20)	3.5 (0.95)	3.1 (0.68)	-4.7 (-16.9, 7.5) [p=0.86 vs. placebo]
	Placebo (n=20)	3.6 (0.84)	3.3 (1.08)	-3.2 (-15.4, 9.0)
Plasma sphingomyelin (µg/mL)	Eliglustat (n=20)	247 (69.4)	280 (50.2)	21 (12.5, 29.4) [p<0.001 vs. placebo]
	Placebo (n=20)	234 (47.5)	230 (39.4)	-2 (-10.5, 6.4)

Health-related quality of life outcomes

HRQL measure	Treatment group	Mean (SD)		Absolute change, LS mean (95% CI)	Difference between treatment groups [p-value]
		Baseline	Week 39		
FSS	Eliglustat (n=20)	3.84 (1.74)	3.87 (1.52)	0.1 (-0.4 to 0.5)	0.7 (0.02, 1.33)

	Placebo (n=20)	3.53 (1.64)	2.96 (1.65)	--0.6 (-1.1 to -0.2)	[p=0.04]
BPI, average pain	Eliglustat (n=19)	1.7 (2.51)	1.2 (2.28)	-0.4 (-0.86 to 0.04)	-0.2 (-0.81 to 0.36) [p=0.52]
	Placebo (n=20)	1.1 (1.96)	0.9 (1.52)	-0.2 (-0.63 to 0.18)	
SF-36 – general health	Eliglustat (n=20)	55.8 (27.7)	56.1 (19.8)	-1.7 (-6.89 to 3.44)	-2.4 (-9.84 to 4.94) [p=0.51]
	Placebo (n=20)	66.7 (24.7)	65.4 (19.4)	0.7 (-4.44 to 5.89)	
SF-36 – physical component score	Eliglustat (n=20)	46.1 (9.3)	46.8 (7.9)	0.8 (-1.95 to 3.55)	3.3 (-0.67 to 7.29) [p=0.12]
	Placebo (n=20)	51.9 (7.2)	48.8 (9.2)	-2.5 (-5.19 to 0.16)	
SF-36 – mental component score	Eliglustat (n=20/19[b])	45,2 (14.0)	46.8 (10.0)	1.6 (-1.79 to 5.01)	-2.2 (-7.01 to 2.59) [p=0.36]
	Placebo (n=20)	49.3 (11.9)	52.5 (12.1)	3.8 (0.51 to 7.13)	

DS3 score

DS3 score	Treatment group	Mean (SD)		Mean change (95% CI)
		Baseline	Week 39	
Total	Eliglustat (n=20)	4.70 (1.0)	4.24 (0.8)	-0.46 (-0.75, -0.17)
	Placebo (n=20)	4.43 (1.2)	4.37 (1.0)	-0.06 (-0.36, 0.24)
Bone domain	Eliglustat (n=20)	2.6 (0.7)	2.4 (0.6)	-0.23 (-0.47, 0.01)
	Placebo (n=20)	2.7 (0.9)	2.6 (0.8)	-0.06 (-0.36, 0.24)
Haematological domain	Eliglustat (n=20)	1.0 (0.4)	1.0 (0.4)	0.0 (0, 0)
	Placebo (n=20)	0.8 (0.4)	0.8 (0.4)	0.0 (0, 0)
Visceral domain	Eliglustat (n=20)	1.1 (0.5)	0.9 (0.5)	-0.24 (-0.44, -0.04)
	Placebo (n=20)	1.0 (0.4)	1.0 (0.4)	0.0 (0, 0)

Key: BMB, bone marrow burden; BMD, bone mineral density; BPI, bone pain inventory; CI, confidence interval; DS3, disease severity score system; FSS, Fatigue Severity Score; HRQL, health-related quality of life; ITT, intention-to-treat; LS, least squares; MN, multiples of normal; NR, not reported; SD, standard deviation; SEM, standard error of the mean.

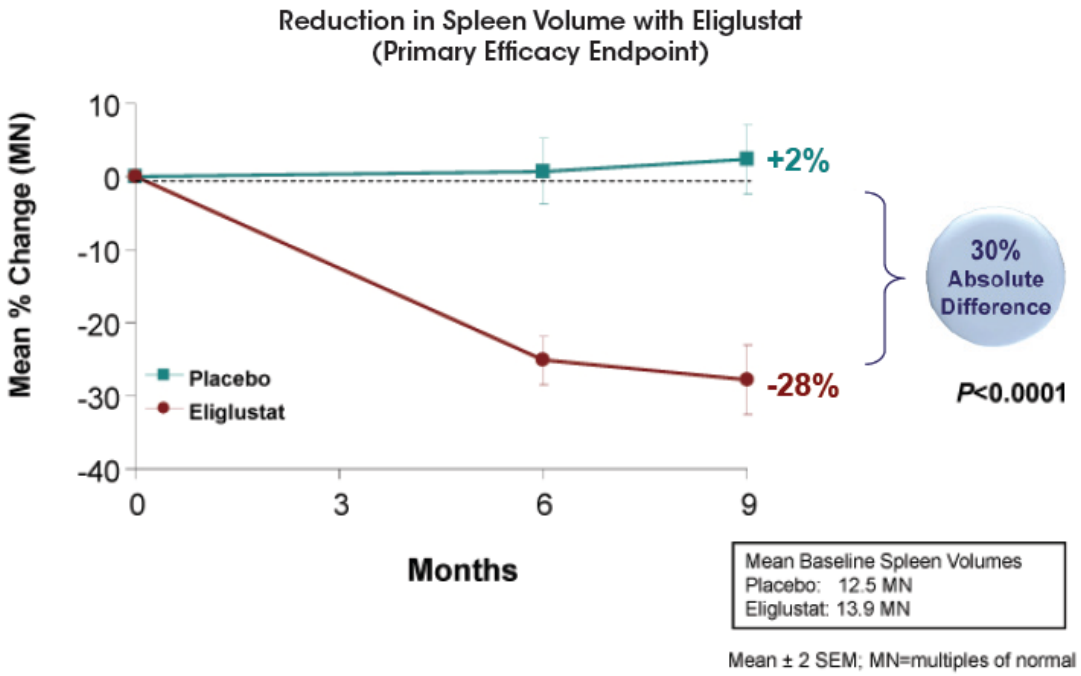
Notes: [a], n=18; [b], one patients had missing data at Week 39.

Source: Mistry et al. 2015[9]; Genzyme, 2013[52]; Amato et al. 2014[88]; Genzyme, 2014[105]

In the ENGAGE study the primary efficacy endpoint of mean percentage change in spleen volume was -28% for the eliglustat treatment group compared with an increase of 2% for

the placebo group, resulting in a statistically significant treatment difference of -30.0% (p<0.0001) (Figure 14).

Figure 14: Mean reduction in spleen volume at 39 weeks in the ENGAGE study

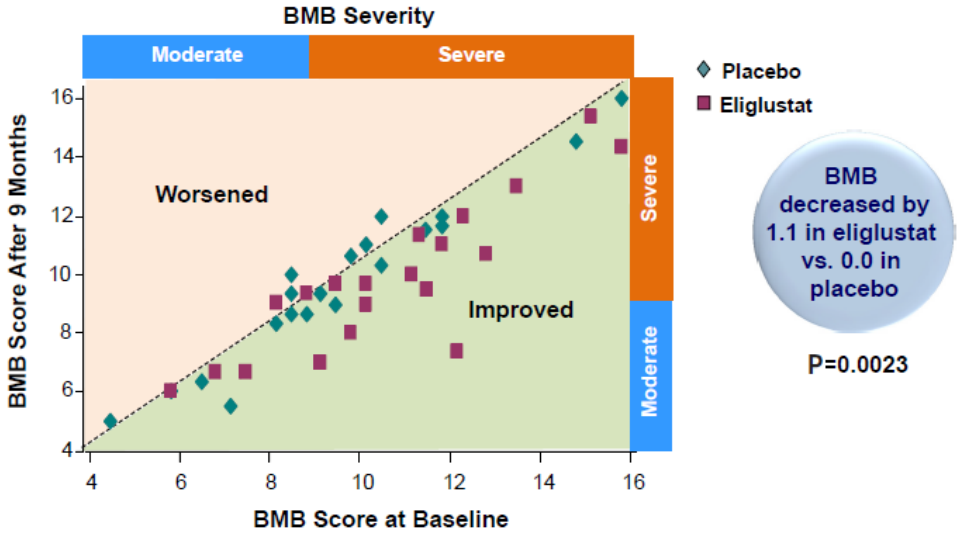


Key: MN, multiples of normal; SEM, standard error of the mean.
Source: Mistry et al. 2015.[9]

Eliglustat demonstrated superior efficacy compared with placebo on all secondary efficacy endpoints. Furthermore, 19 of 20 patients in the eliglustat treatment group met one (n=8), two (n=9) or three (n=2) of the 1-year therapeutic goals established for Gaucher patients.[35, 54]

BMB scores decreased significantly with eliglustat therapy compared with placebo. A total of five eliglustat patients having at least a 2-point (clinically significant) reduction in total BMB score, and three patients had a shift in BMB category from marked/severe to moderate bone marrow infiltration (Figure 15).

Figure 15: Improvement in BMB score in the ENGAGE study



Key: BMB, Bone marrow burden.
Source: Dasouki et al. 2013.[84]

Phase II study

The results of the Phase II study are summarised in Table 19.

Table 19*:* Phase II study results

Study name		**NCT00358150**	
Size of study groups		**Treatment (eliglustat)**	N=26
		Control	NA
Study duration		**Time unit**	52 weeks with extension phase to 4 years
Primary outcome – improvement to Year 1 in at least 2 of the 3 main efficacy parameters (spleen volume, haemoglobin level and platelet count)			
		Eliglustat (n=26)	
Improvement to Year 1, n (%), [95% CI]	ITT patients (n=26)	20 (77) [58 – 89]	
	Completer patients (n=22)	20 (91) [72 - 98]	
Improvement to Year 2, n (%)	ITT patients (n=20)	17 (85)[a]	
Secondary outcome – changes over time in the main efficacy parameters			
Change in haemoglobin levels (g/dL)	Year 1 (n=26)	+1.62 (p<0.001)	
	Year 2 (n=20)	+2.1	
	Year 4 (n=19)	+2.3 (p<0.0001)	
Percentage	Year 1 (n=26)	+40.3 (p<0.001)	

change in platelet count (n/mm^3)	Year 2 (n=20)		+81
	Year 4 (n=19)		+95 (p<0.0003)
Percentage change in spleen volume (MN)	Year 1 (n=26)		-38.5 (p<0.001)
	Year 2 (n=20)		-52
	Year 4 (n=19)		-63 (p<0.0001)
Percentage change in liver volume (MN)	Year 1 (n=26)		-17.0 (p<0.001)
	Year 2 (n=20)		-24
	Year 4 (n=19)		-28 (p<0.0001)
Secondary outcome – changes in bone-related outcomes			
	Bone Mineral Density, mean (SD)		
	Baseline	Timepoint	Change
Lumbar spine (n=19)			
Z-score	-1.41 (0.99)	Year 1: -1.10 (0.99)	0.31 (0.46), P=0.01
		Year 2: NR	0.6 (0.7), p=0.003
		Year 4: -0.48 (1.1)	
T-score	-1.69 (1.07)	Year 1: -1.36 (1.00)	0.33 (0.50), P=0.01
		Year 2: NR	0.6 (0.8), p=0.012; 7.8% change from baseline
		Year 4: -0.9 (1.3)	0.8, p=0.014; 9.9% change from baseline
Femur (n=18)			
Z-score	-0.04 (0.75)	Year 1: -0.03 (0.77)	0.01 (0.40), P=0.95
		Year 2: NR	-0.1 (0.4)
		Year 4: 0.48 (0.8)	
T-score	-0.29 (0.87)	Year 1: -0.32 (0.91)	-0.03 (0.38), P=0.72
		Year 2: NR	0.0 (0.3)
		Year 4: 0.13 (1.0)	NR
Bone crises	None	Year 1: None	No change
		Year 2: None	No change
		Year 4: None	No change
Bone lesions	13 lesions in femurs of 8 of 19 patients (42%)	Year 4: 42% (4/19)	No change
Bone infarctions	12 infarctions in 7 of 19 patients (37%)	Year 4: Improvement of 2 of 4 infarctions in one patient; all other infarctions were stable	N/A
Secondary outcome – median changes in biomarker-related outcomes			

	Baseline	Timepoint	Percentage Change
Chitotriosidase (normal range <15 to 181nmol/h/mL)	8084nmol/h/mL	Year 1: NR	- 51%
		Year 2: NR	- 75%
		Year 4: 1394	- 82%, p<0.0001
CCL18 (normal range: 17 to 246ng/mL)	3560ng/ml	Year 1: NR	- 55%
		Year 2: NR	- 75%
		Year 4: 475.5	- 82%, p<0.0001
GL1 (normal range: <2.0 to 6.6µg/mL)	12.15µg/mL	Year 1: 2.03	NR
		Year 4: 2.0	80%, p<0.001
GM3 (normal range: 5.0 to 9.2µg/mL)	19.4µg/mL	Year 1: 7.08	NR
		Year 4: 5.9	74%,

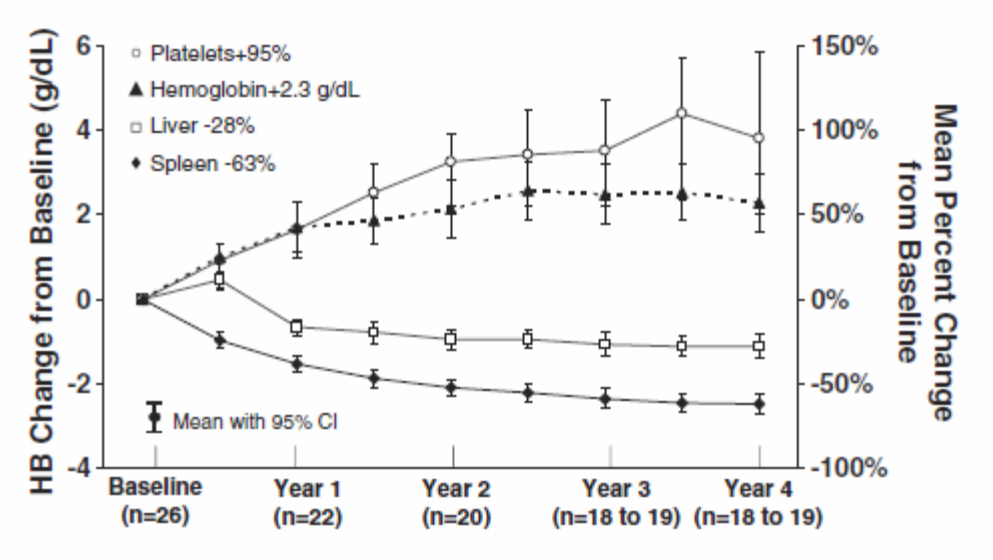
Key: BMD, bone mineral density; CI, confidence interval; GL1, glucosylceramide; GM3, ganglioside; ITT, intention-to-treat; NR, not reported; MN, multiples of normal; SD, standard deviation.

Notes: [a], at least 3 of the 4 therapeutic goals

Sources: Lukina et al., 2010a;[11, 12, 98, 102] Lukina et al., 2014;[11, 12, 98, 102] Lukina et al., 2010b;[11, 12, 98, 102] Kamath et al., 2014[11, 12, 98, 102]; Genzyme, 2012[101].

Improvements in haemoglobin, platelet counts, and liver and spleen volumes were maintained throughout 4 years of treatment demonstrating the long-term efficacy of eliglustat (Figure 16). At 4 years, 100% of patients met therapeutic goals for spleen volume and haemoglobin level, 94% met the goal for liver volume and 47% met the goal for platelet count.

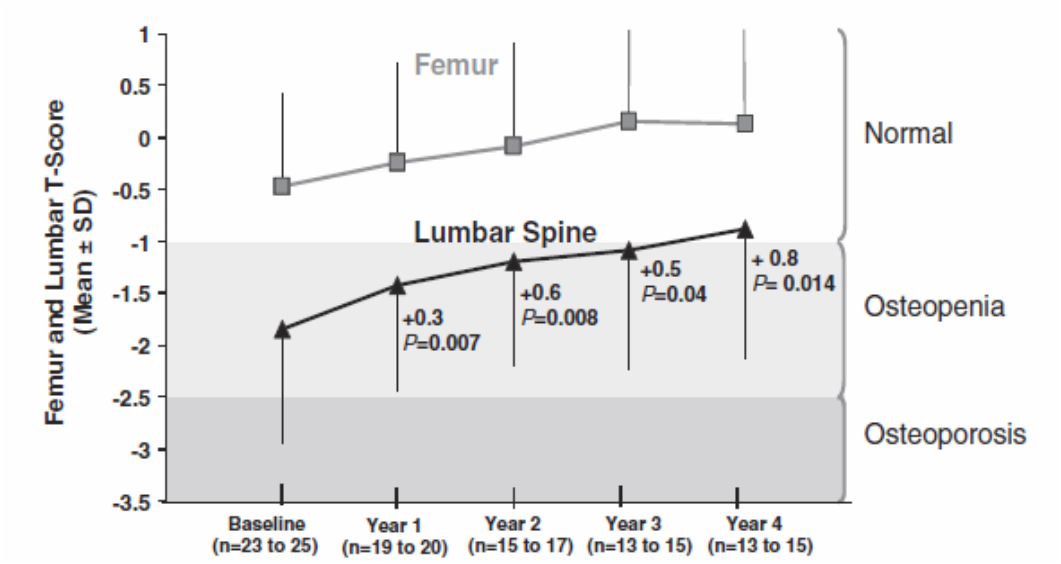
Figure 16: Change in haemoglobin, platelet counts, liver and spleen volumes over 4 years



Key: HB, haemoglobin.
Source: Lukina et al. 2014[12].

At Year 2, mean lumbar spine BMD increased by 7.8% for the 16 patients with bone data available while femur BMD remained normal. By Year 4, lumbar spine BMD increased by 9.9% moving the T-score into the normal range for the 15 patients with evaluable bone data (Figure 17). No bone crises were reported for the duration of the trial and long-term eliglustat treatment maintained improvements in both osseous and marrow bone compartments.

Figure 17: Mean lumbar spine BMD improvement after 4 years of treatment with eliglustat



Key: BMD, bone mineral density; SD, standard deviation.
Source: Lukina et al. 2014.[12]

Chitotriosidase and Chemokine (CC motif) ligand 18 (CCL18) decreased by a median 35% to 50% at Year 1 and had decreased from baseline by a median of 75% at Year 2. After four years of treatment these improvements were sustained with median decreases of 82% ($p<0.0001$). Further exploratory biomarkers were normalised at 6 months and remained normal throughout the study.[12]

9.6.2 Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.

The outcomes were not summarised in one table alone; therefore, our response to this questions relates to all the data presented in Section 9.6.1.

The results quoted in Section 9.6.2 for the ENCORE trial are from analyses based on the per-protocol population. As is typical for non-inferiority studies, the per-protocol population was the primary analysis population used in the evaluation of efficacy. The full analysis set (i.e. ITT population which included all patients who signed informed consent and received at least 1 dose of study drug) comprised 106 and 53 patients in each arm, respectively. The per protocol set (patients in the full analysis set who were ≥80% compliant with treatment during the primary analysis period, had no major protocol deviations expected to interfere with the assessment of efficacy as defined in the statistical analysis plan, and did not exhibit haematological decline as a result of medically determined aetiologies other than Gaucher disease) included 99 patients in the eliglustat arm and 47 in the imiglucerase arm.

For ENGAGE, the intention-to-treat population (equivalent to the full analysis set) was used for analyses of all outcomes.

For the Phase II study, the intention-to-treat population (equivalent to the full analysis set) was used for analyses of all outcomes.

9.7 Adverse events

9.7.1 Using the previous instructions in Sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

Three relevant RCTs of eliglustat were identified in the systematic review along with a Phase II study of eliglustat. These have been described previously in Section 9.1. Please refer to Section 9.1, 9.2 and 9.3 for the methodology and results of this review, Section 9.4

for details of the included eliglustat trials, and Section 9.5 for a critical appraisal of each of the eliglustat trials.

The main eliglustat trials were not designed primarily to assess safety outcomes. However, safety was assessed in the three Phase III trials (ENCORE, ENGAGE and EDGE) and the long-term Phase II trial as a secondary outcome. Furthermore, the ENCORE trial was a large-scale trial (160 patients randomised) studied over a relatively long period (52 weeks, followed by an extension period of a minimum of a further 52 weeks), and as such, provides a very strong and robust safety data evidence base in the context of Gaucher disease.

9.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table C10.

ENCORE

A summary of TEAEs occurring in ≥10% of patients in the primary analysis period and in the extension period of ENCORE is presented in Table 20. The majority of TEAEs in all treatment groups were non-serious with 90% of eliglustat patients and 100% of imiglucerase patients experiencing no serious TEAEs. Few patients experienced severe TEAEs; in the initial 52 weeks, 12% of eliglustat patients and 8% of imiglucerase patients experienced severe TEAEs. Overall, in the 104-week period, 22% of patients receiving eliglustat experienced severe TEAEs, and 6% of the imiglucerase-to-eliglustat group from Week 52 to Week 104.[72, 78]

During the initial 52-week period, SAEs were reported in 11 patients (10%) in the eliglustat group, although none of these were considered treatment related and no SAEs were reported in the imiglucerase group.[78] Including the extension period, SAEs were reported in 18 patients (17%) receiving eliglustat, and three patients (6%) in the imiglucerase-to-eliglustat group from Week 52 to Week 104.[82] Overall, two SAEs (in the extension period, with eliglustat) were considered possibly related to study drug (peripheral neuropathy and bowel obstruction-bowel resection).[72,82]

In the 52-week period, two eliglustat patients (2%) and one imiglucerase patient (2%) discontinued the study, while during the whole 104-week period, a total of five eliglustat patients (5%) and four imiglucerase-to-eliglustat patients (8%) discontinued.[72,82] There were no deaths in either treatment arm throughout the whole study period.[10]

Table 20: ENCORE TEAEs occurring in ≥10% of patients, n (%) (based on table C10 in NICE HST template)

MedDRA SOC Preferred Term	Primary analysis period (52 weeks)		Extension period (104 weeks)	
	Eliglustat (n=106)	Imiglucerase (n=53)	Eliglustat (n=106)	Imiglucerase-to-eliglustat (Weeks 52 to 104) (n=51)
Patients with any TEAE	97 (92)	42 (79)	101 (95)	42 (82)
SAEs	11 (10)	0 (0)	18 (17)	3 (6)
Deaths	0	0	0	0
AEs leading to study discontinuation	2 (2)	1 (2)	5 (5)	4 (8)
Infections and infestations	59 (56)	19 (36)	74 (70)	21 (41)
Nasopharyngitis	11 (10)	5 (9)	18 (17)	6 (12)
Upper respiratory tract infection	11 (10)	4 (8)	17 (16)	5 (10)
Influenza	6 (6)	2 (4)	15 (14)	4 (8)
Sinusitis	11 (10)	1 (2)	17 (16)	3 (6)
Urinary tract infection	5 (5)	5 (9)	12 (11)	2 (4)
Gastrointestinal disorders	57 (54)	10 (19)	69 (65)	21 (41)
Abdominal pain upper	11 (10)	0 (0)	19 (18)	2 (4)
Nausea	13 (12)	0 (0)	16 (15)	5 (10)
Diarrhoea	13 (12)	2 (4)	17 (16)	2 (4)
Abdominal pain	4 (4)	0 (0)	11 (10)	5 (10)
Dyspepsia	7 (7)	2 (4)	12 (11)	2 (4)
Musculoskeletal and connective tissue disorders	41 (39)	17 (32)	56 (53)	18 (35)
Arthralgia	16 (15)	9 (17)	29 (27)	10 (20)
Back pain	13 (12)	3 (6)	20 (19)	2 (4)
Pain in extremity	12 (11)	1 (2)	16 (15)	2 (4)
Nervous system disorders	37 (35)	5 (9)	49 (46)	16 (31)
Headache	14 (13)	1 (2)	22 (21)	7 (14)
Dizziness	9 (8)	0 (0)	15 (14)	3 (6)

MedDRA SOC Preferred Term	Primary analysis period (52 weeks)		Extension period (104 weeks)	
	Eliglustat (n=106)	Imiglucerase (n=53)	Eliglustat (n=106)	Imiglucerase-to-eliglustat (Weeks 52 to 104) (n=51)
General disorders and administration site conditions	29 (27)	5 (9)	35 (33)	11 (22)
Fatigue	15 (14)	1 (2)	18 (17)	4 (8)
Investigations	24 (23)	10 (19)	36 (34)	7 (14)
Blood CPK increased	7 (7)	1 (2)	13 (12)	1 (2)
Injury, poisoning and procedural complications	21 (20)	6 (11)	39 (35)	6 (12)
Respiratory, thoracic and mediastinal disorders	20 (19)	2 (4)	35 (33)	11 (22)
Skin and subcutaneous tissue disorders	16 (15)	2 (4)	25 (24)	9 (18)
Hepatobiliary disorders	5 (5)	7 (13)	8 (8)	2 (4)
Cardiac disorders	9 (8)	1 (2)	15 (14)	6 (12)
Reproductive system and breast disorders	11 (10)	2 (4)	17 (16)	3 (6)
Eye disorders	8 (8)	4 (8)	15 (14)	1 (2)
Psychiatric disorders	5 (5)	3 (6)	15 (14)	2 (4)
Blood and lymphatic system disorders	7 (7)	3 (6)	12 (11)	2 (4)
Ear and labyrinth disorders	8 (8)	0 (0)	11 (10)	4 (8)

Key: AE, adverse event; CPK, creatine phosphokinase; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event.
Source: Cox et al., 2015[10]; Cox et al., 2015[82]; Genzyme, 2014.[72]

ENGAGE

A summary of TEAEs occurring in ≥10% of patients in the primary analysis period and in the extension period of ENGAGE is presented in Table 21. Overall, there were no deaths or AE-related discontinuations in either treatment arm over the entire study period. In the initial 39-week period, no SAEs were reported. All TEAEs reported in the 39-week period

were mild or moderate with most being considered as unrelated to study drug, with the most common being headache, arthralgia and diarrhoea.

In the extension study, two patients (11%) receiving eliglustat experienced severe TEAE, and no patients in the placebo-to-eliglustat group experienced a severe TEAE.[52] In the extension period, one patient (5%) experienced two SAEs (atrioventricular block and atrioventricular block second degree), which were mild, resolved, did not lead to study discontinuation, and were considered to have a probable relationship to study drug.

Table 21: TEAEs occurring in ≥10% patients in at least one treatment group in the ENGAGE study, n (%) (based on table C10 in NICE HST template)

MedDRA SOC Preferred Term	Primary analysis period (39 weeks)		Extension period (78 weeks)	
	Placebo (n=20)	Eliglustat (n=20)	Placebo-to-eliglustat (n=20)	Eliglustat (n=20)
Patients with any TEAE	14 (70)	18 (90)	17 (85)	19 (95)
SAEs	0 (0)	0 (0)	0 (0)	1 (5)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)
AEs leading to study discontinuation	0 (0)	0 (0)	0 (0)	0 (0)
Infections and infestations	9 (45)	9 (45)	11 (55)	11 (55)
Upper respiratory tract infection	4 (20)	1 (5)	4 (20)	4 (20)
Nasopharyngitis	0 (0)	3 (15)	0 (0)	4 (20)
Ear infection	2 (10)	0 (0)	3 (15)	0 (0)
Sinusitis	1 (5)	2 (10)	2 (10)	2 (10)
Influenza	2 (10)	0 (0)	2 (10)	1 (5)
Otitis media	NR	NR	0 (0)	2 (10)
Gastrointestinal disorders	8 (40)	9 (45)	11 (55)	12 (60)
Diarrhoea	4 (20)	3 (15)	5 (25)	4 (20)
Abdominal pain	2 (10)	1 (5)	3 (15)	3 (15)
Toothache	3 (15)	1 (5)	3 (15)	2 (10)
Gastroesophageal reflux disease	NR	NR	3 (15)	1 (5)
Vomiting	2 (10)	1 (5)	3 (15)	1 (5)
Abdominal distension	1 (5)	0 (0)	1 (5)	2 (10)
Abdominal pain upper	1 (5)	0 (0)	2 (10)	1 (5)

MedDRA SOC Preferred Term	Primary analysis period (39 weeks)		Extension period (78 weeks)	
	Placebo (n=20)	Eliglustat (n=20)	Placebo-to-eliglustat (n=20)	Eliglustat (n=20)
Dyspepsia	0 (0)	1 (5)	2 (10)	1 (5)
Flatulence	1 (5)	2 (10)	1 (5)	2 (10)
Nausea	1 (5)	2 (10)	1 (5)	2 (10)
Nervous system disorders	6 (30)	11 (55)	7 (35)	11 (55)
Headache	6 (30)	8 (40)	7 (35)	10 (50)
Dizziness	2 (10)	1 (5)	2 (10)	1 (5)
Migraine	0 (0)	2 (10)	0 (0)	3 (15)
Musculoskeletal and connective tissue disorders	6 (30)	9 (45)	7 (35)	10 (50)
Arthralgia	2 (10)	9 (45)	4 (20)	9 (45)
Back pain	1 (5)	0 (0)	2 (10)	2 (10)
Bone pain	1 (5)	1 (5)	2 (10)	2 (10)
Pain in extremity	1 (5)	0 (0)	2 (10)	1 (5)
Myalgia	0 (0)	1 (5)	0 (0)	2 (10)
Respiratory, thoracic, and mediastinal disorders	5 (25)	6 (30)	6 (30)	9 (45)
Cough	2 (10)	0 (0)	2 (10)	1 (5)
Epistaxis	1 (5)	1 (5)	1 (5)	2 (10)
Oropharyngeal pain	1 (5)	2 (10)	1 (5)	2 (10)
Nasal congestion			0 (0)	2 (10)
Nasal obstruction	0 (0)	2 (10)	0 (0)	2 (10)
General disorders and administration site conditions	4 (20)	7 (35)	5 (25)	9 (45)
Fatigue	2 (10)	1 (5)	3 (15)	2 (10)
Asthenia	1 (5)	1 (5)	1 (5)	2 (10)
Oedema peripheral	0 (0)	1 (5)	0 (0)	2 (10)
Pyrexia	0 (0)	2 (10)	0 (0)	2 (10)
Injury, poisoning and procedural complications	4 (20)	4 (20)	5 (25)	5 (25)
Contusion	3 (15)	2 (10)	3 (15)	2 (10)
Skin and subcutaneous tissue disorders	3 (15)	3 (15)	6 (30)	5 (25)

MedDRA SOC Preferred Term	Primary analysis period (39 weeks)		Extension period (78 weeks)	
	Placebo (n=20)	Eliglustat (n=20)	Placebo-to-eliglustat (n=20)	Eliglustat (n=20)
Acne	1 (5)	1 (5)	1 (5)	2 (10)
Pruritus	2 (10)	0 (0)	3 (15)	0 (0)
Rash	0 (0)	1 (5)	2 910)	0 (0)
Investigations	1 (5)	3 (15)	4 (20)	5 (25)
Blood creatine phosphokinase (CPK) increased	0 (0)	0 (0)	2 (10)	1 (5)
Cardiac disorders	1 (5)	1 (5)	4 (20)	2 (10)
Palpitations	1 (5)	0 (0)	3 (15)	0 (0)
Metabolism and nutrition disorders	3 (15)	1 (5)	4 (20)	1 (5)

Key: CPK, creatine phosphokinase; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event.

Notes: *Values are not reported in source table of ≥10% frequency.

Source: Genzyme, 2013[52]; Mistry et al., 2015[9]

Long-term safety data from Phase II study

The Phase II study described in Section 9.4 reported long-term safety data in patients receiving eliglustat over 4 years.[12] These data showed that the doses of 50mg or 100mg of eliglustat BID were generally well tolerated in the GD1 patient population.

After 4 years, a total of 191 TEAEs were reported in 23 patients, of which 74% were classified as mild and 95% were assessed as unrelated to treatment.[12] Ten related TEAEs, all of which were mild, were reported in eight patients (Table 22); each related AE occurred in one or two patients.[12] All three patients who had peripheral nerve TEAEs considered related to treatment were asymptomatic and had discordant neurological exam and nerve conduction findings; all continued eliglustat treatment.[12] Most related TEAEs (7/10) occurred during the first 74 days of treatment.[12]

Table 22: Treatment-related adverse events over 4 years in the eliglustat Phase II study (ITT) (based on table C10 in NICE HST template)

MedDRA Preferred Term	Patients reporting AE, n*
Non-sustained ventricular tachycardia**	1
Diarrhoea	2
Headache	1
Palpitations	1
Abdominal pain	2
Abnormal nerve conduction studies	2
Peripheral neuropathy	1

Key: AE, adverse event; ITT, intention-to-treat; MedDRA, Medical Dictionary for Regulatory Activities.

Notes: * Ten drug-related AEs reported in eight patients; **Occurred on study day 1; although this AE was mild in intensity, it was assessed as serious because of prolonged hospitalisation, which was uneventful; all other events were non-serious.

Source: Peterschmitt et al., 2012[106]

Over 4 years, five SAEs were reported in three patients, all during the first year of treatment[12]: one spontaneous abortion and three radiation exposures in two pregnant patients were considered unrelated to treatment, and one episode of mild, asymptomatic non-sustained ventricular tachycardia (NSVT) in a 60-year-old man, considered possibly treatment related, was assessed as serious because of hospitalisation for continuation of cardiac telemetry monitoring.[11, 12, 98, 102] No deaths occurred during the 4 years of the Phase II study.[12] Over 4 years, there were seven discontinuations; four in the first year (two due to pregnancy and two due to asymptomatic nonsustained ventricular tachycardia after one dose), two during the second year (pregnancy and bone lesion) and one during the third year (administrative).[12]

Pooled safety analysis

A pooled safety analysis was conducted using data from 393 patients with GD1 who received eliglustat in the clinical trial programme.[5] The analysis included 26 patients enrolled in the Phase II trial, 40 patients from ENGAGE (primary study period and extension), 159 patients from the ENCORE study (primary study period and extension), and 175 patients from the open-label lead-in period of the ongoing EDGE study (date cut-off: 31 January 2014). As such, this analysis includes patients who received placebo or imiglucerase in the randomised primary analysis period and eliglustat in the long-term treatment period.[73] The safety analysis represents 535 patient-years of treatment experience, with 14 patients receiving eliglustat for over 5 years. The number of patients

receiving eliglustat at any dose by duration is presented in Table 23 below. The mean (SD) duration of treatment in the pooled safety population is 1.4 (1.2) years.

Table 23: Eliglustat exposure by duration

Eliglustat exposure (months)	Number of patients
<6 months	44
≥6 months	349
≥1 year	204
≥2 years	62
≥4 years	19
≥5 years	5
Source: Adapted from Ross et al., 2013[73]	

The majority of patients (76%) had an AE onset within the first 6 months of treatment.[107] Across the pooled safety population, most patients experienced TEAEs that were mild or moderate in severity (78% of patients had at least one mild event and 44% of patients had at least one moderate event), with 45 patients (11%) experiencing severe TEAEs. There were no treatment-emergent deaths. Across the programme of eliglustat trials, a total of five deaths were reported.[71] In all cases, the events leading to the deaths were considered not related to eliglustat, and three of the deaths were not during treatment.[71] Two patients in EDGE died while on eliglustat treatment (one due to multiple severe traumas following a downhill skiing accident after completion of the lead-in period, and another from cardiac arrest due to haemorrhaging and massive blood loss from unspecified violence after the 31 Jan 2013 cut-off date and after completion of the lead-in period; both were considered unrelated to study drug treatment).[71]

A total of 35 patients (9%) experienced 42 SAEs, most of which were due to hospitalisations for intercurrent illnesses (e.g. appendicitis) and underlying diseases for which GD patients are at increased risk (e.g. femur fracture, joint dislocation, hepatocellular carcinoma, and cholecystitis.[71] The most frequently reported SAE was syncope, reported in five patients. These events were vasovagal in nature with predisposing risk factors (i.e. blood draw, fasting conditions and pain), and none led to permanent discontinuation from the study. Unscheduled electrocardiograms (ECGs), obtained as part of post-event diagnostic testing, did not reveal any cardiac arrhythmias or increase in ECG intervals as the potential cause for these syncopal events. These syncopal SAEs were severe in four patients, and were considered at least possibly related

to eliglustat in three patients. Other SAEs occurring in more than one patient included myocardial infarction in four patients (one was changed to angina in late-breaking safety reports). All of these patients had pre-existing risk factors for myocardial infarction. In each case, the investigator assessed these events as not related or as remote/unlikely related to eliglustat.[71]

Twelve patients (3%) in the pooled safety analysis experienced TEAEs leading to permanent study drug discontinuation, with 10 of the TEAEs considered possibly or probably related to eliglustat.[5] These TEAEs included ventricular tachycardia; lethargy and exfoliative rash in the same patient; upper abdominal pain; palpitations; and nausea, headache, and anaemia in the same patient.[71]

A summary of TEAEs is presented in Table 24.[73]

Table 24: Summary of TEAEs and SAEs in eliglustat trials

Parameter	Value	Patients (n=393), n (%*)
Patients with any AE		334 (85)
Related to eliglustat		159 (40)
Severity	Mild	308 (78)
	Moderate	171 (44)
	Severe	45 (11)
Study discontinuation		12 (3)
Patients with SAE		35 (9)
Related to eliglustat		5 (1)
Severity	Mild	6 (2)
	Moderate	11 (3)
	Severe	19 (5)

Key: AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Notes: *Patients could experience TEAEs or SAEs in one or more categories.
Source: Mankoski et al., 2013[5]; Ross et al., 2013[73]; Ross et al., 2014[107]

The most common TEAEs occurring in ≥5% of patients in the pooled safety analysis presented in Table 25. The most common system organ classes reported in the pooled set were similar to the pattern for each individual study.

Table 25: Most common TEAEs occurring ≥5% of patients

MedDRA SOC **Preferred term**	**Patients (n=393), n (%*)**
Patients with events	334 (85)
Infections & Infestations	184 (47)
Nasopharyngitis	53 (13)
Upper respiratory tract infection	43 (11)
Influenza	23 (6)
Sinusitis	23 (6)
Urinary tract infection	23 (6)
Gastrointestinal disorders	163 (41)
Diarrhoea	39 (10)
Abdominal pain upper	33 (8)
Nausea	33 (8)
Dyspepsia	28 (7)
Abdominal pain	25 (6)
Constipation	23 (6)
Gastroesophageal reflux disease	20 (5)
Nervous system disorders	136 (32)
Headache	66 (17)
Dizziness	38 (10)
Musculoskeletal and connective tissue disorders	125 (32)
Arthralgia	55 (14)
Back pain	35 (9)
Pain in extremity	31 (8)
Bone pain	18 (5)
General disorders and administration site conditions	88 (22)
Fatigue	29 (7)
Respiratory, thoracic and mediastinal disorders	81 (21)
Cough	23 (6)
Investigations	75 (19)
Blood creatine phosphokinase increased	18 (5)
Skin and subcutaneous tissue disorders	63 (16)
Injury, poisoning, and procedural complications	57 (15)
Cardiac disorders	41 (10)
Palpitations	20 (5)
Reproductive system and breast disorders	32 (8)

MedDRA SOC Preferred term	Patients (n=393), n (%*)
Blood and lymphatic system disorders	24 (6)
Psychiatric disorders	23 (6)
Vascular disorders	20 (5)
Renal and urinary disorders	19 (5)

Key: MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class; TEAE, treatment-emergent adverse event.

Notes: * Patients could experience AEs in one or more categories.

Source: Mankoski et al., 2013[5]; Ross et al., 2013[73]; Ross et al., 2014[107]

The overall results of the pooled safety analysis demonstrate that eliglustat was generally well-tolerated, with few patients (3%) discontinuing treatment due to AEs. Most patients reported TEAEs as mild (78%) or moderate (44%), and in 79% of patients TEAEs were considered not related to eliglustat treatment. The most common TEAEs in the pooled safety analysis were headache (17%), arthralgia (14%), nasopharyngitis (13%), upper respiratory tract infection (11%), diarrhoea (10%), and dizziness (10%), most of which were mild events. The clinical development programme for eliglustat is the largest for GD1, and the pooled AE profile in this safety analysis demonstrates that eliglustat was generally well-tolerated.[107]

The TEAEs in the pooled safety set were also analysed by metaboliser status.[71] The proportions of patients with poor and intermediate metaboliser status who experienced TEAEs at any dose (79% and 73%, respectively) was lower than that observed for those with extensive metaboliser status (88%).

Drug interactions

Eliglustat is metabolised primarily by CYP2D6 and to a lesser extent by CYP3A4, and is also an inhibitor of P-gp and CYP2D6 in vitro. As a result, potential drug interactions need to be considered when administering eliglustat.[1]

Eliglustat is contraindicated in patients with CYP2D6 IM or EM status who are taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor, and in patients with PM status who are taking a strong CYP3A inhibitor. Use of eliglustat under these conditions results in substantially elevated eliglustat plasma concentrations.

For concomitant use of a strong CYP2D6 inhibitor (e.g. paroxetine, fluoxetine, quinidine, bupropion), in patients with EM or IM status, a dose of 100mg eliglustat QD is

recommended. For concomitant use of moderate CYP2D6 inhibitors (e.g. duloxetine, terbinafine, moclobemide, mirabegron, cinacalcet, dronedarone) in patients with EM or IM status, caution should be used because of the associated rises in eliglustat exposure.

In addition, concomitant administration with strong CYP3A inhibitors (e.g. clarithromycin, ketoconazole, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir) and moderate CYP3A inhibitors (e.g. erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine) also increase eliglustat exposure in patients with EM and IM status; as such, caution should be used with strong and moderate CYP3A inhibitors in these patients. In patients with PM status, the use of strong CYP3A inhibitors is contra-indicated, moderate CYP3A inhibitors not recommended, and weak CYP3A inhibitors (e.g. amlodipine, cilostazol, fluvoxamine, goldenseal, isoniazid, ranitidine, ranolazine) should be used with caution. Grapefruit products, which contain CYP3A inhibitors, should also be avoided.

Conversely, strong CYP3A inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, rifabutin and St. John's wort) may decrease eliglustat exposure and as such, concomitant use of strong CYP3A inducers is not recommended in patients with EM, IM or PM status.

Eliglustat also interacts with some substances in a manner that actually affects their exposure. Since eliglustat may increase the exposure of P-gp substrates (e.g. digoxin, colchicine, dabigatran, phenytoin, pravastatin), lower doses of P-gp substrates may be recommended. Furthermore, eliglustat may also increase exposure of CYP2D6 substrates (e.g. certain antidepressants such as tricyclic antidepressants, nortriptyline, amitriptyline, and imipramine); phenothiazines, desipramine, dextromethorphan and atomoxetine, and as such, lower doses of CYP2D6 substrates may be required.

A full risk management plan is available.[108] There are no identified important risks, but there are some potentially important risks listed in the plan. Most of these risks are managed using routine risk minimisation measures, as described in the SPC. However, additional risk minimisation measures are required in the cases listed in Table 26.

Table 26: Important potential risks of eliglustat and additional risk minimisation measures

Potential risk	Objective and rationale	Additional risk minimisation measure
Interaction with other medicines that may increase or decrease the level of eliglustat in the blood, with grapefruit products, and with medicines for which eliglustat may slow down their breakdown (use with CYP2D6 and/or CYP3A inhibitors; use with strong CYP3A inducers; use with P-gp or CYP2D6 substrates)	To prevent situations that may cause large increases in eliglustat levels in the blood to very high levels and to prevent situations where eliglustat may increase the levels of other medicines in the body. Educating health care professionals and patients on what medicines, over-the-counter medicines or herbal products they cannot prescribe or should not be used together with eliglustat, and to inform patients not to consume grapefruit products.	**Healthcare professional educational material:** The guide for the prescriber includes a checklist of actions to be taken before starting treatment with eliglustat, including checking and warning for medicines that may alter the effect of eliglustat or that may be affected by eliglustat. **Patient educational material**: Patient alert card to remind the patient to consult their doctor before starting any new prescription medicine, over-the-counter medicine or herbal product. The patient alert card informs about current treatment with eliglustat and medicines that should not be prescribed or used together with eliglustat.
Use in patients whose body breaks down eliglustat at unknown speed (use of eliglustat in patients for whom the ability to break down the medicine is unknown or for whom no test has been done)	To remind healthcare professionals to determine for each patient at what speed their body breaks down eliglustat. Patients for whom the ability to break down the medicine is unknown or for whom no test has been done should not use eliglustat	**Healthcare professional educational material**: The guide for the prescriber includes a checklist of actions to be taken before starting treatment with eliglustat, including the need to determine the speed at which the patient's body breaks down eliglustat
Source: EMA, 2014[108].		

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

Overview of eliglustat safety

Safety data for eliglustat are available from 393 patients with GD1, who received eliglustat in the largest clinical trial programme to be conducted in Gaucher disease.[5] This represents 535 patient-years of safety data collected over 4 years.

Eliglustat was generally well-tolerated, with the majority of AEs being mild (78%) and transient. In 79% of patients, TEAEs were considered not related to eliglustat treatment. The most commonly reported AE with eliglustat was diarrhoea (6%), with other commonly reported TEAEs being headache, arthralgia, nasopharyngitis, upper respiratory tract infection, and dizziness, most of which were of mild severity.

Across the eliglustat studies, 9% experienced SAEs, 1% experienced eliglustat-related SAEs, and few patients (3%) discontinued treatment due to AEs. No deaths were reported. The most frequently reported SAE was syncope (0.76%). All events were associated with predisposing risk factors and appeared to be vasovagal in nature. None of these events led to discontinuation from the study.

Safety data from 535 patient years of treatment support the safety of eliglustat in treatment-naïve and ERT-stable adults with GD1 as an oral alternative to IV administered ERT.

Overview of comparator safety

Table 27 summarises AEs associated with all the relevant comparator treatments. The key common AEs related to the ERTs, imiglucerase and velaglucerase are infusion-related reactions, and antibody-mediated hypersensitivity reactions. As such, ERT should be administered with caution, and in some cases, pre-treatment with antihistamines and/or corticosteroids may be required for patients where symptomatic treatment was previously required, as recommended in the EU label for velaglucerase.[51] Conversely, eliglustat is an oral treatment that is not associated with the infusion-related reactions or hypersensitivity reactions associated with ERT. Discontinuation rates are generally low with ERTs, with rates of 1.9% for imiglucerase as reported in the 12-month ENCORE study, and 0% for velaglucerase after 9 months in one RCT.[63]

Table 27: Summary list of very common and common adverse events by treatment

Intervention	Key adverse events	
	Very common (≥1/10)	**Common (≥1/100 to <1/10)**
Imiglucerase IV	NR	Dyspnoea*, coughing*, hypersensitivity reactions, urticaria/angioedema*, pruritus*, rash* *= hypersensitivity reactions
Velaglucerase IV	Headache, dizziness, bone pain, arthralgia, back pain, infusion-related reaction, asthenia/fatigue, pyrexia/body temperature increased	Hypersensitivity reactions, tachycardia, hypertension, hypotension, flushing, abdominal pain/abdominal pain upper, nausea, rash, urticarial, activated partial thromboplastin time prolonged, neutralising antibody positive
Eliglustat	None	Common (≥2/100 to <1/10): Headache, nausea, diarrhoea*, abdominal pain*, flatulence, arthralgia, fatigue
Key: IV, intravenous; NR, not reported. **Notes:** * The incidence of the adverse reaction was the same or higher with placebo than with eliglustat in the placebo-controlled pivotal study. **Source:** Genzyme, 2009[50]; Shire 2013[51]; Actelion 2009[53]; Genzyme, 2014[1]		

9.8 Evidence synthesis and meta-analysis

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Sections 9.1 and 9.2 provide full details of the methodology of the systematic literature review which was carried out and identified one comparator head-to-head RCT, which compared imiglucerase to velaglucerase in ERT-naïve patients.[63] This trial has been used to inform a formal indirect comparison. The full details of the indirect comparison are included in Section 19.4. In summary, the indirect comparison was focused on four key outcomes; change from baseline in haemoglobin levels, platelet counts, spleen volume and liver volume. There are four treatment comparisons of interest in this decision problem, and Table 28 details if, and how, the four treatment comparisons (direct or indirect) can be made.

Table 28: Possible treatment comparison strategy

Comparison	How to construct comparison	Limitations
1. (ERT-naïve): eliglustat vs imiglucerase	Direct comparison of eliglustat and imiglucerase from ENCORE	ENCORE is in patients that are ERT-stable rather than ERT-naive
2. (ERT-naïve): eliglustat vs velaglucerase	Adjusted indirect comparison using ENCORE and Ben-Turkia (2013) and imiglucerase as the common comparator	ENCORE includes patients that are ERT-stable rather than ERT-naïve. Different doses (ranges) for imiglucerase have been used in the studies, and baseline severity (spleen measures) differ between the studies.
3. (ERT-stable/treated): eliglustat vs imiglucerase	Direct comparison of eliglustat and imiglucerase from ENCORE	None
4. (ERT-stable/treated): eliglustat vs velaglucerase	Adjusted indirect comparison using ENCORE and Ben-Turkia (2013) and imiglucerase as the common comparator	Ben-Turkia (2013) includes patients that are ERT-naïve rather than ERT-stable. Different doses (ranges) for imiglucerase have been used in the studies, and baseline severity (spleen measures) differ between the studies.
Key: ERT, enzyme replacement therapy.		

There are major limitations for three of these four treatment comparisons, due to the heterogeneity between trials, with respect to the differing treatment experience and severity of patients at baseline, as determined by trial design, and differing treatment regimens for imiglucerase between the trials. The heterogeneity in this limited evidence base is fundamental, but because we do not recommend the indirect comparisons to be used as the base-case, we have not explored heterogeneity further. However, A simple adjusted indirect comparison has been performed for illustration purposes only, to compare eliglustat with velaglucerase, using imiglucerase as the common comparator. Table 29 presents the inputs and results from the adjusted indirect treatment comparison of eliglustat versus velaglucerase at both 6 and 9 months, using ENCORE and Ben-Turkia (2013), and imiglucerase as a common comparator.

Table 29: Indirect treatment comparison of eliglustat versus velaglucerase-

	ENCORE Eliglustat – imiglucerase	Ben-Turkia, 2013 Velaglucerase - imiglucerase	Adjusted indirect comparison Eliglustat - velaglucerase
	Mean (SE)	**Mean (SE)**	**Mean (95% confidence interval)**
6 months data			
Haemoglobin (g/dL)	-0.35 (0.13)	-0.23 (0.40)	XXX (XXXXXX)
Platelet count (x10^9/L)	-0.48 (5.02)	-35.80 (24.60)	XXX (XXXXX)
Spleen volume	-0.03 (0.08)	-0.17 (0.33)	XX (XXXXXX)
Liver volume	-0.02 (0.02)	0.00 (0.19)	XX (XXXXXX)
9 months data			
Haemoglobin (g/dL)	-0.50 (0.13)	0.16 (0.39)	XX (XXXXXX)
Platelet count (x10^9/L)	-8.26 (4.85)	-38.70 (25.36)	XXXX (XXXX)
Key: SE, standard error.			

Differences between eliglustat and velaglucerase are XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX. Acknowledging the limitations of the indirect comparison, there is no evidence to suggest a difference between eliglustat and velaglucerase. This is also supported by the SOP by the Lysosomal Storage Disorder Expert Advisory Group that considers velaglucerase and imiglucerase of equivalent potency[34]; as such, it follows that if eliglustat has demonstrated non-inferiority to imiglucerase in the ENCORE trial, eliglustat is also likely to be non-inferior to velaglucerase. Although not a direct, randomised comparison, there is further evidence to support similarity of eliglustat and velaglucerase in Section 9.6.1, where the subgroup of patients switching from velaglucerase to eliglustat maintain their treatment effects.

Additional indirect comparison (non-statistical)

A post hoc comparison of imiglucerase in a real-world setting to the clinical response to eliglustat in ENGAGE and Phase II has been published.[109] Four-year data from eliglustat-treated patients in the open-label Phase II study (n=26) and 9-month data from the randomised, double-blind, placebo-controlled ENGAGE study (n=20 in the eliglustat arm) were compared with 75 matched imiglucerase-treated patients enrolled in the ICGG Gaucher Registry who had received at least 15 U/kg/2 weeks. At baseline, haematological parameters were similar between the two treatment groups but patients receiving eliglustat

had slightly larger spleen and liver volumes. Time course and degree of improvement were similar for eliglustat- and imiglucerase-treated patients for most parameters. After 4 years, mean spleen volume decreased by 63% and 48%, mean liver volume decreased by 27% and 30%, mean platelet count increased by 95% and 99%, and mean haemoglobin level (g/dL) increased by 2.27 and 0.71 in eliglustat and imiglucerase patients, respectively. Improvements in lumbar spine and femur z-scores were consistently higher in the eliglustat group at all time points; however, bone data were limited from the imiglucerase-treated patients. The z-score increases observed with eliglustat were higher than those observed by Wenstrup and colleagues (2007) during low to high-dose treatment with imiglucerase (0.06–0.13 z-score/year) in patients who had similar mean baseline bone mineral density. Although not a head-to-head trial, this post hoc analysis suggests that eliglustat, in treatment-naïve patients, results in improvements in organ volumes and haematological parameters that are comparable to those observed with imiglucerase in a real-world setting.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

This is covered in Section 9.8.1 and Section 19.4.

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

Summary of efficacy: primary evidence from clinical trials

The clinical programme for eliglustat in Gaucher disease was easily the largest conducted to date in terms of patient numbers, duration of observation and quality and completeness of data recording. It demonstrated the significant efficacy of eliglustat on all disease measures in ERT-stable patients, and treatment-naïve patients, as determined in two Phase III trials and supported by the long-term observations, particularly on bone mineral density and accepted markers of disease activity over four years in the Phase II cohort.

The head-to-head ENCORE trial reported that eliglustat met the criteria in the study to be declared non-inferior to the current standard of care, imiglucerase, in terms of maintaining patient stability (i.e. improvements in haematological and organ parameters for 1 year in adult patients with GD1 who were ERT-stable), based on the aggregate data from all doses tested in this study.[71] The primary composite endpoint (percentage of patients stable at 52 weeks) was met by 84.8% of patients on eliglustat and 93.6% on imiglucerase. Eliglustat was also non-inferior to imiglucerase in terms of percentage change in spleen volume.[71]

The placebo-controlled ENGAGE trial reported that eliglustat demonstrated clinically meaningful and statistically significant benefits versus placebo in adult treatment-naïve patients with GD1. The primary efficacy endpoint of change in spleen volume was -27.8% for the eliglustat treatment group compared with an increase of 2.3% for the placebo group, resulting in a statistically significant treatment difference ($p<0.0001$). Eliglustat also demonstrated superior efficacy compared with placebo on all secondary efficacy endpoints including change in haemoglobin levels ($p=0.0006$), percentage change in liver volume ($p=0.0072$), and percentage change in platelet counts ($p<0.0001$).

Both ENCORE and ENGAGE also reported a positive impact on bone manifestations, in both treatment-naïve patients and ERT-stable patients. As stated in the EPAR, “overall, these data demonstrate an improvement in bone marrow infiltration and BMD with eliglustat treatment in treatment-naïve patients, particularly those with more severe bone disease at baseline, and maintenance of stable bone disease in patients switched from ERT to eliglustat.”[71] In ERT-stable patients, similar results for bone endpoints were reported for eliglustat and imiglucerase. For treatment-naïve patients in the ENGAGE study, eliglustat demonstrated significant improvements in bone endpoints, including significant reductions in total BMB score, compared with placebo ($p=0.002$). After 52 weeks of treatment in ENCORE, remarkable reductions from baseline in the biomarker chitotriosidase were reported for patients receiving eliglustat and for those receiving imiglucerase. This reduction was numerically greater with eliglustat compared with imiglucerase (26.5% vs. 15.9%), helping to confirm the efficacy of eliglustat in maintaining control of the disease.

A single-arm, Phase II study of eliglustat also reported significant improvements in key haematological, organ and skeletal endpoints in treatment-naïve patients. After 1 year, 77% of patients met the composite primary endpoint of improvements in at least two of the three main disease parameters (spleen volume, haemoglobin level and platelet count). In

addition, significant reductions were reported in all individual haematological and organ endpoints (spleen volume, liver volume, platelet count and haemoglobin level). Improvements were maintained throughout 4 years of treatment demonstrating the long-term efficacy of eliglustat; 100% of patients met therapeutic goals for spleen volume and haemoglobin level, 94% met the goal for liver volume and 47% met the goal for platelet count. Significant improvements in lumbar spine BMD were seen after 1 year of treatment and continued to improve throughout the 4 years of treatment. Furthermore, these long-term data for eliglustat compare favourably to registry data for long-term ERT treatment. After 4 years of treatment, eliglustat demonstrated similar, and for some outcomes, greater improvements when compared with ERT treatment in the Gaucher Registry.[110] After 4 years of ERT, haemoglobin was increased by 2.7g/dL and 2.3g/dL (patients with spleen and without spleen, respectively), compared with a 2.3 g/dL increase with eliglustat; platelet count increased by 82% and 259% (patients with spleen and without spleen, respectively) compared with a 95% increase with eliglustat; liver volume was decreased by 38% and 50% (patients with spleen and without spleen, respectively), compared with a 28% decrease with eliglustat; and a 57% decrease in spleen volume compared with a 63% decrease with eliglustat treatment.

Indeed, based on a review of the efficacy data for eliglustat, the Committee for Medicinal Products for Human Use (CHMP) held the opinion that eliglustat is a "valuable addition to the treatment options for patients with GD type 1."[71]

Summary of indirect comparisons

Given the sizeable heterogeneity of trial design, patients, observations periods and cohort size, results from indirect treatment comparisons in this evidence base must be approached with great caution.

While acknowledging these limitations, one indirect comparison has been conducted to compare eliglustat with velaglucerase in the absence of direct head-to-head data from clinical trials for this comparison. For this indirect treatment comparison, the outcomes of interest were spleen volume, liver volume, platelet count and haemoglobin level.

The indirect comparison had the major limitation of combining trials that are fundamentally different with respect to the trial design (one trial included ERT-stable patients while the other included ERT-naïve patients). The analysis reported relatively small differences between eliglustat and velaglucerase that were XXXXXXXXXXXXXXXXXXXXX. The

significant limitations in this indirect comparison must be considered when interpreting these results.

Summary of safety

Eliglustat is well-tolerated, as determined from 535 patient-years of safety data collected over 4 years. No deaths, few discontinuations (3%), minimal SAEs (9%), and eliglustat-related SAEs (1%) were reported in the eliglustat clinical trials.

Most patients reported TEAEs as mild (78%) or moderate (44%), and in 79% of patients TEAEs were considered not related to eliglustat treatment. The most common TEAEs were headache, arthralgia, nasopharyngitis, upper respiratory tract infection, diarrhoea, and dizziness, most of which were of mild severity.

Summary of HRQL

Eliglustat has shown positive effects on HRQL, with significant improvements in the physical functioning domain of the SF-36 compared with placebo in the ENGAGE study ($p=0.01$).[111] Furthermore, in the ENGAGE study, eliglustat led to slight but consistent improvements in SF-36 scores in treatment-naïve patients, and a maintenance of HRQL was reported in ERT-stable patients in ENCORE. These benefits of eliglustat have also been observed over the long term. After 4 years of treatment in the Phase II study, eliglustat showed small but consistent improvements in SF-36 scores and reductions in the FSS score to levels similar to those of individuals without fatigue.

In the ENCORE study, patients who received eliglustat for 12 months and were questioned regarding treatment preference all confirmed a preference for oral treatment citing the reasons: convenience, the capsule form, taking the drug at home, and feeling better after treatment. Eliglustat is a convenient, oral treatment that has demonstrated improvements in HRQL and is a preferred treatment compared with IV ERT in patients with GD1. Furthermore, given that the oral administration mode of eliglustat negates the need for any hospital visits for infusions, this would subsequently reduce the initial costs associated with healthcare visits for ERT administration. Although many patients receive ERT at home, at least the first three visits must be administered in hospital for safety reasons. In addition, the absence of any infusion-related reactions with eliglustat will also avoid associated costs of management of these reactions.

Number needed to treat/Number needed to harm

It is not possible to estimate numbers needed to treat from the trial data. This would require a study which compares treatment with eliglustat to no treatment/placebo and which provides as an outcome a categorical measure of a “good” / “positive” outcome. The only placebo-controlled study within the eliglustat trial programme, ENGAGE, did not report any categorical data that could be used to estimate numbers needed to treat. Of potential relevance in considering the outcomes associated with eliglustat is that within the ENCORE study, 85% and 87% of patients achieved disease stability at 52 weeks and 104 weeks, respectively. In considering number needed to harm it is worth noting that across the pooled trial data that 3% discontinued due to AEs on eliglustat and there were no discontinuations due to AEs amongst the 20 patients in ENGAGE on placebo. This would suggest a number needed to harm of 33 in relation to AEs which cause discontinuation on eliglustat.

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

Strengths of eliglustat evidence base

Eliglustat has been investigated in the largest clinical trial programme conducted in GD1, including 393 patients and 535 patient-years of safety data collected over 4 years. Furthermore, the trials investigate eliglustat in both treatment-naïve and treatment (ERT)-stable patients, which are the two major populations in which eliglustat will be used in clinical practice.

Long-term data are available for eliglustat, over 4 years of treatment. In addition, eliglustat is also being investigated for periods of up to 6 years in extension studies which are currently ongoing.

The clinical trial programme includes the ENCORE trial, which represents a direct comparison with current standard of care, the ERT imiglucerase, in ERT-stable patients.

The two key Phase III trials, ENCORE and ENGAGE and the Phase II trial all provide data for clinically relevant endpoints, namely spleen volume, liver volume, platelet count and haemoglobin level, along with markers of bone disease. The EMA considered such endpoints as the most important in analysis of effect and “typical for studies in patients suffering from Gaucher disease.”[71] Other endpoints investigated in ENGAGE and

ENCORE are considered “useful for they give additional information on the patient’s perceived benefit of the treatment or the pharmacodynamic effect of SRT.”[71]

The clinical trial programme also captures the impact of eliglustat on HRQL on several measures including the generic measure, SF-36.

An indirect comparison has been conducted to compare eliglustat with velaglucerase. However, results must be interpreted with caution because of the differences between the patient populations in the trials being analysed.

Limitations of eliglustat evidence base

Eliglustat has not been directly compared versus velaglucerase, although an indirect comparison has been conducted.

There is no direct evidence comparing eliglustat versus imiglucerase in treatment-naïve patients. The CHMP also acknowledged this. As stated in the EPAR, the manufacturer “explored the possibility of a non-inferiority study for such a study that would address the issue of the efficacy of eliglustat compared to imiglucerase in the best possible way.” Given that such a study would need at least 76 patients to gain sufficient power, and because of the rareness of the disease, the CHMP agreed that this is not considered feasible.[71] However, some comparative data have been published in which results in treatment-naïve patients treated with eliglustat in ENGAGE and the Phase II study were compared with patients treated with imiglucerase in the ICGG Gaucher Registry.[109]

The indirect comparison of eliglustat versus velaglucerase had substantial limitations because of the different patient populations that were combined in the analysis. In this analysis, one trial in ERT-stable patients was combined with another in ERT-naïve patients. These limitations are described in more detail in Section 9.8.1. Given the extensive limitations/heterogeneity within the network for the indirect treatment comparison, the use of these data to inform the economic analysis is limited, and they are not recommended for use within the base-case.

Finally, there are no data available on the impact of eliglustat on carers; this would be useful to explore.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The evidence base for eliglustat addresses the scope with the exception of the exclusion of miglustat from this submission. Miglustat is not considered a relevant comparator for eliglustat in this submission as it is used in a very small proportion of adult GD1 patients in England for whom ERT is unsuitable (i.e., unwilling or unable to receive ERT; (<2% in 2013).

The ENCORE study was a head-to-head trial with the ERT imiglucerase, which is reflective of standard of care in the UK. The trial was conducted in ERT-stable patients to directly compare eliglustat with imiglucerase, which represents the main positioning of eliglustat in the treatment pathway; i.e. patients who are ERT-stable but switch to eliglustat because of a preference for oral therapy or because they are failing on ERT. Within ENCORE, patients were initiated on eliglustat 50mg BID, but received intermittent dose increases to 100mg and later to 150mg, if needed, based on their plasma trough concentration. At the end of the protocol-defined titration period, 32% of patients in the eliglustat arm received 100mg BID, in line with the licensed dose.

Both the Phase III trials, ENCORE and ENGAGE, as well as the Phase II trial all provide data relating to the Gaucher therapeutic goals for anaemia (haemoglobin level), thrombocytopenia (platelet levels), hepatomegaly (liver volume), splenomegaly (spleen volume), skeletal pathology (BMD, bone crises, bone pain, and mobility), and functional health and well-being (SF-36, FSS, Brief Pain Inventory [BPI]), in line with the clinical guidance for England[34] and more widely recognised therapeutic goals.[54] The therapeutic goal of pulmonary involvement was not measured in the trials; however, pulmonary manifestations are infrequent in GD1 (<5%).[112] The primary efficacy evidence (ENCORE, ENGAGE, Phase II trial) included outcomes measuring the direct clinical benefits experienced by patients in terms of bone manifestations, in terms of reducing bone crises, and bone pain and associated improvements in mobility. Bone manifestations are considered to be an area of unmet need in these patients, particularly in light of evidence of persistent bone complications in patients treated with ERT. For example, one study of 1,028 patients in the Gaucher Registry revealed that 48% of patients with pre-treatment bone pain or bone crises, continued with some pain after 2 years of ERT therapy, while 6% reported additional bone crises.[110] Furthermore, a UK cohort study has also been conducted to specifically assess the residual bone disease in Gaucher patients despite

receiving ERT (imiglucerase or alglucerase).[23] The study included 100 patients, of which 92 had been receiving ERT at a median dose of 30U/kg every 4 weeks for a mean of 8.5 years. Despite ERT treatment, many patients reported bone manifestations, including Erlenmeyer flask deformity (59%), osteonecrosis (43%), mobility problems (32%), fragility fractures (23%), and osteomyelitis (6%).[23]

The primary evidence base also included HRQL measures in terms of the generic instrument, SF-36, as well as specific instruments to measure fatigue (FSS), and pain (BPI). Incorporating these instruments in the trials allowed the measurement of key symptoms to help understand the impact of eliglustat on the Gaucher disease patient experience. Furthermore, patients who received eliglustat within the ENCORE study were questioned as to their preference for oral treatment. Capturing this preference measure was important as this will be considered within clinical practice, since eliglustat will be an option for those ERT-stable patients who would prefer an oral treatment. Indeed, all patients who were asked this question after 12 months' treatment with eliglustat confirmed a preference for oral treatment.

The EMA considered such endpoints as the most important in analysis of effect and "typical for studies in patients suffering from Gaucher disease."[71] Other endpoints investigated in ENGAGE and ENCORE are considered "useful for they give additional information on the patient's perceived benefit of the treatment or the pharmacodynamic effect of SRT."[71]

The indirect comparison versus velaglucerase was also conducted based on key therapeutic goals (spleen volume, liver volume, platelet count and haemoglobin level), although as already described, the substantial limitations of this comparison must be noted.

Benefits to specialised services will include replacing ERTs, which require infusion, with the oral treatment eliglustat. This will have a consequent reduction in the need for infusion support services e.g. nursing support at home, but most importantly, will give patients freedom.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

Dosing in clinical trials

In ENCORE, patients were initiated on eliglustat 50mg BID, but received intermittent dose increases to 100mg and later to 150mg, if needed, based on their plasma trough concentration. The plasma trough concentration was kept above 5 ng/ml while peak plasma was not to exceed 150 ng/ml. However, this method was not the advised dose regimen in the SPC. At the end of the protocol-defined titration period, 32% of patients received eliglustat 100mg BID, in line with the licensed dose. The appropriateness of the full trial data set to provide efficacy estimates for patients with IM and EM status receiving 100mg BID was discussed within the EPAR.[71] A population pharmacokinetic analysis using data from healthy subjects and GD1 patients showed that CYP2D6 metaboliser status was the most significant determinant of exposure to eliglustat. Therefore, a dosing regimen based on the CYP2D6 phenotype has been proposed. Pharmacokinetic/pharmacodynamic modelling and simulations (i.e., using a PopPK/PD model) were then conducted to assess the efficacy of all IM and EM patients if receiving 100 mg BID.[99] For the ENCORE study, individual IM or EM patients' observed efficacy results were projected to the values if they had all received 100 mg BID, based on the established PK/PD-efficacy relationship and individual observed exposures. Exposure projection was done with PopPK-simulated mean within-subject exposure ratio. Simulations were also conducted to assess the robustness of the modelling results.[99] As reported in the EPAR, the model found that "the expected loss of efficacy in patients treated with 100mg BID (IM and EM patients) or 100mg QD (PM patients) [was calculated to be] clinically negligible."[71, 99] This is justified by the data that do not show a difference between EM patients treated with 100 or 150 mg BID."[71] The EPAR concluded that because "a considerable proportion of the patients falls [outside of] the 95% CI of the PopPK predictions, patients should be closely monitored and in case of deterioration other treatment options should be considered."[71] This is stated in the SPC.[1]

In ENGAGE, patients received eliglustat 50mg OD on Day 1 and repeat doses of 50mg BID from Day 2 to Week 4. From Week 4 to Week 39, patients could receive an increased dose of eliglustat 100mg BID, again based on their plasma trough concentration. At the end of the protocol-defined titration period, 85% of patients received eliglustat 100mg BID, in line with the licensed dose.

In ENCORE, patients in the imiglucerase arm were treated according to the regimen advised in the imiglucerase SPC. Patients received a mean dose of 42.4 U/kg imiglucerase with patients weighing a mean of 67.5kg. In clinical practice England adult imiglucerase patients receive XXXX units per month based on the prescribing data (n=XXX). Although the weight of these patients is not known, this equates for patients with a weight of 67.5kg to XXU/kg. Data for the UK from the International Gaucher Register suggests imiglucerase dosing of XXX /kg (n=XX) with patients weighing a mean of XXXU/kg. This would suggest that dosing of patients on imiglucerase in ENCORE is XXXXX than in UK clinical practice. In this context it is worth noting that the Gaucher Disease Standard Operating Procedure for England[34] states that a maintenance dose of 15-30 U/kg every two weeks is expected to be adequate in most cases although this may be increased incrementally to 60 U/kg every two weeks if therapeutic goals are not met within the expected timeframe. Furthermore, after the 52-week primary analysis treatment period, all patients were treated with eliglustat. Each patient's total duration of participation in this study will be at least 104 weeks, and participation may continue for a total of up to 5.5 years or until the study is terminated by the Sponsor. According to the EPAR, "the study duration was considered to be sufficient to observe any change in the major endpoints (spleen, liver, bone marrow)."[71]

Metabolism status of patients

The EMA licence was granted for patients with PM, IM and EM metabolism status. It is noted in this regard that 97.5% of patients in ENGAGE and 92.5% in ENCORE had IM or EM status. As stated in the EPAR, only approximately 3% of the GD population are ultra-rapid metabolisers and are excluded currently from the treatment with eliglustat.[71] A higher dosage of 150 mg of eliglustat or more may be required as indicated by the observed plasma levels in these patients. Further data are required in this subgroup of patients, as stated in the risk management plan.

Selection of eligible patients

The proposed use of eliglustat within the current clinical pathway is as a first-line treatment option for patients with GD1 as an alternative treatment option to the ERTs and for patients who are stable on ERT but who have a preference for oral therapy. In the very small number of patients for whom ERT is unsuitable, miglustat is used at present and eliglustat would be expected to be used in place of it. Key inclusion criteria for ENCORE, which compared eliglustat with imiglucerase in ERT-stable patients, were: aged ≥18 years; received ERT for at least 3 years; received total monthly dose of 30 U/kg to 130 U/kg of

ERT for at least 6 of the 9 months prior to randomisation; reached Gaucher disease therapeutic goals prior to randomisation; spleen volume <10 times normal or total splenectomy (if occurred >3 years prior to randomisation); and liver volume <1.5 times normal. As such, the population is in line with the indication for eliglustat for use in ERT-stable patients, and the EPAR also stated that "Except for the criteria used for CYP3A4 and CYP2D6, this population is typical for a population suffering from Gaucher disease."[71]

Key inclusion criteria for ENGAGE, which compared eliglustat with placebo in treatment-naïve patients are: ≥16 years of age, splenomegaly 6-30 MN, no splenectomy, thrombocytopenia and/or anaemia (platelet count: 50,000–130,000/mm^3; haemoglobin: 8.0–11.0 g/dL females or 8.0–12.0 g/dL males); no ERT within 9 months; no miglustat within 3 months. As such, the population is in line with the indication for eliglustat for use in treatment–naïve patients. The inclusion and exclusion criteria are typical for studies evaluating the effects on patients suffering from Gaucher disease.[71]

Generalisability of patient population to clinical practice

There is evidence that the severity and demographic profile of patients at baseline in ENGAGE of treatment naïve patients is comparable to those being initiated on treatment in England[21] and a similarity between years on treatment, demographic profiles and percentage splenectomised between those on ERT in England and the ERT-stable patients in ENCORE.[42] This was also supported by the EPAR, which stated that "the included patient population is comparable with the population intended to be treated."[71] There is also a similar level of disease severity in the ERT stable patients at baseline in ENCORE and international data of disease severity after 5 years and up to 20 years after ERT initiation.[110, 113] This evidence is summarised below.

There is evidence from a study at the Royal Free Hospital, London (at which approximately 40% of GD1 patients in England are treated) that there is a similarity between the severity and other characteristics of patients presenting with GD1 and who received diagnosis at this trust (n=45) of whom 96% received ERT and the severity of the treatment-naïve patients at baseline in the ENGAGE study (Table 30).

Table 30: Patient characteristics in ENGAGE and the Royal Free Hospital

	Royal Free Hospital London[21]	ENGAGE
Number of patients	45	40
Splenomegaly	87%	100%
Hepatomegaly	44%	63% moderate or severe
Bone pain	36%	67%
Avascular necrosis	11%	Not reported (note: prior bone crisis was an exclusion criterion, and only 1 patient had severe bone disease)
Anaemia	20% had anaemia as an indication for ERT	20%
Thrombocytopenia	82%	100%
Skeletal disease	75% severe enough to be an indication for ERT	53%
Median age at presentation	26 years	21 years
Male	57%	50%
A least 1 N370S allele	79%	83%
Key: ERT, Enzyme replacement therapy.		

The characteristics of the adult GD patients in England reported in Wyatt et al. (2012)[42] (of whom 87% were receiving ERT) (n=150) are shown below in Table 31 where these details may be compared with those of the ERT-stable patients within the ENCORE trial:

Table 31: Patient characteristics in ENCORE and a UK observational study

	Eliglustat (ENCORE)	Imiglucerase (ENCORE)	UK observational study[42]
Number of patients	99	47	150
Age, mean years	37.2	38.6	46.4
Male %	43%	21%	43%
Splenectomised %	29%	19%	32%
Age at Gaucher disease diagnosis, years, mean	17.1	20.8	24.8
Years on imiglucerase, mean	9.8	10.2	10.8

It is not possible from Wyatt et al. (2012)[42] nor other UK/England published or unpublished source to obtain as estimate of disease severity / symptomology in ERT treated patients to compare to the ENCORE baseline trial data in ERT stable patients. The International

Gaucher registry[114] reported on the outcomes associated with 507 patients on ERT for 10 years from a number of countries. The 10 year results from this study are similar to those at baseline in ENCORE with the exception of spleen volume (Table 32). ENCORE patients on imiglucerase prior to study entry were on treatment for a mean of 10 years. The larger spleens in patients in the registry may be related to the cut off of ≤10 in spleen size in the ENCORE inclusion criteria. Patients in the registry may be skewed by relatively small numbers of patients with very large spleens. This is supported by the fact that median value in the registry data for spleen volumes (3.7 MN) at 10 years following ERT are close to the median values in ENCORE (2.9 MN and 2.2 MN for the eliglustat and imiglucerase arms, respectively).

Table 32: Baseline characteristics of patients in ENCORE and the Gaucher registry

	Eliglustat (ENCORE)	**Imiglucerase (ENCORE)**	**Weinreb et al., 2013[114]**
Number of patients	99	47	507
Splenectomised	29%	19%	26%
Spleen volume, MN, mean	3.2	2.6	5.2
Liver volume, MN, mean	0.9	0.9	1.0 (both non-splenectomised and splenectomised)
Haemoglobin levels, g/dL, mean	13.6	13.8	13.6 (non-splenectomised) and 13.4 (splenectomised)
Platelet count, 10^9/L, mean	206.8	192.3	167 (non-splenectomised) and 311 (splenectomised)

The economic model (described in Section 10) is based on GD-DS3 derived health states and the disease severity at treatment initiation is a reflection of DS3 scores at baseline in the clinical trials. No UK/England-specific DS3 data have been identified in the literature nor has this been possible to collect from UK-specific disease registries. It is noted that in a study of US GD1 patients, mean DS3 score at ERT initiation was 5.6 (n=173).[113] This compares to a mean of 4.7 in treatment naïve patients receiving eliglustat in the ENGAGE study. After 5 years, patients receiving ERT in the US study had a mean DS3 of 3.1; further analysis of this data set shows a high degree of stability in these patients between Years 5 to 20 with a mean DS3 of 3.6 in patients who have been on ERT for 20 years. Patients in ENCORE which consisted on ERT-stable patients had a mean DS3 at baseline of 2.37 and 2.08 in the eliglustat and imiglucerase arms, respectively. For those prior to study entry who had received imiglucerase, treatment had been initiated 10 years previously. In England, ERT-stable patients receive ERT for a mean length of 10 years.[42]

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

In clinical practice, and in line with the SOP by the Lysosomal Storage Disorder Expert Advisory Group, patients with GD1 eligible for treatment would be those with early presentation of specific clinical features or patients with genotypes known to be associated with rapid progression.[34]

Eligible patients would have a discussion with the clinician as to whether an oral treatment would be more suitable for the patients than an infusion. If the patient has a preference for oral treatment, or the physician recommends an oral treatment, eliglustat would be the recommended option rather than ERT.

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

The health-related quality of life (HRQL) impacts of Type 1 Gaucher disease has been assessed in several published studies. The literature indicates that patient utility falls as patients' progress into more severe disease, which is attributable to changes in haematological, bone and visceral symptoms. The haematological consequences of Gaucher disease include anaemia and thrombocytopenia, which impact patients' physical functioning and mobility. This is further impeded by fatigue and joint pain.

In severe disease, HRQL is further diminished by increasing bone damage (with corresponding pain) and the incidence of fragility fractures, which can lead to the replacement of joints becoming necessary. These health states have the largest detriments to patient utility.[37]

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

As patients progress to more severe disease states, they experience worse utility decrements from blood, bone and visceral symptoms. Patient HRQL is assumed to be related to the severity of the disease, rather than changing over time, so utility values used in the model are held constant in each of the DS3 health states. Changes to patient HRQL are modelled as the transitions between the different symptomatic health states.

HRQL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in Section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.

- Appropriateness for cost-consequence analysis.
- Results with confidence intervals.

HRQL data collection

HRQL data were collected from patients enrolled in the ENGAGE and ENCORE trials, the Gaucher DS3 Score Multi-site Study Group (referred to here as "DS3 Score Study") and the Phase II study. The ENGAGE and ENCORE RCTs and the Phase II study used Version 2 of the SF-36 instrument while the DS3 Score Study used Version 1.

The main differences between the two versions that are relevant to these analyses are the response categories for Question Four ("*During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?*") and Question Five ("*During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?*"). There were 2 response levels for each of these questions in version 1 of the instrument (Yes or No), but 5 levels in version 2, allowing for a more graduated response. To be able to combine the SF-36 data from the trials and from the DS3 Score Study, we coded the "Yes" responses in Version 1 as a 1 for version 2 ("All of the time") and the "No" responses in Version 1 as a 5 in version 2 ("None of the time").

SF-36 data, clinical outcomes, and patient reported outcomes associated with the DS3 measure were collected at baseline (randomisation) in all of the clinical studies, at Week 39 in the ENGAGE trial, Week 52 in the ENCORE trial, and at Weeks 52, 104, 156, and 208 in the Phase II study.

SF-36 data were not collected consistently or at similarly fixed time intervals in the DS3 Score Study. As a result, we matched the DS3 measures, and hence the health state, to the closest SF-36 responses within a 90-day window around the dates that DS3 scores were measured. Only data that could be matched within this time frame were used to derive utilities.

Prior to being included in the utility analyses, SF-36 observations were mapped to the EQ-5D the published algorithm by Brazier and Roberts (2004)[115], to satisfy the recommendations of the NICE Methods Guide.[116]

Health state utilities

The relationship between health state and utilities was estimated by pooling 105 observations from 26 patients from the Phase II study, 80 observations from 40 patients from the ENGAGE trial, 243 observations from 125 patients from the ENCORE trial, and 275 observations from 101 patients from the DS3 Score Study.

This combined dataset contains 428 patient-year observations from the Genzyme trials and 275 patient-quarter observations from the DS3 Score Study. The number of observations by health state ranged from 2 for health state 9 (severe plus severe skeletal complications [SSC]) to 315 for health state 1 (mild); no patients were observed in health state 8 (severe without SSC). Table 33 contains the distribution of patients according to health state for each source and Table 34 contains the demographic and clinical characteristics of the individual sources and the pooled sample used to derive the health state utilities.

Table 33: Number of observations per health state, by data source

Health State	Phase II	ENGAGE	ENCORE	DS3 Score Study	Total
1. Mild	40	16	187	72	315
2. Mild + bone pain	2	0	23	78	103
3. Mild + SSC	6	0	4	3	13
4. Moderate	14	61	21	92	188
5. Moderate + SSC	31	0	8	6	45
6. Marked	0	3	0	8	11
7. Marked + SSC	12	0	0	14	26
8. Severe	0	0	0	0	0
9. Severe + SSC	0	0	0	2	2
Total number of observations	105	80	243	275	703
Total number of patients	26	40	125	101	292
Key: SSC, severe skeletal complications.					

Table 34: Characteristics of the samples used to derive health state utilities

Health State	Phase II	ENGAGE	ENCORE	DS3 Score Study	All
Age at first observation, years	34.5	31.8	35.2	52.5	40.6
Female, %	61.5	50.0	54.4	61.4	56.8
Health state at first observation					
1. Mild, %	26.9	17.5	77.6	34.7	47.9
2. Mild + bone pain, %	0.0	0.0	12.0	20.8	14.4
3. Mild + SSC, %	0.0	0.0	0.0	0.0	0.0
4. Moderate, %	26.9	77.5	9.6	33.7	29.5
5. Moderate + SSC, %	19.2	0.0	0.8	2.0	2.4
6. Marked, %	0.0	5.0	0.0	2.0	1.4
7. Marked + SSC, %	26.9	0.0	0.0	5.9	4.1
8. Severe, %	0.0	0.0	0.0	0.0	0.0
9. Severe + SSC	0.0	0.0	0.0	1.0	0.3
Key: SSC, severe skeletal complications.					

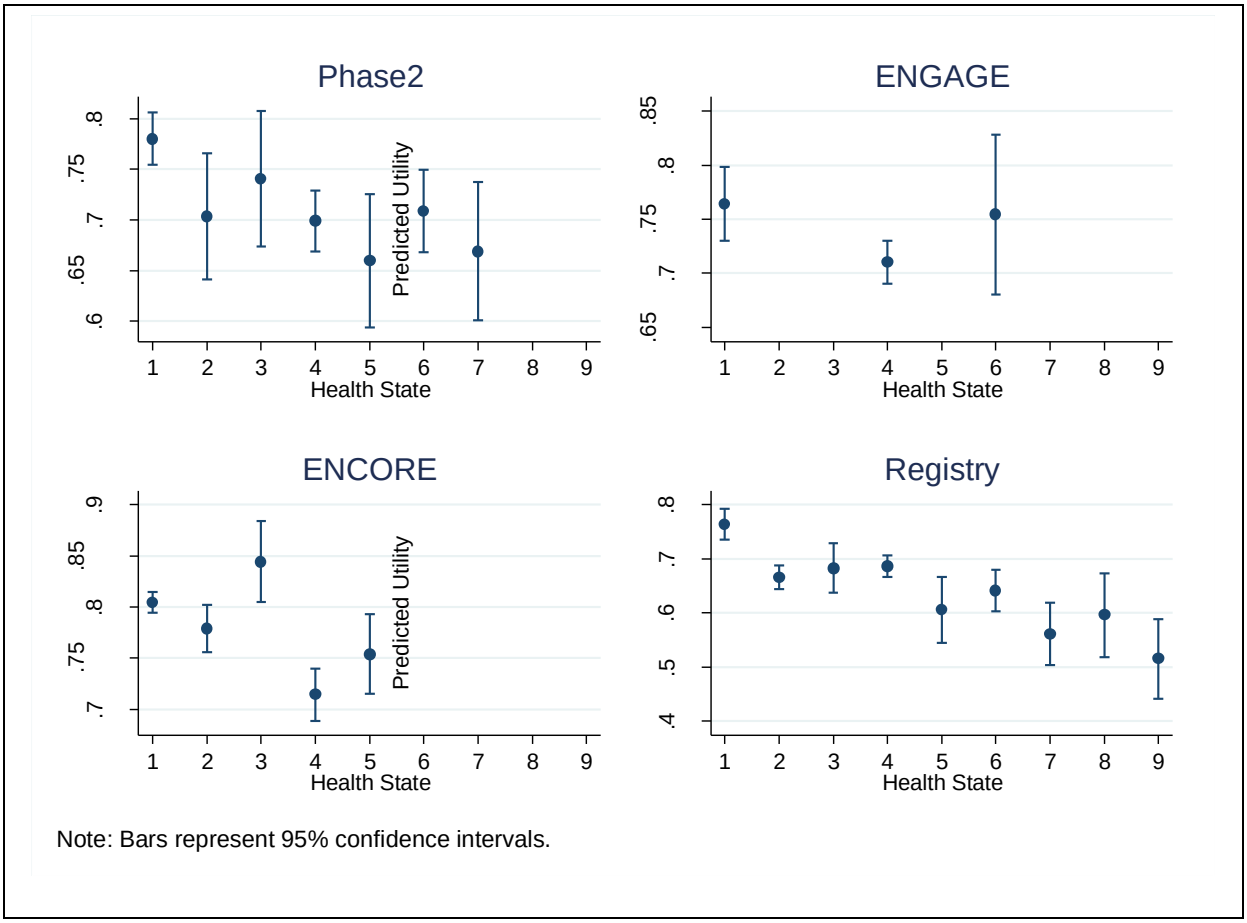
Although it was expected that more severe health states would be associated with lower utility, it was not assumed that the decrease would be linear with the ordinal value of the health states.

As a result, a regression model for utility was defined, that included terms for the DS3 severity categories (mild, moderate, marked and severe), bone pain, SSC, sex and age at initiation of treatment. This regression model was fitted using a generalised estimating equation (GEE) approach, using a Gaussian error term and the identity link, to account for multiple observations per patient. The regression was estimated using Stata 11.2.

Utility data were analysed separately by source (Phase II, ENGAGE, ENCORE, and the DS3 Score Study) to avoid confounding study design and participant characteristics with the health state-utility relationships.

Figure 18 displays the health state-utility results using a combination of variables capturing the DS3 category (mild, moderate, marked, severe) and the absence or presence of bone pain or SSC (severe skeletal complications) to measure health state.

Figure 18. Predicted utilities fitted from DS3 category and bone pain/SSC variables



Key: DS3, disease severity scoring system; SSC, severe skeletal complications.

The number of predicted utility values is limited for the ENGAGE and ENCORE trials because of the restrictive inclusion and exclusion criteria. Data from the Phase II and DS3 Score Studies provide a wider range of health states from which to predict utilities, but because of the availability of the most severe health states and because of the better precision (smaller standard errors and confidence intervals), we recommend using the predicted health state utilities derived from the registry data. (Table 35 displays the regression analysis results).

Table 35: GEE regression results for health state utility based on severity, bone pain, and severe skeletal complications

	Coefficient	Standard error	95% CI
DS3 Severity (vs. Mild)			
Moderate	−0.078**	0.035	−0.15 – -0.01
Marked	−0.122***	0.046	−0.21 – -0.03
Severe	−0.168**	0.079	−0.32 – -0.01
Bone Pain	−0.098***	0.036	−0.17 – -0.03
Severe Skeletal Complications	0.018	0.040	−0.06 – 0.10
Female	−0.049	0.031	−0.11 – 0.01
Age at Treatment Initiation	−0.002*	0.001	0.00 – 0.00
Constant	0.880***	0.057	0.77 – 0.99
Number of observations	97		
Number of patients	50		

Key: CI, confidence interval; GEE, generalised estimating equation; DS3, disease severity scoring system.
Notes: *** p<0.01, ** p<0.05, * p<0.10.
Source: Ganz et al. 2015[117]

The utilities for each health state were calculated by computing the average predicted utilities for each health state based from the estimated coefficients (these utilities are conditional on observed age, sex)[117]. For health states experiencing SSC, the coefficient for bone pain was also included. The utility estimates by health state are displayed in Table 36. As the majority of patients in the DS3 score study were on treatment with IV ERT, it is assumed that the utility values generated reflect the quality of life of patients with IV treatment, and patient preference for oral therapy is accounted for separately (and is discussed at the end of this section).

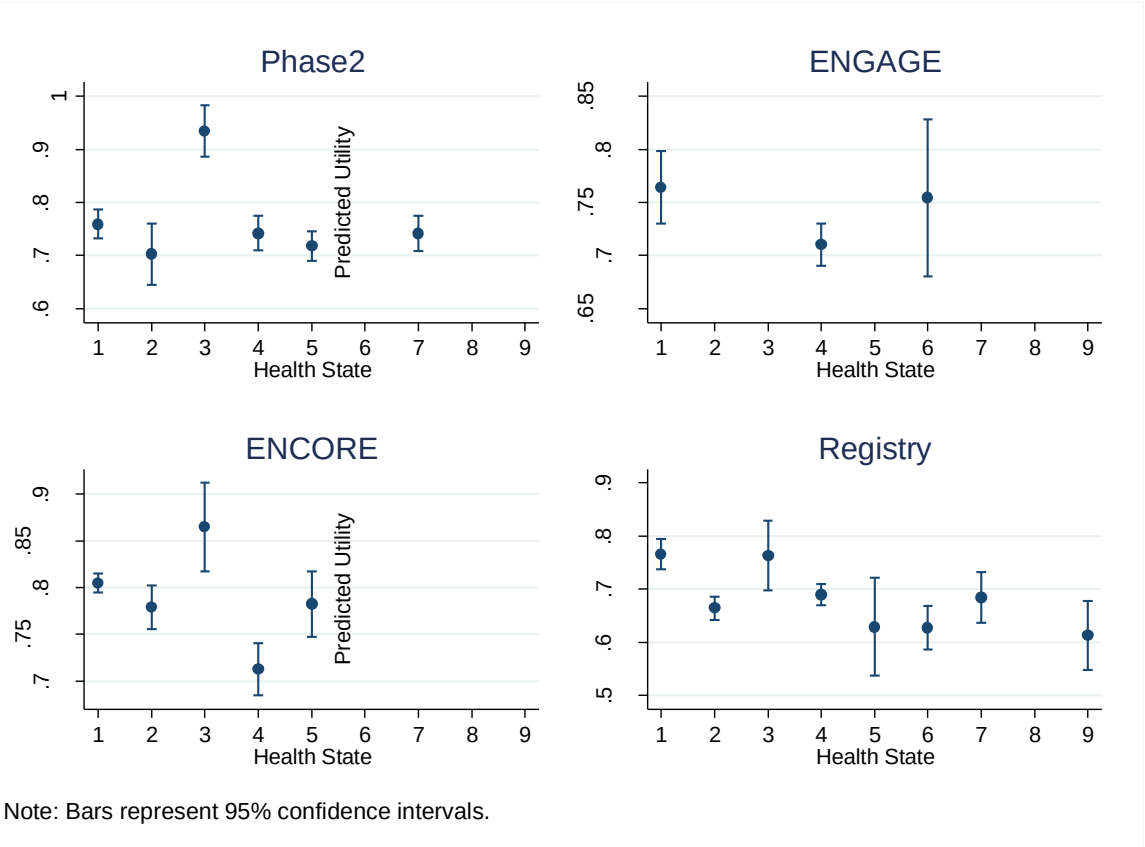
Table 36: Predicted utilities based on severity, bone pain, and severe skeletal complications

Health state	Predicted utility	Standard error	Confidence interval
Mild (1)	0.764	0.028	0.709–0.820
Mild + Bone Pain (2)	0.666	0.022	0.623–0.708
Mild + SSC (3)	0.683	0.046	0.593–0.774
Moderate (4)	0.686	0.020	0.648–0.725
Moderate + SSC (5)	0.606	0.061	0.487–0.724
Marked (6)	0.642	0.038	0.567–0.717
Marked + SSC (7)	0.561	0.058	0.448–0.674
Severe (8)	0.596	0.078	0.443–0.749
Severe + SSC (9)	0.515	0.074	0.371–0.659

Key: SSC, severe skeletal complications.
Note: Error bars depict 95% confidence intervals.
Source: Ganz et al. 2015[117]

Figure 19 displays the health state-utility results using individual dummy variables to represent each health state. The predicted health state-utility relationships are quite similar to those derived from the DS3 category and bone pain/SSC variables. However, using the health state dummy variables to predict utilities exaggerates the differences between the predicted utilities for health states 2 (mild with bone pain) and 4 (moderate) and health state 3 (mild with SSC) and results in inconsistent predictions.

Figure 19: Predicted utilities fitted from health state dummy variables



Disutility to administration disutility

During the ENCORE trial, 92% of respondents on the eliglustat arm responded to a survey on preference for different routes of administration. Of these, 100% stated that they preferred oral treatment over the infusion they previously received while on ERT. The model incorporated this preference by including a utility increment associated with oral administration.

The model incorporates this preference via a utility benefit or increment related to treatment with oral eliglustat, in the form of an oral treatment utility increment (XXX). This utility benefit for an oral treatment compared with infusions was obtained from a vignette study commissioned by Genzyme[2]. By assumption, this utility increment is applied during all model cycles regardless of treatment duration.

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

The SF-36 items were mapped to EQ-5D utilities using Equation 2 (Table 4 of the published article) published in Brazier and Roberts (2004), an established method for mapping SF-36 items to utility values.[115]

HRQL studies

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

A systematic review of utility studies was conducted to consider the evidence base for HRQL in GD1.

The full search strategies used in the searches are shown in Section 17.4, (Appendix 4). Medline, Medline In-process, EMBASE, The Cochrane Library (NHS EED and HTA database) and EconLit were searched between 30 May 2014 and 12 June 2014. The most recent records of two conferences (EWGGD and ASHG) were also hand searched for relevant abstracts. These hand searches are described in Section 17.4, (Appendix 4). Searches were then updated between 27 July and 14 August 2015 to identify any new publications. Identical search strategies were re-run with date of publication restricted to 2014 to present.

Records identified in the searches underwent primary screening of titles and abstracts, assessed against defined inclusion and exclusion criteria. These criteria are presented in Table 37. Studies that were considered eligible underwent secondary screening of full text. Studies that met all of the inclusion criteria and none of the exclusion criteria were included in the review.

Table 37: Inclusion and exclusion criteria for utility studies review

Inclusion Criteria		
Category	**Criteria**	**Rationale**
Study type	Quality of life studies and economic evaluations reporting patient utility values.	Both these study types will report relevant values.
Population	Studies must include patients with Type 1 Gaucher disease, but may include other types of the disease.	The aim was to restrict the search to the relevant population, but other types of Gaucher disease could be included in combination.
Interventions	No restriction by treatment. Untreated patients included.	Any utility values were to be included, regardless of treatment status
Outcomes	Utility values produced using generic, preference-based measures of patient utility, disease-specific measures or vignettes. Instrument responses should be elicited from patients (not by proxy). Valuations of utilities must be based on general population preferences.	These are the appropriate methods for obtaining utilities for economic evaluation.
Comparators	No restriction by treatment. Untreated patients included.	Any utility values were to be included, regardless of treatment status
Language	Studies must be available in English.	
Exclusion Criteria		
Category	**Criteria**	**Rationale**
Publication type	Systematic and non-systematic reviews, letters and comment articles.	These study types are not appropriate.
Publication date	Studies published before 1 January 1990	It is not expected that any relevant studies were published prior to this date.

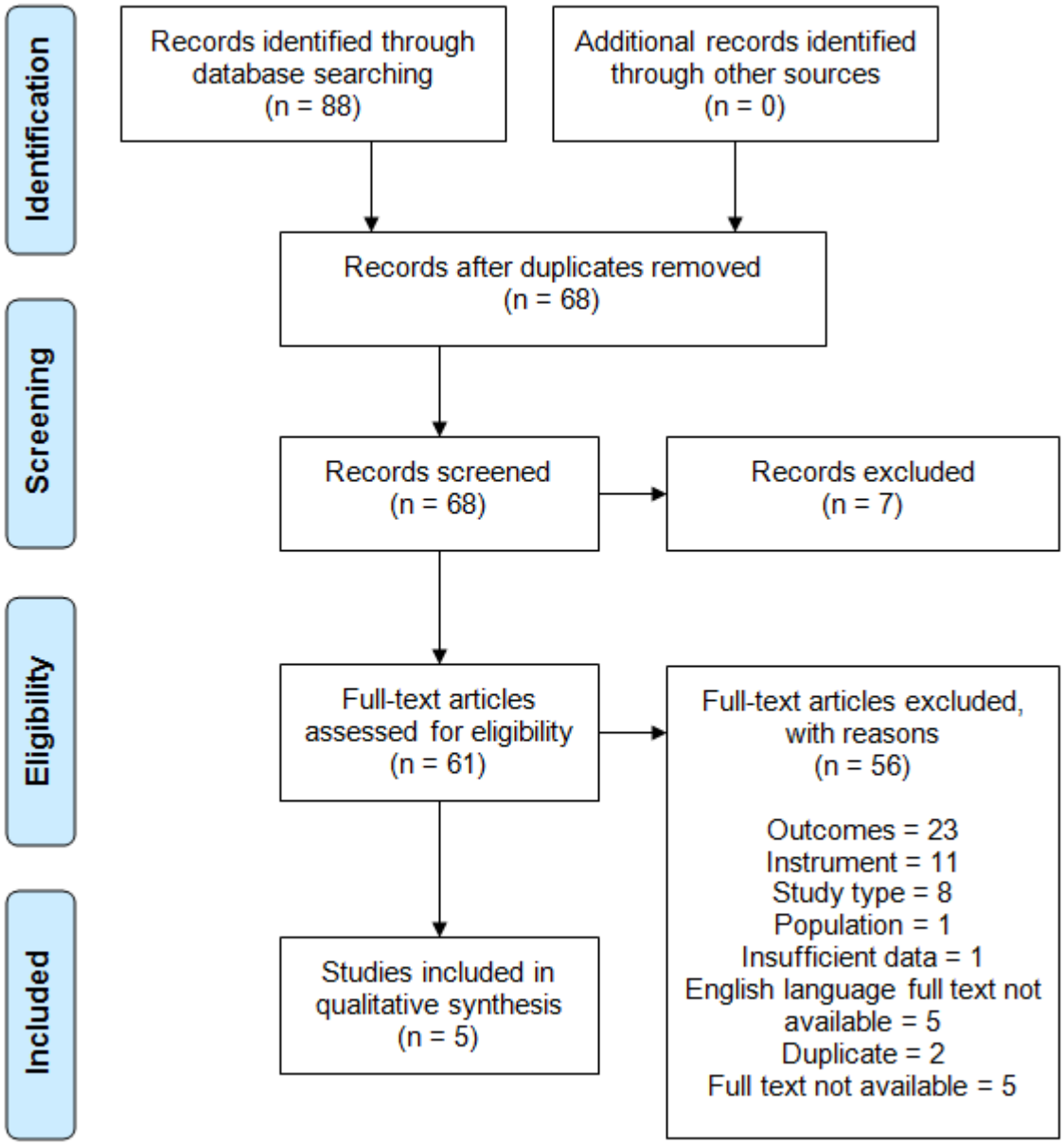
10.1.6 Provide details of the studies in which HRQL is measured.

Screening of search results

The process of study identification and screening is presented diagrammatically in Figure 20. The initial electronic searches identified 60 unique records, and another 8 were identified in the update searches. Of these, 7 were excluded based on assessment of titles and abstracts. In secondary screening of full text papers, 56 studies were excluded, with the most common reason for exclusion being irrelevant outcomes or inappropriate

instrument (e.g. which did not produce a preference-based utility value). Five studies were eligible for inclusion and are summarised below.

Figure 20: PRISMA diagram for utility study review



Summary of included studies

Full details of the data extracted from the included studies are presented in Appendix 4. The results of the studies are presented in Table 38.

Clarke et al. used three approaches to elicit utility values from three cohorts in the US; healthy individuals, patients with a chronic condition and patients with Gaucher disease.[118] These cohorts valued three health states, each representing a hypothetical patient with

Gaucher disease; a boy with low blood counts (Patient 1), a middle-aged parent with bone pain (Patient 2), and a teenage girl with an enlarged abdomen (Patient 3). The values elicited by the healthy individuals using time trade-off were considered most relevant to the NICE reference case, and therefore are included in the study summary in Table 38. The full results are presented in Appendix 4.

Connock et al. report the design of cost-utility model, and report the quality of life estimates used, as derived from published literature.[37] These are primarily sourced from Clarke et al. (summarised above)[118], but also include additional weighting to account for patients with bone crises, depending on the symptom severity index (SSI) of patients in each health state. The authors conclude that visceral symptoms have only a small effect on HRQL, but skeletal complications and bone pain are significantly associated with lower patient utility.

Deegan et al. assessed the impact of bone complications on HRQL.[23] In a cohort of 100 patients with GD1 or GD3, the authors used time trade-off to evaluate the utilities of patients with and without osteonecrosis and with and without fragility fractures. Utilities were derived from UK participants using the EQ-5D questionnaire. Mean utilities were not presented; the figures in Table 38 are the median values.

The study by van Dussen et al. consisted of a cost-utility analysis, in which the HRQL estimates were based on EQ-5D questionnaires administered to ERT-treated patients.[119] HRQL observations were categorised into the health states included in the model and were combined and corrected for bias to generate utility estimates. Patients could contribute to more than one disease state, and the bias correction and bootstrapping were not described in detail. The figures presented in Table 38 are the utility values derived using the UK EQ-5D tariff.

Wyatt et al. collected 214 EQ-5D observations from Types 1 and 3 Gaucher disease.[42] Summary statistics of the utility measures were not presented, but the authors present the results of a mixed-effects model that were used to examine the changes in utility that are attributed to patient gender, age and time on ERT. The authors conclude that there is no significant relationship between time on ERT and utility, but there was a small, but significant, trend for decreased utility with age.

Table 38: Summary of included utility studies

Publication	Utilities	Number of participants	Elicitation technique
Clarke et al., 1997[118]	Three Gaucher disease health states valued: Patient 1: 0.87 (0.83-0.91) Patient 2: 0.86 (0.81-0.91) Patient 3: 0.82 (0.78-0.86)	39 healthy participants	Time trade-off
Connock et al., 2006[37]	Mild: 0.82 Moderate: 0.66 Severe: 0.54	n/a	n/a Based on Clarke et al.
Deegan et al., 2011[23]	Patients with a history of osteonecrosis: 0.679 (median) Patients with no history of osteonecrosis: 0.796 (median) Those who had suffered a fragility fracture: 0.626 (median) Those who had not suffered a fragility fracture: 0.796 (median)	100	EQ-5D, Time trade-off
van Dussen et al., 2014[119]	Symptoms/recovery 0.8716 (0.8177-0.9225) Splenectomy 0.7532 (0.6768-0.8215) Bone complication 0.8614 (0.7530-0.9685) Multiple complications 0.7323 (0.6601-0.8202) Malignancy 0.15 (no CI, n=1)	Symptoms/recovery: 17 Splenectomy: 4 Bone complication: 6 Multiple complications : 13 Malignancy: 1	EQ-5D, Time trade-off
Wyatt et al., 2012[42]	Gender Male: 0.00 Female: -0.02 (-0.11, 0.06) Age Linear effect/year: -0.003 (-0.006, -0.0005) Time on ERT Not on ERT: 0.00 <12 months: -0.02 (-0.26, 0.23) 12-36 months: 0.02 (-0.19, 0.23) >36 months: -0.02 (-0.23, 0.18)	214 EQ-5D observations	EQ-5D, Time trade-off

Key: EQ-5D, EuroQoL 5 dimensions; ERT, enzyme replacement therapy.

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The values used in the economic model, derived from the clinical trial data, ranged from 0.764 for the mildest state to 0.515 for the most severe state. These figures are similar to those identified in the published literature, especially those reported by Deegan et al. and Connock et al. for severe patients. The literature generally suggests a wider range of values, with particular deviation for more severe health states; Connock et al. report a utility of 0.54 for patients with severe disease.[37] Estimation of the HRQL of patients with severe disease is limited, both in the literature and in the trial data, by the small sample sizes for these health states.

Van Dussen et al. also present a utility value for patients with a malignancy (0.15, n=1). Patients with Gaucher disease have an increased risk of developing blood-related malignancies (e.g. myeloma and various forms of leukaemia). The outcomes for these patients are not explicitly modelled in this analysis, as the number of patients that will develop a malignancy is low, and they expect to occur at an older age, and would therefore be heavily discounted in the model.

The figures reported by Clarke et al. are higher than those derived from the trial data. The patient profiles described in the vignettes valued in this study represent comparatively mild health states and these states were defined by the authors, not using validated health measurement instruments.

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

HRQL measurements as a result of AEs were not recorded in the ENGAGE or ENCORE clinical trials. Therefore a systematic literature review was conducted to identify any disutilities/utilities associated with AEs for patients with Gaucher disease. From the safety data available, events that occurred in 15% of patients or greater were deemed frequent enough to be included in the systematic literature review of AEs to obtain relevant HRQL values. The selection of AEs included in the economic model are discussed in Section 12.2.4.

The full search strategies used are shown in Section 17.4 (Appendix 4). Medline, Medline In-process, EMBASE, The Cochrane Library (NHS EED and HTA database) and EconLit were searched between the 15th and 20th October 2015. Records identified in the

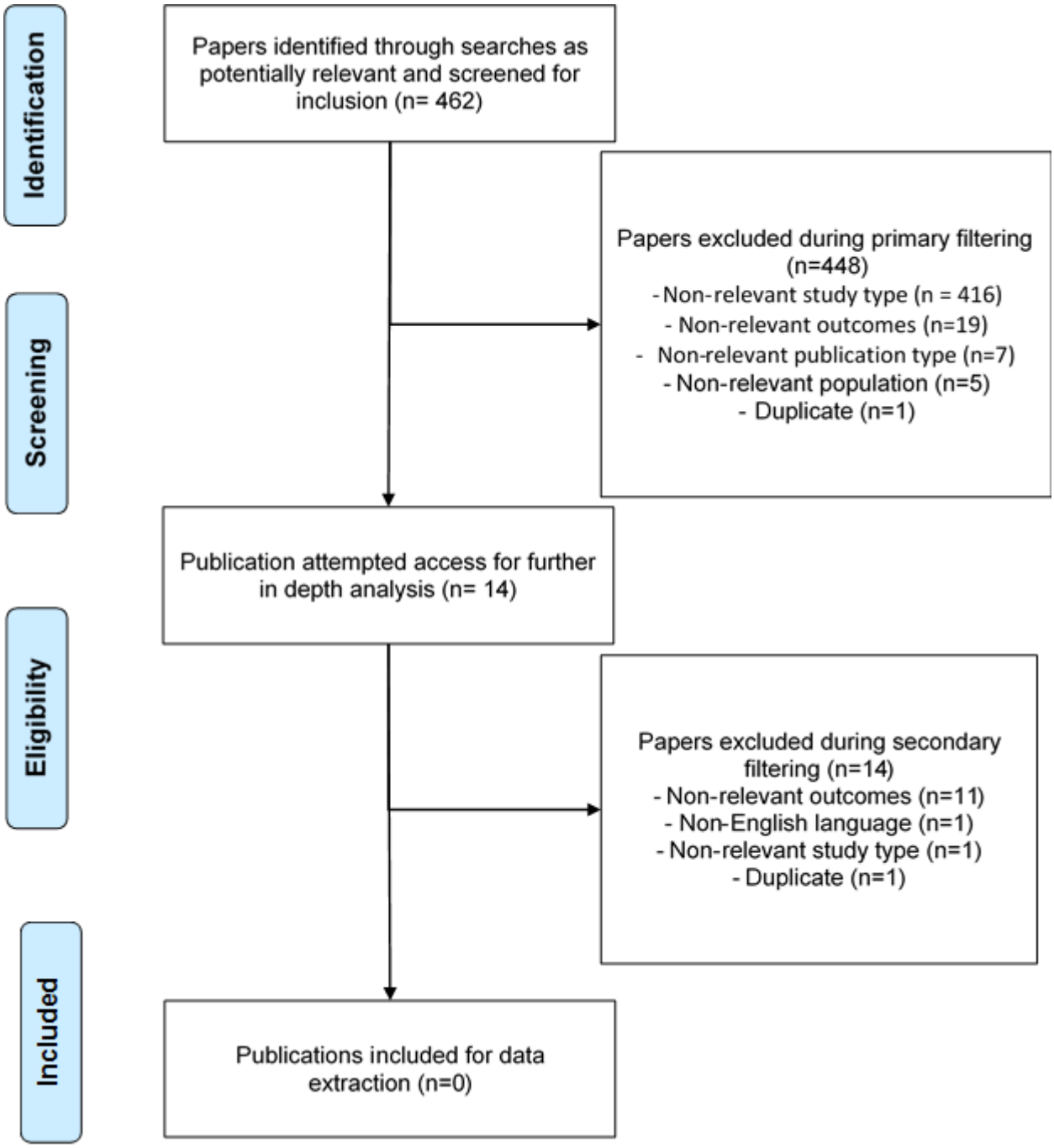
searches underwent primary screening of titles and abstracts, assessed against defined inclusion and exclusion criteria (presented in Table 39), considering the relevant AEs. Studies that were considered eligible underwent secondary screening of full text. Studies that met all of the inclusion criteria and none of the exclusion criteria were included in the review.

Table 39: Inclusion and exclusion criteria for adverse event utility studies review

Inclusion criteria		
Category	**Criteria**	**Rationale**
Study type	Quality of life studies and economic evaluations reporting patient utility values	Both these study types may report relevant values
Population	Studies will include adult patients with Gaucher disease	The aim was to restrict the search to the relevant population
Interventions/ comparators	No restriction by treatment	Any disutilities were to be included if they were relevant adverse events, regardless of treatment status
Outcomes	Utility values associated with adverse events produced using generic, preference-based measures of patient utility, disease-specific measures or vignettes Instrument responses should be elicited from patients Valuations of utilities should be based on general population preferences	These are the appropriate methods for obtaining utilities for economic evaluation
Language	Studies must be available in English	
Exclusion criteria		
Category	**Criteria**	**Rationale**
Publication type	Systematic and non-systematic reviews, letters and comment articles	These study types are not appropriate
Publication date	Studies published before 1 January 1990	The first Gaucher disease therapy, imiglucerase, only became available in 1997 when it was approved by the EMA
Key: EMA, European Medicines Agency.		

The process of study identification and screening is presented in Figure 21. The initial electronic searches identified 462 records. Of these, 448 were excluded based on assessment of titles and abstracts. In secondary screening of full text papers, 14 studies were excluded, with the most common reason for exclusion being irrelevant outcomes.

Figure 21: PRISMA diagram of systematic search of utility studies relating to adverse events in Gaucher disease



As no studies reported clear disutilities associated with AEs from the literature search, published literature was used to derive utilities based on the incidence and duration of AEs experienced by patients treated with a given drug. The ENCORE trial collected data on the duration of some AEs experienced, and these were used to annualise the utility decrement expected to be incurred as a result of an AE. Where durations of the event were not available, these have been supplemented with published literature and assumptions. The

selection of AEs included in the economic model and derivation of the incidence rates is discussed in Section 12.2.4.

The utility decrements applied per annual cycle of the cost-effectiveness model are presented in Table 40. Certain events were considered to have minimal impact on patients' HRQL and these have been assumed to be associated with a disutility of 0. Utility decrements were applied within the model throughout the duration of risk for AEs, which was assumed to be 36 months, after which time it is assumed that patients are stable on treatment.

Table 40: Adverse event utility decrements applied in economic model

	Disutility	Duration	Annualised disutility	Source of disutility/duration
Back pain	-0.25	27.27 days	-0.0187	[120]
Abdominal pain	-0.053	4 days	-0.0006	[121] Duration assumed equal to diarrhoea (on eliglustat and ERT)
Joint pain	-0.174	2.5 days	-0.0012	[122]
Fever	0	0	0.0000	Assumption
Weakness	0	0	0.0000	
Infusion reaction	-0.011	365.25 days	-0.011	[123] Applied for whole year, while patients are on IV treatment
URTI	N/a	N/a	-0.0001	[124]
Dizziness	-0.01	16 days	-0.0004	[125] Duration assumed equal to fatigue (on eliglustat and ERT)

Key: ERT, enzyme replacement therapy; IV intravenous; URTI, upper respiratory tract infection.

Quality-of-life data used in cost-consequences analysis

10.1.9 Please summarise the values you have chosen for your cost-consequence analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

Table 41 displays the health state utilities and disutilities used in the model.

Table 41: Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Confidence interval	Reference in submission	Justification
Mild (1)	0.764	0.709–0.820	Section 10.1.3	Point estimates and standard errors were estimates in an analysis of pooled trial data
Mild + Bone Pain (2)	0.666	0.623–0.708		
Mild + SSC (3)	0.683	0.593–0.774		
Moderate (4)	0.686	0.648–0.725		
Moderate + SSC (5)	0.606	0.487–0.724		
Marked (6)	0.642	0.567–0.717		
Marked + SSC (7)	0.561	0.448–0.674		
Severe (8)	0.596	0.443–0.749		
Severe + SSC (9)	0.515	0.371–0.659		
AE: Back pain	-0.0187	-0.0121 to -0.0267	Section 10.1.8 Published estimates of HRQL impact of AEs	
AE: Abdominal pain	-0.0006	-0.0004 to -0.0008		
AE: Joint pain	-0.0012	-0.0008 to -0.0017		
AE: Infusion reaction	-0.0110	-0.0071 to -0.0157		
AE: URTI	-0.0001	-0.0001 to -0.0001		
AE: Dizziness	-0.0004	-0.0003 to -0.0006		
SC administration increment	See page 195	See page 195	Section 10.1.3	

Key: AE, adverse event; IV, intravenous; SC, subcutaneous; SSC, severe skeletal complications, URTI, upper respiratory tract infection.

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

The methods used to incorporate clinical opinion into the design and validation of the analyses is described in Section 12.2.5.

10.1.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

By distributing the disease population across the DS3 health states, the model stratifies the cohort by disease severity and accounts for the heterogeneity inherent in Gaucher disease. As such, the patients within each health state should experience a similar quality of life, and heterogeneity of the disease should be accounted for across the whole modelled cohort.

The variances that are included in the modelling of HRQL are the incidence of AEs, which are incurred at different rates across all the treatment arms for the first 3 years of the model, and the utility decrement associated with IV administration of treatment for comparator arms.

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No health effects were excluded from the literature or clinical data that would be relevant to the analysis.

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The majority of health states had their associated utility values estimated independently from the clinical trial data, not as relative changes from an assumed baseline.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

The utility assigned to each health state is held constant over the duration of the model.

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

The values presented in this Section have not been amended, other than the revised estimate for patients with mild disease with SSC, which was recalculated based on the utility for mild patient with bone pain without SSC. This is described above in Section 10.1.3.

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators.

No discontinuation rules are applied in the economic evaluation, although some degree of discontinuation is modelled to account for the impact of the AE profiles immediately following treatment initiation.

Discontinuation is not associated with higher DS3 scores in the model; patients in the model are assumed to continue treatment throughout, despite progression to more severe health states. Other than a proportion of patients that are assumed to receive ERT after discontinuation, no treatment switching is modelled. For those patients in whom treatment is considered clinically appropriate, discontinuation rates on first line ERTs are low. This is shown in the study of Gaucher disease treated patients in Section 8.2 in which, of 139 patients initiated on ERT in England, 96% were still on an ERT after a mean follow up of 10.8 years.[42]

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in Section 17.3.

A systematic literature review was undertaken to identify previous cost-effectiveness analyses relevant to the decision problem.

The search strategies used in the electronic searches are provided in full in Section 17.3, (Appendix 3). The databases searched were Medline and Medline In-process, EMBASE, The Cochrane Library (NHS EED and HTA database) and EconLit. Proceedings from the last meetings of two conferences (EWGGD and ASHG) were also hand-searched to identify any studies that had yet to be published. These additional searches are described in Section 17.3 (Appendix 3). The initial searches were performed between 30 May 2014 and 12 June 2014, and update searches were performed between 27 July 2015 and 14 August 2015, using the same search strategies, but restricted to studies published from 2014 to present.

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in table D1 below. Other headings should be used if necessary.

The papers identified in the searches were then assessed against defined inclusion and exclusion criteria. These criteria, and the rationale behind them, are presented in Table 42. In the first instance, the title and abstracts were assessed. This was followed by the assessment of the full text articles. The studies that met all of the inclusion criteria and none of the exclusion criteria are described in the next section.

Table 42: Inclusion and exclusion criteria for economic evaluation review

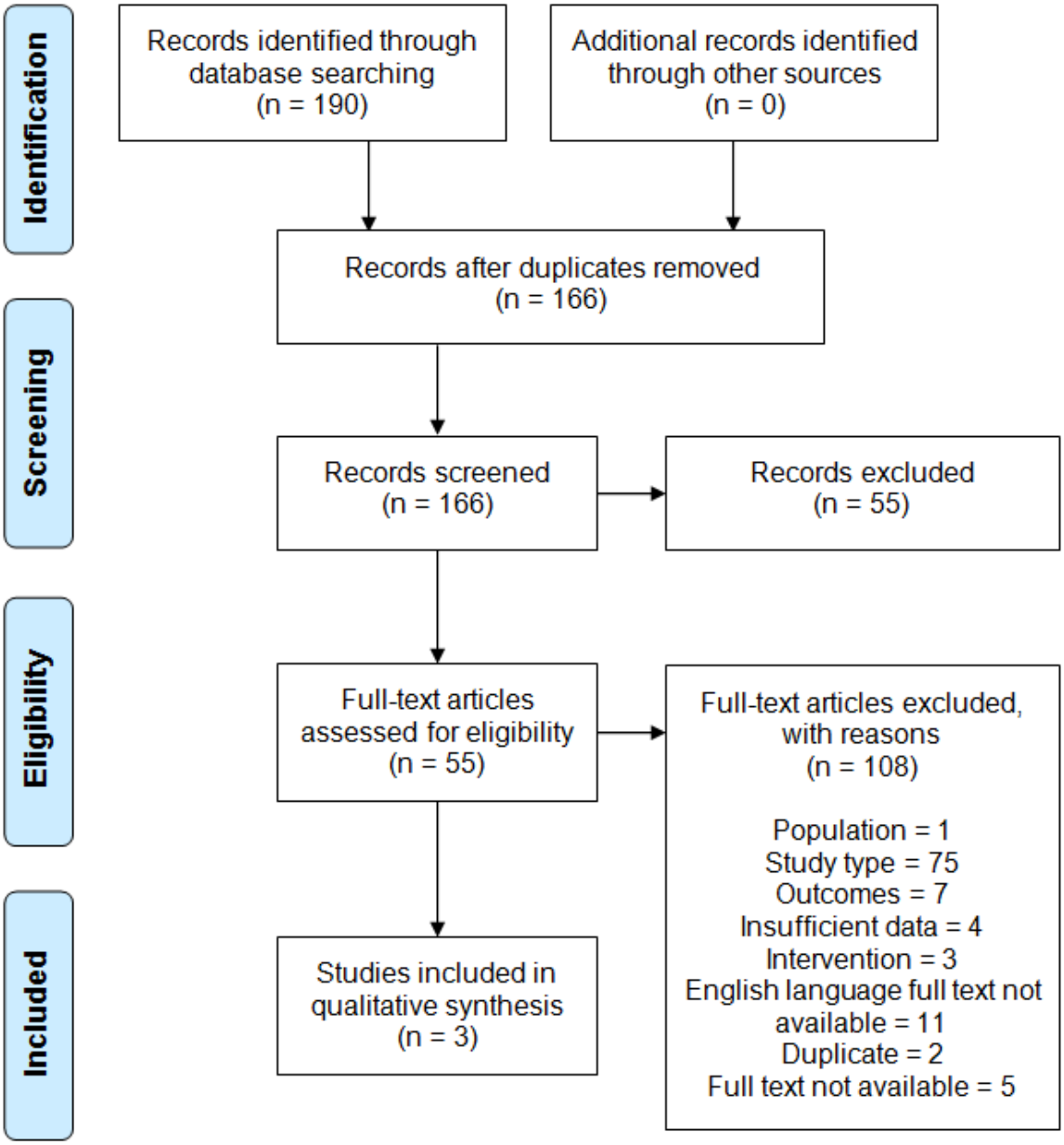
Inclusion criteria		
Category	**Criteria**	**Rationale**
Study type	Full economic evaluation (including cost-consequence, cost-minimisation, cost-effectiveness, cost-utility and cost-benefit evaluations) that compares two or more interventions.	This is the relevant study type.
Population	Studies will include patients with Type 1 Gaucher disease, but may include other types of the disease, as long as data/results are presented separately for the different groups.	The aim was to restrict the search to the relevant population, but other types of Gaucher disease could be included in combination in order to ensure relevant analyses were not overlooked.
Interventions	Any medical treatment of Gaucher disease, or best supportive care, no treatment or placebo.	It was not expected that any evaluation of eliglustat would be found. The searches were left open to consider any medical intervention. Non-pharmacological interventions (e.g. surgery) were not included.
Outcomes	Studies must include a comparison of costs between the intervention and comparator arms, and be structured as a cost-minimisation argument or include either incremental QALYs or another measure of effectiveness (e.g. life years or disease specific event).	This criterion satisfies the aims of the review.
Comparators	Any medical treatment of Gaucher disease, or best supportive care, no treatment or placebo	It was not expected that any evaluation of eliglustat would be found. The searches were left open to consider any medical intervention. Non-pharmacological interventions (e.g. surgery) were not included.
Language	Studies must be available in English at least in summary form.	
Exclusion criteria		
Category	**Criteria**	**Rationale**
Publication type	Systematic and non-systematic reviews, letters and comment articles	Primary studies are required.
Publication date	Studies published before 1 January 1990	It is not expected that any relevant studies were published prior to this date.
Key: QALY, quality-adjusted life year.		

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

The results of the searching and screening process are presented in Figure 22, presented again below. The searches identified 190 unique records, of which 55 were excluded at the primary screening stage (assessment of titles and abstracts). A further 108 were excluded upon assessment of the full text article, with the most common reason for exclusion being an irrelevant study type.

Three economic evaluations met the inclusion criteria and were included in the review.

Figure 22: PRISMA diagram of economic evaluation review



11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.

A summary of the eligible economic evaluations is presented in Table 43.

Connock et al.

This evaluation was conducted as a part of the NHS Health Technology Assessment Program and used the results of a systematic literature review to build a Markov model comparing cost and quality-adjusted life year (QALY) outcomes of patients treated with ERT and standard supportive care from the perspective of the UK NHS.[37] The health states were based on Zimran SSI scores[126], modelling the progression of symptomatic disease through mild, moderate and severe states, each with associated costs and HRQL estimates.

In their discussion of the model results, the authors conclude that the incremental cost-effectiveness ratios (ICERs) associated with ERT are many times higher than established willingness-to-pay thresholds. They attribute this to the high costs of medical treatment and the fact that the condition does not represent an immediate mortality risk for many patients, resulting in long periods on treatment. They acknowledge the limitations of the evidence base and modelling approaches. In particular, they comment on the significant heterogeneity of the disease and the degree to which patient genotype affects disease progression and severity. The authors also conclude that the effectiveness of ERT in improving visceral symptoms and bone pain is more strongly supported by the evidence base than the long-term complications. They comment that the use of SSI scores as a measure of disease progression is crude, and that there could be significant variation of patients within each of the SSI categories.

Van Dussen et al.

The analysis presented by van Dussen et al. consisted of a Markov model with eight health states[119], comparing treatment with ERT with standard care (which did not include ERT, and consisted of medical treatment of symptoms). Unlike the Connock et al. economic model[37], splenectomy was included as a complication of progressive disease, rather than a treatment in the non-ERT arm, as it is performed in patients with splenomegaly and/or cytopenia. Efficacy for the comparator cohort of the model was derived from historical records from a Dutch Gaucher Disease registry. Efficacy data for

the interventional cohort were collected from prospectively identified registry patients treated with ERT, along with HRQL and resource use data.

The authors comment that, due to uncertainty in the evidence base, the results of the model cannot conclusively determine the cost-effectiveness of ERT. They acknowledge that the costs of treatment are dominated by the medical costs of ERT, and that estimates of the ICER are only marginally affected by changes in other cost sources e.g. the inclusion of productivity and societal costs. The authors comment on the large health gains achieved compared with standard care, a total of 12.8 incremental years free of end-organ damage and 6.27 incremental QALYs per patient (undiscounted). The authors consider the health gains and incremental costs of treatment within the context of providing treatment for a disease with large unmet need. The authors acknowledge that the cost-effectiveness of ERT will be dependent on the willingness of society to pay more for the treatment of rare disease.

The generalisability of the study to other countries is also discussed. The authors acknowledge that the ERT dosing regimens and treatment practices differ by country, and that this will impact cost-effectiveness analyses. However, the authors state the results of the model are broadly in line with other published estimates.

AWMSG/Shire Plc assessment report

The AWMSG report summarises the cost-minimisation model that was submitted in support of the assessment of velaglucerase in Wales, comparing velaglucerase to imiglucerase. The model estimates the differences in drug acquisition cost, and other costs in the model are assumed to be the same across the two arms of the model, in line with the assumption of clinical equivalency on which the cost-minimisation is based. The report goes into little detail of the specification of the model itself, but states that patients in the model are assumed to have a weight of 75kg and receive an average of 32 units/kg every two weeks, not including wastage, and that the accrued costs are discounted at a rate of 3.5% per year. This results in 2,400 units administered per dose. Within the model produced for this analysis the assumed weight is 67.5kg (the average weight of patients within the ENCORE trial) with an average dose of 42.4 unit/kg every two weeks, leading to an administration of 2,862 units every other week.

The model estimates the total lifetime costs of patients treated with velaglucerase to be £5,120,956, compared to £3,903,338 for imiglucerase, a difference of £1,217,619. The report states that medicine costs accounted for 99% of the total costs. The report redacts

the results of the model based on the discounted price for velaglucerase put forward by Shire. This discount was estimated to be 40%.

Table 43: Summary list of other cost-effectiveness evaluations

	Connock *et al.*[37]	**van Dussen *et al.*[119]**	**All Wales Medicines Strategy Group (AWMSG)**
Title	The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher disease: a systematic review	Cost-effectiveness of enzyme replacement therapy for Type 1 Gaucher disease	AWMSG secretariat assessment report: Velaglucerase (VPRIV®)
Year	2006	2014	2014
Country(ies) where study was performed	UK	The Netherlands	UK
Intervention	ERT	ERT	Velaglucerase
Comparator	Standard supportive care (No ERT)	Standard supportive care (No ERT)	Imiglucerase
Summary of model	A cohort Markov model with health states based on severity scale indices (SSI). The model compared ERT with standard supportive care in the UK, which did not include ERT, but did include splenectomy. The effectiveness data in the model was derived primarily from published literature identified by a systematic review of studies in Type 1 Gaucher disease.	A Markov model including 8 states of consecutive stages of Gaucher disease progression, plus a death state. This was structured as an iterative decision tree. The model compared ERT with standard medical care in The Netherlands, which did not include ERT. The effectiveness data in the model was derived from a Dutch Gaucher disease registry, with historical control cases. The definitions of the health states implemented in the model are provided in a related paper by the same authors.[67]	Cost minimisation model comparing velaglucerase and imiglucerase, assuming clinical equivalence between the two ERTs. The acquisition costs of treatment were differentiated, but other treatment costs (administration, monitoring and AE management, etc.) and all health benefits were assumed to be equal for both treatments. The model included a patient access scheme (PAS) discount for velaglucerase, but this is not disclosed and results with this discount are not reported.
Patient population (average age in years)	0 (from birth)	0 (from birth)	NR
QALYs (intervention, comparator)	24.432, 18.659	37.33, 34.65	N/A

	Connock *et al.*[37]	van Dussen *et al.*[119]	All Wales Medicines Strategy Group (AWMSG)
Costs (currency) (intervention, comparator)	(GBP) £2,312,342, £53,692	(Euros) €1,206,933, €50,048	(GBP) £5,120,956, £3,903,338
ICER (per QALY gained)	£391,275 (base case, discounted)	€432,540 (base case, discounted)	N/A
Key: ERT, enzyme replacement therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; N/A, not applicable; NR, not reported.			

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.

Table 44 presents the quality assessment undertaken of the economic evaluations identified in the systematic searches. Quality assessment of the cost-minimisation model summarised in the AWMSG assessment report could not be performed, as the level of detail reported was insufficient.

Table 44: Quality assessment of economic evaluations

	Connock *et al.*[37]		van Dussen *et al.*[119]	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design				
1. Was the research question stated?	Yes	To estimate differences in costs and QALYs of ERT in the management of Type 1 Gaucher disease compared with standard supportive care in the UK	Yes	To evaluate the cost-effectiveness of ERT compared to standard medical care without ERT in Type 1 Gaucher disease patients in The Netherlands
2. Was the economic importance of the research question stated?	Yes	Significance of expensive treatments for orphan diseases was stated	Yes	High cost of treatment considered

	Connock *et al.*[37]		van Dussen *et al.*[119]	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**	**Grade (yes/no/not clear/N/A)**	**Comments**
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	Analyses took a UK NHS perspective	Yes	Analysis took societal perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	ERT was the focus of the study	Yes	ERT was the focus of the study question
5. Were the alternatives being compared clearly described?	No	The specific ERT included in the analysis was not stated	No	The specific ERT included in the analysis was not stated
6. Was the form of economic evaluation stated?	Yes	Cost-utility	Yes	Cost-utility and cost-effectiveness
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	This was the aim of the *de novo* analysis	Yes	This form of evaluation addresses the research question
Data collection				
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Primarily published literature, some estimates and assumptions	Yes	Data obtained from a Dutch Gaucher disease registry
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	Not based on a single study	N/a	Model based on registry data
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	Sources used were identified in systematic reviews of the literature, but no meta-analysis was reported.	No	No data synthesis methods were reported

	Connock *et al.*[37]		van Dussen *et al.*[119]	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**	**Grade (yes/no/not clear/N/A)**	**Comments**
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost per QALY	Yes	Cost per year free of end-organ damage and cost per QALY
12. Were the methods used to value health states and other benefits stated?	N/A	Utility values were based on studies identified in systematic literature searches	Yes	EQ-5D observations of registry data, health state descriptions in supplementary information
13. Were the details of the subjects from whom valuations were obtained given?	No	Some basic information reported	No	Information not reported
14. Were productivity changes (if included) reported separately?	N/A	Not included	Yes	Unit costs and results presented separately
15. Was the relevance of productivity changes to the study question discussed?	N/A	Not included	Yes	Impact on results discussed
16. Were quantities of resources reported separately from their unit cost?	Yes		Yes	Aggregated numbers of procedures required reported
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Quantities largely based on assumptions	Yes	Quantities sources from registry data
18. Were currency and price data recorded?	Yes	2003/04 GBP (£)	Yes	2009 Euros (€)
19. Were details of price adjustments for inflation or currency conversion given?	No		Yes	General price indices used to adjust costs from other reference years
20. Were details of any model used given?	Yes	Model description and diagram presented	Yes	Model description and diagram presented

	Connock *et al.*[37]		van Dussen *et al.*[119]	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**	**Grade (yes/no/not clear/N/A)**	**Comments**
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	Model compartments based on Zimran SSI scores, but no justification of modelling approach	No	No justification of modelling approach
Analysis and interpretation of results				
22. Was the time horizon of cost and benefits stated?	No		Yes	85 years
23. Was the discount rate stated?	Yes	3.5%	Yes	1.5% for health effects, 4% for costs
24. Was the choice of rate justified?	No	But used standard values for economic evaluations	Yes	Choice of discount rates referenced to published literature
25. Was an explanation given if cost or benefits were not discounted?	N/A		N/A	Scenario with undiscounted costs were presented
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No		No	
27. Was the approach to sensitivity analysis described?	Yes	Alternative scenarios tested were described, but the number of runs used in stochastic analyses was not reported	Yes	Alternative scenarios and stochastic analysis
28. Was the choice of variables for sensitivity analysis justified?	No		No	
29. Were the ranges over which the parameters were varied stated?	Yes	Details of distributions used reported	Yes	Distributions and confidence intervals used in probabilistic modelling reported

	Connock *et al.*[37]		van Dussen *et al.*[119]	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**	**Grade (yes/no/not clear/N/A)**	**Comments**
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Only two treatment arms were considered	Yes	Only two treatment arms were considered
31. Was an incremental analysis reported?	Yes	Only two treatment arms were considered	Yes	Only two treatment arms were considered
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Disaggregated by genotype	No	Disaggregated results were not presented
33. Was the answer to the study question given?	No	Uncertainty in the evidence base precluded a solid conclusion	No	Authors concluded that cost-effectiveness will be dependent on willingness to pay
34. Did conclusions follow from the data reported?	Yes	Estimated ICERs are higher than typical willing-ness to pay thresholds	Yes	Conclusion reflects uncertainty in data
35. Were conclusions accompanied by the appropriate caveats?	Yes	Paucity of data acknowledge	Yes	Limitations of the data and analyses were explored
36. Were generalisability issues addressed?	Yes	Heterogeneity of disease acknowledged	Yes	The generalisability of the registry data and the variation of dosing regimens by country were considered

Key: ERT, enzyme replacement therapy; EQ-5D, EuroQoL 5 dimensions; ICER, incremental cost-effectiveness ratio; N/A, not applicable; NHS, National Health Service; QALY, quality-adjusted life year.

Notes: Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.

12 De novo cost-consequence analysis

Section 12 requires the sponsor to provide information on the de novo cost-consequence analysis.

The de novo cost-consequence analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.1 Description of the de novo cost-consequence analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-consequence analysis?

No models identified in the systematic review of cost-effectiveness evidence adequately addressed the decision problem, so the construction of a de novo model was necessary.

The economic model designed to evaluate the cost-effectiveness of eliglustat considered two patient groups: treatment-naïve patients and patients stable on ERT. Within each of these, the model also considers patient subgroups based on metaboliser status. In line with the eliglustat licence, intermediate and extensive metabolisers (IM and EM) are treated with 100mg of eliglustat tartrate twice daily, and poor metabolisers (PM) receive 100mg once daily. Collectively, these groups cover the indication for eliglustat in the treatment of GD1.

The model compares treatment with eliglustat, an oral substrate reduction therapy (SRT), with imiglucerase and velaglucerase, IV ERTs. The comparisons made to each of these treatments are made within the same defined patient populations.

Patient characteristics

The starting age of patients in the treatment-naïve population was assumed to be 32 years based on the mean age in the ENGAGE trial. It should be noted that both the age of diagnosis of adult patients with GD1 and the age at which symptoms develop to the point at which treatment is initiated varies substantially between patients.

The mean age for patients in the model who are stable on ERT and are switched to eliglustat is 38 years. This is the mean age of the patients in the ENCORE trial.

All patients in the treatment naïve population are assumed to have an intact spleen, and it is assumed that throughout the model, the incidence of splenectomy is zero. This is based on the notion that patients who are well controlled on medical treatment should not require surgical intervention to remove enlarged spleens. Similarly, despite a proportion of patients in the treatment-stable population (25%, based on the patients in the ENCORE trial) having been splenectomised, no additional splenectomies are assumed to occur during the model time horizon.

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-consequence analysis is different from the scope.

The comparators included in the model are consistent with the NICE scope. The technologies included are summarised in Table 45.

The intervention under consideration is twice daily oral administration of 100 mg of eliglustat tartrate for IM and EM patients, and 100mg once daily for PM patients. Of the comparator technologies included in the evaluation, imiglucerase and velaglucerase, both are administered intravenously at a dose of 42.4U/kg infused every 2 weeks, the average dosing of the imiglucerase arms of the ENCORE trial. The rationale behind assuming equivalent dosing for these ERTs is that both have been shown to have similar efficacy at the same dose (60 U/kg every 2 weeks) in a head-to-head RCT as described in Section 9.8.1.[63] This assumption has been further validated by clinical expert opinion[127].

Table 45: Summary of technologies included in the model

Technology	Dose	Source
Eliglustat tartrate[6]	2x100mg capsules daily	Licensed dose
Imiglucerase	42.4U/kg every 2 weeks	The mean dosing of imiglucerase patients in the ENCORE trial
Velaglucerase	42.4U/kg every 2 weeks	Assumed the same as imiglucerase

Model structure

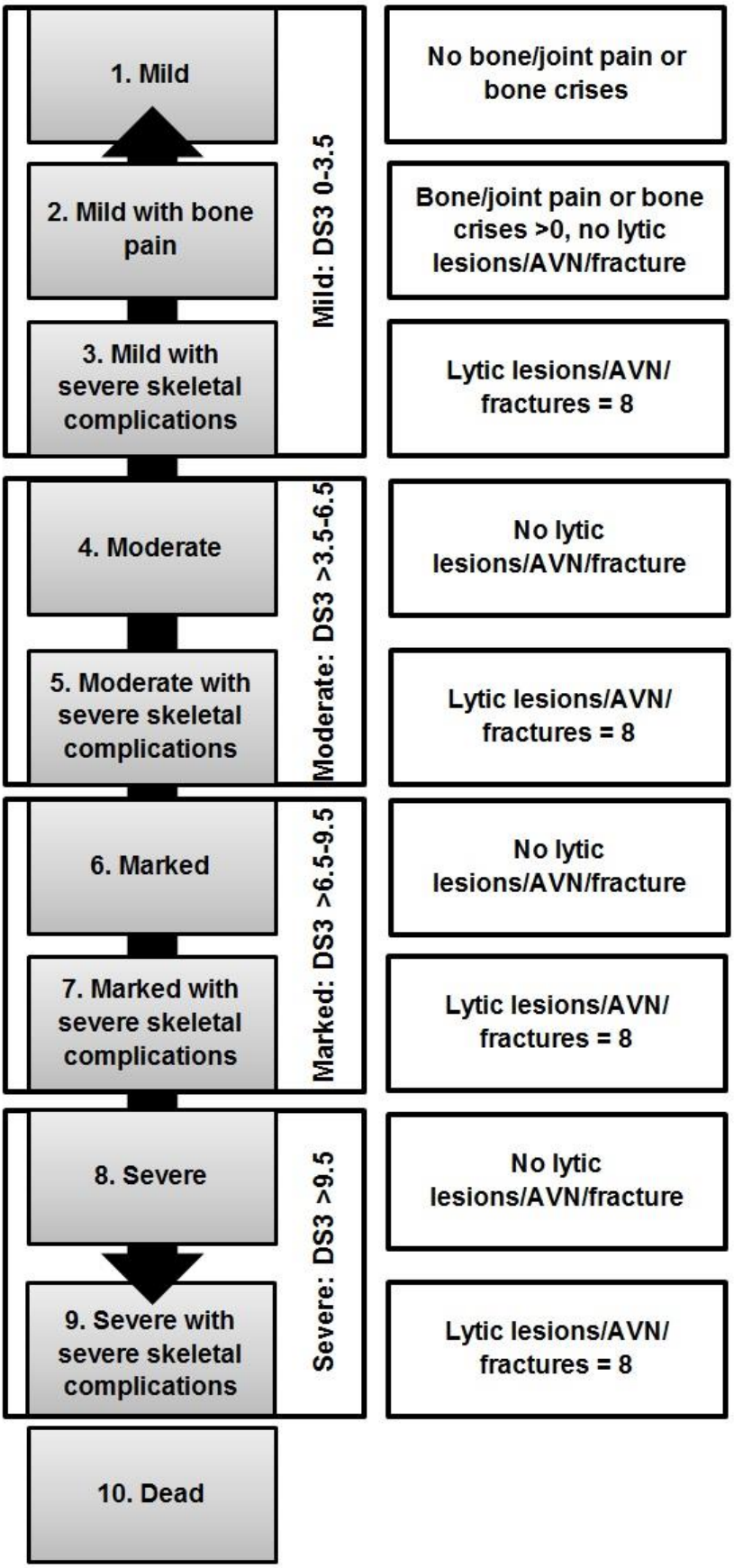
12.1.3 Provide a diagram of the model structure you have chosen.

Figure 23 shows the model schematic and a brief definition of the health states. Health states are defined by a patient's score on the GD-DS3. An overview of this validated GD1 specific measure is provided in Section 6.1. Patients can transition between any of the

living states per cycle, becoming more or less severe, or remaining in their current state. Patients can transition to the absorbing death state from any of the living DS3 states.

Within mild, moderate, marked and severe, the health states are divided by the presence of bone symptoms, based on individual assessment of the bone domain. All patients with moderate, marked and severe are assumed to have at least one instance of bone or joint pain or bone crisis, based on the contribution of this domain to the overall DS3 score. These higher DS3 states are split only by the presence of lytic lesions, avascular necrosis (AVN) or fracture.

Figure 23: Model schematic with description of health states



Notes: Lytic lesions / AVN/fractures have two response items on the GD-DS3 either absent "0" or present "8" – see Section 6.1 for details

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

The model states were chosen to be able to represent the distribution of patients across the severity range for symptoms. This will allow the model to account for the inherent heterogeneity in the Gaucher disease population.

Validation of the DS3 scoring system has been published and it has been found to be a suitable measure of disease status in GD1 and for assessing changes in symptom burden over time.[33] Health states are defined by a patient's score on the GD-DS3. An overview of this validated GD1-specific measure is provided in Section 6.1. The validation study for this measure reported that patients with "mild" disease as assessed by the CGI-S had GD1-DS3 scores <3, "moderate" disease correlated with DS3 scores of 3 to 6, "marked" disease 6 to 9, and "severe" disease >9. Correlation with the CGI-S was R^2 = 0.89 when both bone density and infiltration data were available. In the absence of these data points, the correlation was R^2=0.77 Weinreb et al. (2012).[128] These definitions are approximate to the definitions used in this model.

Eliglustat will be used in those adult patients with GD1 who are either stable on ERT, or as a first-line treatment option for those that are treatment naïve. These patient groups are further split by metaboliser status, which determined the recommended dose of eliglustat. Comparing to both imiglucerase and velaglucerase, this means that there are eight comparisons relevant to the decision problem:

- Versus imiglucerase for IM and EM patients initiated on treatment for the first time
- Versus imiglucerase for PM patients initiated on treatment for the first time
- Versus velaglucerase for IM and EM patients initiated on treatment for the first time
- Versus velaglucerase for PM patients initiated on treatment for the first time
- Versus imiglucerase for IM and EM patients stable on imiglucerase at baseline
- Versus imiglucerase for PM patients stable on imiglucerase at baseline
- Versus velaglucerase for IM and EM patients stable on velaglucerase at baseline
- Versus velaglucerase for PM patients stable on velaglucerase at baseline

In the Standard Operating Procedures (SOP) for Gaucher disease in England[34], it is stated that imiglucerase and velaglucerase are at present considered equivalent in potency. It is stated that velaglucerase is the first choice for initiation of therapy on the grounds that the acquisition cost of velaglucerase is lower than that for imiglucerase (taking into account

the commercially confidential discount on its list price agreed through a tendering process with the NHS Commercial Medicines Unit). Imiglucerase has been included as a comparator as an option for initiation of therapy because it is thought there may not be complete adherence to the Gaucher disease SOP. Prevalent ERT stable patients are on both imiglucerase and velaglucerase.

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Assumptions were made where there was a paucity of data, or where data limitations restricted the scope and flexibility of the disease pathway. These assumptions included:

- The treatment efficacy of eliglustat and the comparators is assumed to be equal in the treatment-naïve patient population. This is due to the absence of head-to-head trial data in these patients and no link between eliglustat and the comparators being possible in the indirect comparison in treatment naïve patients. As the eliglustat licence indicates non-inferiority of eliglustat to imiglucerase, this is expected to be a suitable assumption.
- After the trial period, it is assumed that the state transitions derived from DS3 Score Study data are the same for eliglustat and all the comparators analysed. This reflects the long-term stability of patients and the assumptions of comparable efficacy between the treatments.
- GD1 mortality is assumed to be equivalent across all patients regardless of their current health state or the proportion with splenectomy at the beginning of the model.
- ERT -naïve and ERT stable patients without splenectomy at the beginning of the model will not receive one during their time within the model. This assumption was supported by clinical expert opinion.[129]
- Patients receiving an ERT that discontinue treatment are assumed to go onto to receive the alternative ERT comparator. Patients within the eliglustat arm that discontinue are assumed to then receive the initial ERT comparator.
- It is assumed that ERT stable patients will not encounter any adverse events or discontinue from treatment (within the ERT arm), as they have been stable on treatment for several years.

- It is assumed discontinuation does not affect the efficacy of ERT treatment, and thus does not affect transitions between states. This is supported by the assumption of comparable efficacy between the treatments included in the model. It was assumed that no patients would be untreated, and this was supported by clinical expert opinion and the Wyatt et al. (2012) data.
- Although the ENGAGE trial was less than one year (39 weeks) in duration, the outcomes at 39 weeks are assumed to be those for patients at 1 year.
- AEs do not result in resource utilisation related to the events as all AEs within the model are all grades. This is because only a few serious (Grade 3/4) adverse events result in resource utilisation.
- Cost estimates developed based on each respective health state were based on assumptions, guidelines and key opinion leader (KOL) feedback. Published estimates were not comprehensive or reported by disease severity. These costs may be underestimating the cost of care for patients with higher DS3 scores, for example nursing home care for rehabilitation after surgery was not considered in these estimates.
- The model assumes that the availability of a well-tolerated oral therapy will not substantially alter clinical practice in the management of GD1; for example, by increasing the numbers of treated patients in England.

12.1.6 Define what the model's health states are intended to capture.

The distribution of the patient cohort by DS3 score and bone symptoms allows for meaningful differentiation of a heterogeneous patient population with regards to the cost and utility burdens associated with the disease. Combined, these health states cover the treated patient population for GD1, and death.

The health states are defined by a combination of the four DS3 severity levels, mild (DS3 score 0.0 to $\leq$ 3.5), moderate (DS3 score > 3.5 to $\leq$ 6.5), marked (DS3 score > 6.5 to $\leq$ 9.5), and severe (DS3 score > 9.5) and the absence or presence of bone pain/bone crisis or severe skeletal complications. SSC are defined by the presence of lytic lesions, AVN, or pathological fractures. The definitions of the nine health states are given in Table 46.

Table 46: Definition of health states used in economic model

Health state description	Definition of health state
1. Mild	DS3 score is 0-3.5 and no bone pain in past 30 days or no bone crises in past 12 months (both pain and bone crises items on the DS3 measure are 0) and the lytic lesions, AVN or pathological fractures are absent (relevant item on the DS3 measure is 0).
2. Mild + bone pain	DS3 score is 0-3.5 and no bone pain in past 30 days or no bone crises in past 12 months (either or both pain and bone crises items on the DS3 measure are > 0) and the lytic lesions, AVN or pathological fractures are absent (relevant item on the DS3 measure is 0).
3. Mild + SSC	DS3 score is 0-3.5 and no bone pain in past 30 days or no bone crises in past 12 months (either or both pain and bone crises items on the DS3 measure are > 0) and the lytic lesions, AVN or pathological fractures are present (relevant item on the DS3 measure is 8).
4. Moderate	DS3 score is >3.5-6.5 and the lytic lesions, AVN or pathological fractures are absent (relevant item on the DS3 measure is 0).
5. Moderate + SSC	DS3 score is >3.5-6.5 and the lytic lesions, AVN or pathological fractures are present (relevant item on the DS3 measure is 8).
6. Marked	DS3 score is >6.5-9.5 and the lytic lesions, AVN or pathological fractures are absent (relevant item on the DS3 measure is 0).
7. Marked + SSC	DS3 score is >6.5-9.5 and the lytic lesions, AVN or pathological fractures are present (relevant item on the DS3 measure is 8).
8. Severe	DS3 score is >9.5 and the lytic lesions, AVN or pathological fractures are absent (relevant item on the DS3 measure is 0).
9. Severe + SSC	DS3 score is >9.5 and the lytic lesions, AVN or pathological fractures are present (relevant item on the DS3 measure is 8).
Key: AVN, avascular necrosis; SSC, severe skeletal complications (response “8” on the AVN / fracture / lytic lesions item on the DS3 scale – “0” = absent and “8” = present).	

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in Table 47.

Table 47: Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon	70 years	Lifetime horizon for both treatment naïve and stable patient populations	NICE[116]
Cycle length	1 year	Cycle length used in previous evaluations of Gaucher disease interventions, appropriate given data available	Van Dussen *et al.* Connock *et al.*[37, 119]
Half-cycle correction	Half-cycle correction is applied	In line with recommendation	NICE[116]
Were health effects measured in QALYs; if not, what was used?	QALYs	In line with recommendation	
Discount of 3.5% for utilities and costs	3.5%	In line with recommendation	
Perspective (NHS/PSS)	NHS and PSS in England	In line with recommendation	

Key: NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; QALYs, quality-adjusted life years.

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-consequence analysis.

The description of how the data from clinical evidence were used in the cost-consequence analysis are shown in Section 17.5 (Appendix 5).

Short-term transitions

The transition probabilities for the first cycle of the model were derived from the ENGAGE and ENCORE clinical trials and represent patients' responses to treatment during the trial period. For the ENCORE trial this was from randomisation to 52 weeks. For the ENGAGE trial, this was from randomisation to 39 weeks. The movements of patients within this 9 month period are applied for the first year-long cycle of the model.

In the base case, these transition probabilities were derived from the respective trial arms of the ENCORE trial, or the eliglustat arm of the ENGAGE trial.

For the treatment-naïve population, both arms were parameterised using the eliglustat arm of the ENGAGE trial, with the assumption that there is no significant difference in efficacy. This assumption is made as there is insufficient data to create a network meta-analysis including the comparators in the model, and the ENGAGE trial was placebo controlled. The limitations of the evidence base in this patient population have been described previously in Section 9.4.

In the ERT stable population, eliglustat is modelled using transition probabilities based on the eliglustat arm of the ENCORE trial, and both comparators (imiglucerase and velaglucerase) were modelled using the imiglucerase arm of the trial. This assumed that both imiglucerase and velaglucerase have equivalent efficacy. This assumption is supported by available RCT evidence and the ITC undertaken to assess the relative efficacy of treatments (Section 9.8). In sensitivity analyses, a scenario was run in which the treatment efficacy between eliglustat and comparators was assumed to be the same, and the transition probabilities applied were derived from the pooled data from both arms of the ENCORE trial.

Transitions for Longer-Term Projections

Data from the DS3 Score Study were used to estimate the annual transition probabilities for time periods beyond that of the clinical trials. Observations from all of the patients in the DS3 Score Study data were pooled, excluding patients whose clinical assessments were made before starting ERT, who were missing a DS3 score (and hence the health state), or were missing information on when they initiated ERT. Each patient's follow-up time in the DS3 Score Study was divided into years (12-month intervals) starting with each patient's date of ERT initiation. The first 12 months that a patient was using ERT was defined as Year 0, the second 12 months (Months 13 through 24) were defined as Year 1, and so on.

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Patient transitions between the DS3 health states are extrapolated beyond the trial period for which comparative data are available, and beyond the period covered by the available registry data. As such, the model assumes that there is no incremental clinical benefit of

eliglustat in the long-term. Costs are applied using health state-specific healthcare resource use profiles and UK-specific unit costs and these are held constant over the duration of the model, based only on patient survival and DS3 state. The extrapolation of transition probabilities in the long term is described previously.

Costs for each annual cycle in the model, including the trial-based period and all post-trial periods, are assessed using health state-specific healthcare resource use profiles and UK-specific unit costs.

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

No intermediate outcomes were used. The health states were defined according the components of the DS3 score. The DS3 score, which is a validated measure, synthesises information regarding haematological, organ, and skeletal symptoms.[33]

12.2.4 Were adverse events included in the cost-consequence analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Adverse events

The studies identified in the systematic literature review in which adverse event data were identified are shown in Table 48 and Table 49. Safety data from these publications were pooled and split between patient populations (treatment naïve and stable on ERT or SRT), to provide the incidence of AEs for each patient population. These event rates are shown in an additional appendix in Section 19.2.

Table 48: Source of adverse data in treatment experienced patients

Study used	Drug	Time point (months)	Source of AE data
Elstein, 2007	Imiglucerase	6	FDA review P6, table 158, page 4 of 46
Genzyme (ENCORE)	Eliglustat	12	Table 14-3-1-5, page 1783 of 2439. CSR table 11-3 and below (p124)
Genzyme (ENCORE)	Imiglucerase	12	Table 14-3-1-5, page 1783 of 2439. CSR table 11-3 and below (p124)
Zimran, 2013	Velaglucerase	12	FDA review Table 38 (p103)
Key: AE, adverse event; CSR, clinical study report; FDA, Food and Drug Administration.			

Table 49: Source of adverse event data in treatment naïve patients

Study used	Drug	Time point (months)	Source of AE data
Genzyme (ENGAGE)	Eliglustat	9	CSR table 11-2 (p145) to table 14.3.1.4 (p1365), table 14.3.5.8 (p1664)
Ben Turkia, 2013	Velaglucerase	9	FDA review (p57), Vpriv EPAR (p48)
Ben Turkia, 2013	Imiglucerase	9	FDA review (p57), Vpriv EPAR (p48)
Zimran, 2010	Velaglucerase	9	Publication
Gonzalez, 2013	Velaglucerase	12	FDA review text (p44), Table 11 (p45), Table 40 (p107)
Genzyme (Phase II)	Eliglustat	48	CSR table 11-2 (p125), Table 14.3.1.4 (p1408), Table 14.3.5.9 (p3240)
Key: AE, adverse event; CSR, clinical study report; FDA, Food and Drug Administration. **Notes:** * Data for neuropathy has 24 months of follow-up.			

From the safety data available for the modelled treatments, events that occurred in 15% of patients or greater were deemed frequent enough to be included in the model. The adverse events considered within the model were derived from pooled data from the ENGAGE and ENCORE trials and published studies. The treatment populations were pooled to obtain anticipated adverse event rates for both populations. The pooled rates are presented in Table 50. The rates presented are for all grades of severity, and there is no differentiation between high and low grade events.

The duration of risk of all AEs was assumed to be 36 months for all the treatments in the model. This is in line with the assumption that patients are stable on treatment after this time and will not discontinue due to AEs.

Table 50: Annualised adverse event rates by treatment - Pooled rates by ENCORE and ENGAGE and published studies

Adverse event*	Eliglustat	Imiglucerase	Velaglucerase
Back pain	9.21%	4.62%	19.48%
Abdominal pain	9.21%	1.54%	18.18%
Joint pain	18.42%	12.20%	23.81%
Fever	3.95%	2.44%	14.63%
Weakness	0.00%	0.00%	16.22%
Infusion reaction	0.00%	7.14%	39.36%
URTI	10.53%	5.66%	33.85%
Dizziness	7.24%	0.00%	29.73%
Headache	16.45%	3.66%	32.98%

Key: URTI upper respiratory tract infection.
Notes: * see Table 48 and Table 49 for sources of AE rates

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Table 51 presents details of the approach taken to obtain expert validation of the modelling methods and parameterisation. Two clinicians with extensive experience in treating Gaucher disease were approached to validate general model assumptions and specific data sources for efficacy and resource use. Their input was used to tailor model parameterisation to the perspective of the NHS in England, and ensure the relevance of clinical and treatment assumptions.

Table 51: Approach taken to obtain clinical validation of model assumptions and parameters

Detail	Response
Criteria for selecting experts	Prominence in field and involvement in previous clinical and economic assessments in treatments for GD1
Number of experts approached	Two
Number of experts who participated	Two
Declaration of conflict of interest	No conflicts stated
Background information provided	Description of the data analysis methods, final results of transition probabilities and resource use profile derivations, and the general Markov model and assumptions
The method used to collect opinions	Individual interviews
The medium used to collect opinions	Telephone interviews and circulation of minutes for approval
Questions asked	Interviews were not structured, questions were not pre-specified
Use of iteration to obtain consensus	Not used, although experts approved minutes of the interviews, and were presented with amended analyses and methods for approval following their feedback

12.2.6 Summarise all the variables included in the cost-consequence analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table D5 below.

The parameters included in the model are listed in Table 52. Due to their size, the complete matrices for DS3 health state distribution at baseline and transition probabilities are not included here, but are presented elsewhere (Section 17.5 [Appendix 5]).

Table 52: Summary of variables applied in the economic model

Variable	Value			CI (distribution)	Reference to section in submission
Model settings					
Discount rate – health outcomes	3.5%			Not tested in sensitivity analyses	0
Discount rate – cost outcomes	3.5%			Not tested in sensitivity analyses	
Patient characteristics					
Starting age	32 years treatment naive and 38 years for ERT stable			Not tested in sensitivity analyses	12.1.1
Patient weight	67.5kg			SE = 1.3738 (Normal)	12.3.6
Proportion of patients splenectomised at baseline	0% for treatment naïve population, 25% for ERT stable population			± 20% of mean (Beta)	12.1.1
Mortality					
Gaucher mortality - intercept	7.1626			Not tested in sensitivity analyses	17.5 (Appendix 5)**Error! Reference source not found.**
Gaucher mortality - gamma	0.0647				
Discontinuation					
Treatment discontinuation rate per annum – eliglustat	1.89%			± 20% of mean (Beta)	17.5 (Appendix 5)
Treatment discontinuation rate per annum – imiglucerase and velaglucerase (treatment naïve)	1.89%			± 20% of mean (Beta)	
Treatment discontinuation rate per annum – imiglucerase and velaglucerase (ERT stable)	0%				
Period in which patients can discontinue – All treatments	3 years			± 20% of mean (Normal)	
Adverse events					
Adverse event rates (per year)	Eli	Imi	Vel		
Back pain – Pooled populations	9.21%	4.62%	19.48%	± 20% of mean (Beta)	12.2.4
Abdominal pain – Pooled populations	9.21%	1.54%	18.18%		
Joint pain – Pooled populations	18.42%	12.20%	23.81%		

Variable	Value			CI (distribution)	Reference to section in submission
Fever – Pooled populations	3.95%	2.44%	14.63%		
Weakness – Pooled populations	0.00%	0.00%	16.22%		
Infusion reaction – Pooled populations	0.00%	7.14%	39.36%		
URTI – Pooled populations	10.53%	5.66%	33.85%		
Dizziness – Pooled populations	7.24%	0.00%	29.73%		
Headache – Pooled populations	16.45%	3.66%	32.98%		
Period in which patients can suffer AEs – All treatments	36 months			± 20% of mean (Normal)	
Dosing					
Capsules per year – eliglustat	730.5			Not tested in sensitivity analyses	12.3.6
Infusions per year – imiglucerase, velaglucerase	26.09			Not tested in sensitivity analyses	
Costs					
Cost per capsule of eliglustat	£282.34			Not tested in sensitivity analyses	12.3.6
Cost per vial – imiglucerase (400 U)	£1071.29			Not tested in sensitivity analyses	
Cost per vial – velaglucerase (400 U)	£1,410.00			Not tested in sensitivity analyses	
Drug cost per year – eliglustat	£206,249.37			Not tested in sensitivity analyses	
Drug cost per year – imiglucerase	£199,976.46			Not tested in sensitivity analyses	
Drug cost per year – velaglucerase	£263,203.06			Not tested in sensitivity analyses	
Admin cost – Home	£0.00			Not tested in sensitivity analyses	12.3.6
Admin cost – Home with nurse care	£114.00			± 20% of mean (Gamma)	
Admin cost – Day unit	£309.45			± 20% of mean (Gamma)	
Direct medical resource use cost: DS3 state 1	£2,583.05			± 20% of mean (Gamma)	12.3.7
Direct medical resource use cost: DS3 state 2	£2,707.01			± 20% of mean (Gamma)	
Direct medical resource use	£5,371.82			± 20% of mean	

Variable	Value	CI (distribution)	Reference to section in submission
cost: DS3 state 3		(Gamma)	
Direct medical resource use cost: DS3 state 4	£2,688.03	± 20% of mean (Gamma)	
Direct medical resource use cost: DS3 state 5	£5,385.57	± 20% of mean (Gamma)	
Direct medical resource use cost: DS3 state 6	£4,536,95	± 20% of mean (Gamma)	
Direct medical resource use cost: DS3 state 7	£6,303.61	± 20% of mean (Gamma)	
Direct medical resource use cost: DS3 state 8	£4,536.95	± 20% of mean (Gamma)	
Direct medical resource use cost: DS3 state 9	£6,303.61	± 20% of mean (Gamma)	
Social services cost: DS3 state 3	£108.02	± 20% of mean (Gamma)	
Social services cost: DS3 state 5	£108.02	± 20% of mean (Gamma)	
Social services cost: DS3 state 6	£108.02	± 20% of mean (Gamma)	
Social services cost: DS3 state 7	£108.02	± 20% of mean (Gamma)	
Social services cost: DS3 state 8	£108.02	± 20% of mean (Gamma)	
Social services cost: DS3 state 9	£108.02	± 20% of mean (Gamma)	
Utilities			
Utility – DS3 state 1	0.764	SE = 0.028 (Beta)	
Utility – DS3 state 2	0.666	SE = 0.022 (Beta)	
Utility – DS3 state 3	0.683	SE = 0.046 (Beta)	
Utility – DS3 state 4	0.686	SE = 0.020 (Beta)	
Utility – DS3 state 5	0.606	SE = 0.061 (Beta)	10.1.3
Utility – DS3 state 6	0.642	SE = 0.038 (Beta)	
Utility – DS3 state 7	0.561	SE = 0.058 (Beta)	
Utility – DS3 state 8	0.596	SE = 0.078 (Beta)	
Utility – DS3 state 9	0.515	SE = 0.074 (Beta)	
Disutility – AE: Back pain	-0.0187	± 20% of mean (Beta)	10.1.8
Disutility – AE: Joint pain	-0.0012		
Disutility – AE: Abdominal pain	-0.0006		
Disutility – AE: Infusion	-0.0110		

Variable	Value	CI (distribution)	Reference to section in submission
reaction			
Disutility – AE: URTI	-0.0001		
Disutility – AE: Dizziness	-0.0004		
Oral administration increment	0.12[1]	0.146 to 0.326 (Beta)	
Key: AE, adverse event; CI, confidence interval; SE, standard error; Eli, eliglustat; ERT, enzyme replacement therapy; Imi, imiglucerase; Vel, velaglucerase; URTI upper respiratory tract infection.			

12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The HRG codes used in the model to cost the direct medical resource use in the management of Gaucher disease Type 1 are presented below in Table 53. These reflect how the disease is assumed to be monitored and managed in UK clinical practice, and how the cost inputs of the model have been derived from NHS Reference Costs[130]. The costs applied broadly correspond to routine clinic visits and non-face to face contact, periodic scans to monitor the development of clinical symptoms, and non-elective inpatient stays and accident and emergency (A&E) visits for the management of disease-related complications (liver disease, lung disease and skeletal complications).

The frequencies of the use of these resources, and how these change based on disease severity is described in more detail in Section 12.3.7. The choice of resources required was based on a published survey of medical resource use for Gaucher disease patients in the UK.[42]

[1] Nalysnyk *et al.,* 2016: Poster presented at European Working Group on Gaucher Disease (June 30 – July 2, 2016)

Table 53: Healthcare Resource Group codes used in the model

HRG Code	Use in analysis
WF01A: Non-consultant led face to face outpatient attendance, follow-up - Clinical Genetics (311)	Nurse clinical visits
N29AN: Community Health Services - Nursing: Other Specialist Nursing, Adult, Non face to face	Specialist nurse telephone call
WF01A: Consultant led face to face outpatient attendance, follow-up - Clinical Genetics (311)	Consultant clinic visits
DAPS04: Clinical Biochemistry. Total.	Routine blood testing
DAPS05: Haematology. Total.	
RA01A: MRI scan, 1 area, no contrast, 19+ years	Periodic MRI scans for monitoring bone marrow burden
RA04Z: MRI scan, 2-3 areas, no contrast	
RA07Z: MRI scan, extensive repositioning and /or >1 contrast agent.	
DIAGIMOP - RD50Z: Dexa Scan	Bone scans to monitor the progression of bone symptoms
DIAGIMOP –: RAD40Z Ultrasound Scan, < 20 minutes	Ultrasound scans to monitor visceral symptoms
Consultant led outpatient attendance: WF01B: Non-admitted face to face attendance, first – Diagnostic imaging (812)	Periodic face-to-face clinician contact accompanying diagnostic scans
GC17A-K –Average of non-elective long and short stays	Used to cost the management of lung and liver disease associated with Gaucher disease
EB12A-E – Other Acquired Cardiac Conditions Average of non-elective long and short stays	
C HN13A-F HB12A-C and HB61A-C by number of FCEs – Trauma and Orthopaedics REHABL2 - VC18Z: Rehabilitation for joint replacement	Orthopaedic inpatient stays required during which joint replacement is necessary
Unspecified pain: WH08A-B, HD23H. HD23J Inflammatory, Spine, Joint or Connective Tissue Disorders with CC score 0-2 and 3-4	Orthopaedic inpatient stays for bone pain and skeletal disorders, but not requiring joint replacement
TA01NA-TA04NA by number of FCEs. All A&E visits not leading to admission.	Accident and emergency visits
Key: HRG, Healthcare Resource Group; MRI, magnetic resonance imaging.	

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

A systematic review of cost and resource use data was performed to gather and examine the available data for the costs of Gaucher disease and its management.

The full strategies used in the electronic database searches are included in Section 17.3 (Appendix 3). The following databases were searched: Medline, Medline In-process, EMBASE, The Cochrane Library (NHS EED and HTA database) and EconLit. The initial searches were run between 30 May 2014 and 12 June 2014, with update searches performed between 27 July and 14 August 2015, to identify newly published studies. The updates used identical search strategies but were restricted to studies published in or after 2014.

In primary screening, records that were identified in the electronic searches were assessed for relevance against the inclusion and exclusion criteria shown in Table 54. Assessment of the full text articles of those carried through from primary screening determined final eligibility of studies.

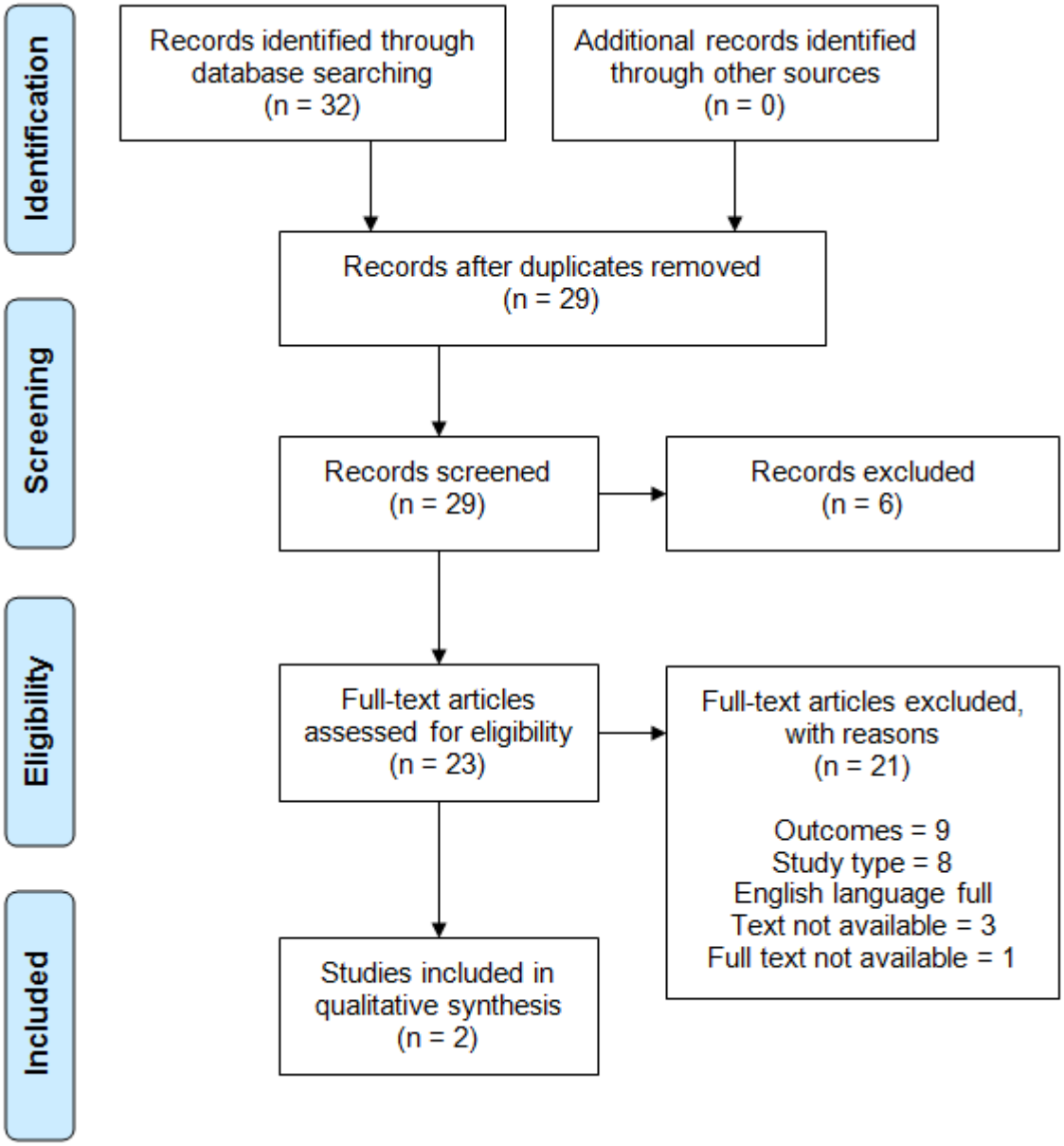
Table 54: Inclusion and exclusion criteria for cost and resource use review

Inclusion Criteria		
Category	**Criteria**	**Rationale**
Study type	Primary studies, economic evaluations reporting cost and/or resource use outcomes, costing studies of trial patients	These study types will report the relevant outcomes.
Population	Studies will include patients with Type 1 Gaucher disease, but may include other types of the disease.	The aim was to restrict the search to the relevant population, but other types of Gaucher disease could be included in combination.
Interventions	No restriction by treatment. Untreated patients included.	Any cost outcomes were included in the search, regardless of treatment status.
Outcomes	Any outcomes quantifying the costs and/or resource use requirements of Gaucher disease, its management and disease or treatment-related adverse events, as incurred by the NHS in the UK and HSE in Ireland	This criterion satisfies the aims of the review.
Comparators	No restriction by treatment. Untreated patients included.	Any cost outcomes were included in the search, regardless of treatment status.
Language	Studies must be available in English.	
Exclusion Criteria		
Category	**Criteria**	**Rationale**
Publication type	Systematic and non-systematic reviews, letters and comment articles	These study types are not appropriate.
Publication date	Studies published before 1 January 1990	It is not expected that any relevant studies were published prior to this date.
Key: NHS, National Health Service; HSE, Health Service Executive.		

Screening of search results

The electronic searches identified 32 unique records, of which 6 were excluded following assessment of the titles and abstracts. At secondary screening, 21 papers did not meet the inclusion criteria, with the main reason for exclusion being inappropriate study type or irrelevant outcomes. The selection process is shown diagrammatically in Figure 24. Two studies met the inclusion criteria and are summarised below.

Figure 24: PRISMA diagram for cost and resource use review



Summary of included studies

Connock *et al.* built a *de novo* model to assess the cost-effectiveness of ERT compared with standard care.[37] The costs that the authors included in the model were obtained from standard UK references (British National Formulary and National Schedule of reference costs). Assumptions were made regarding the underlying frequency of medical resource use requirements. The costs included per-cycle costs for each health state based on SSI levels, plus additional costs for splenectomy and ERT. The annual health state costs and cost of ERT are presented in the study summary in Table 55. Unit costs and assumed frequency of resource requirement are described in Section 17.3 (Appendix 3).

Wyatt et al. conducted a longitudinal study of a cohort of patients with lysosomal storage disorders.[42] Of the cost and resource use outcomes reported in the study, the authors report the average annual costs of each resource and the percentage of patients in the cohort that required different health care services. The average medical costs of ERT and SRT treatments were also reported. The costs and frequency of the resources and services included in the study are presented in full in Section 17.3 (Appendix 3). The mean costs presented include patients for which the resource use (and therefore cost) was zero, and so should be interpreted as a mean annual resource use cost across the patient population (i.e. this incorporates the frequency of resource requirements). The median costs presented include only non-zero costs.

Table 55: Summary of cost and resource use studies

Publication	Country	Population	Study type	Resource use and costs included
Connock *et al.*[37]	UK	Type 1 Gaucher disease	Economic model	**Annual health state costs** Mild SSI: £912 Moderate SSI: £3,144 Severe SSI: £7,857 Annual cost of ERT: £85,501
Wyatt *et al.*[42]	UK	Types 1 and 3 Gaucher disease	Costing study of patients treated with ERT and SRT	• Unit costs and frequency for: • Hospital services • Social care services • Medical treatment

Key: ERT, enzyme replacement therapy; SRT, substrate replacement therapies; SSI, severity scale index.

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[1].

The costing and resource use parameters of the model were validated with clinical experts, as part of the general validation of the model and analysis, as described earlier in Section 12.2.5.

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

The anticipated list price per capsule for eliglustat is £282.34. Section 12.3.6 below presents the estimated cost per year of treatment.

12.3.5 If the list price is not used in the de novo cost-consequence model, provide the alternative price and a justification.

The analyses presented in this document include only the anticipated list price for eliglustat.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost consequence model. A suggested format is provided in tables D6 and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

Determination of metaboliser status

Eliglustat is indicated for patients with poor, intermediate and extensive metaboliser status. This requires a laboratory test to determine the status of patients prior to the initiation of treatment. This cost is not included in the model, as this cost will be covered by Genzyme.

Drug costs

The unit costs of the drugs used in the model are listed in Table 56. The dosing of each drug and the cost per annual cycle applied in the model are also presented in Table 57. Where the dosing is based on weight, an average weight of 67.5kg has been used, which was the mean weight in the imiglucerase arm of the ENCORE study. This is assumed to remain constant over the duration of the model.

Patients receiving eliglustat take two 100mg capsules daily, a total of 730.5 capsules over the course of the average year. The anticipated price per capsule for eliglustat presented in Table 56; the total drug cost is £206,249.37 per year. For poor metabolisers, who will receive a total of 365.25 capsules per year, the total drug cost is £103,124.69 per year.

Imiglucerase is dosed at 42.4 U/kg every 2 weeks, with a total of 26.09 doses per year on average. This dose is based on the mean dose received by patients in the imiglucerase

arm of the ENCORE clinical trial. The weight used to calculate the amount of drug required by patients is 67.5 kg, the mean weight of patients in the imiglucerase arm of the ENCORE. Applying the unit cost for the smallest vial of imiglucerase presented in Table 56, this gives a total drug cost per year of £199,976.

Velaglucerase is assumed to be dosed at 42.4 U/kg every 2 weeks, matching the dosing of imiglucerase as described above. The rationale for this assumption is that the two drugs have been shown to have comparable efficacy at the same dose, as outlined in Section 9.8.1[63], and the drugs share the same efficacy in the model. In the absence of more appropriate data, this assumption is expected to be the most suitable. The unit cost of a 400U vial is presented in Table 56. Over a year of treatment, the total of 26.09 doses received is expected to cost £263,203, although Genzyme are aware that a confidential discount exists for velaglucerase. This discount has been tested in scenario analysis ranging from a 0% to 80% discount on the list price.

Table 56: Technologies unit costs

Drug	Tablet dose (pack size) /vial dose	Cost per vial/pack/capsule	Source
Eliglustat	100mg	£282.34 per capsule	Genzyme
Imiglucerase	200U	£535.65	BNF 2014[131]
	400U	£1,071.29	
Velaglucerase	400U	£1,410	MIMS 2015[132]
Key: BNF, British National Formulary; MIMS, Monthly Index of Medical Specialities.			

Table 57: Dosing and drug cost per year

Drug	Total dose required	Frequency of administration	Number of doses/tablets per year	Total drug cost per cycle/year (incl. any PAS)
Eliglustat	2 x 100mg (IM and EM) 1 x 100mg (PM)	Daily	730.5 (IM and EM) 365.25 (PM)	£206,250 (IM and EM) £103,125. (PM)
Imiglucerase	42.4U/kg	Every 2 weeks	26.09	£199,976
Velaglucerase	42.4U/kg	Every 2 weeks	26.09	£263,203
Key: EM, extensive metaboliser; IM, intermediate metaboliser; PAS, patient access scheme; PM, poor metaboliser.				

Administration costs

Administration of IV ERT treatment was assumed to be within one of three settings; self-administration at home, home requiring nurse support or day unit hospital attendance. A separate category is also considered for self-administration for oral treatment with eliglustat. The unit costs and proportions of patients assumed to receive IV treatment in each setting are presented in Table 58.

Two assumptions were made in deriving the distributions of administration settings for each treatment. Firstly, it was estimated that 96% of ERT administration would happen outside of hospital. Secondly, of those administered inside the home, 50% would be performed without nurse attendance. The proportions of administrations happening in each location are presented in Table 58. These figures were derived from practice at the UK treatment centres, responsible for the management of approximately 80% of GD1 patients in the UK (Addenbrooke's Hospital, Cambridge and the Royal Free Hospital, London).[47] These data were used to produce a weighted average of the administration of IV ERT.

In addition to the administration costs, further costs were applied in the model relating to the provision of home care services. These provisions include delivery of the drug to the home, nursing costs and the provision of a refrigerator and administration pump. These costs were calculated by assuming that they were equal to 7.3% of the list price of imiglucerase.[3] As only 48% of patients receive support from a nurse to administer ERT, to avoid double counting or overestimating costs, the annual cost of homecare has been reweighted to account for homecare costs with and without nursing support. These costs are presented in Table 58. The model also includes an assumed £40 monthly cost of delivery for eliglustat. Exact costs of ERT infusion are available in the agreed Homecare costs to the NHS agreed by the Commercial Medicines Unit. These costs are not available to Genzyme and are the commercially confidential property of the Homecare companies.

Table 58: Cost and setting of administration of intravenous (IV) ERT

Administration Setting	Proportion	Unit Cost	Source
Home: independent administration	48%	£0.00	Assumption
Home: with nurse support	48%	£114	PSSRU 2015. 10.1: Community nurse. Unit cost per hour of patient-related work, including qualifications. Assumed 2 hour infusion time (2 x £58)[133]
Day unit (haematology)	4%	£309.45	NHS Reference costs 2014-2015: Other haematological or Splenic Disorders with CC score 0-2 – Day Case
Average administration cost		£67.10	Weighted average
Annual cost of homecare services applied to ERTs		£12,569	Assumption that homecare costs are 7.3% of list price of imiglucerase[3] for 50% of patients and for 50% of patients this cost minus cost of nurse support
Annual cost of delivery of eliglustat		£40 x 12 = £480	Assumption
Key: PSSRU**,** Personal Social Services Research Unit.			

Table 59 and Table 60 below present the total costs per patient per year for eliglustat and the comparators in the model. It is assumed that neither eliglustat nor comparators require additional training of healthcare staff. The calculations of the drug and administration costs are presented above, and the treatment-specific monitoring costs are assumed to be zero. The medical and social services resource use costs are modelled based on DS3 state, and the calculation of these is presented in Section 12.3.7.

Table 59: Costs per treatment/patient per year associated with eliglustat in the cost-consequence model

Items	Value	Source
Price of the technology per treatment/patient – IM and EM patients	£206,249.95	See cost calculations above. Anticipated list price
Price of the technology per treatment/patient – PM patients	£103,124.97	
Management cost (delivery, homecare services etc.)	£480	Assumption of the cost of the delivery of eliglustat to the patient's home
Training cost	£0.00	Assumption
Other costs (monitoring, tests, etc.)	£0.00	Assumption
Total cost per treatment/patient – IM and EM patients	£208,249.95	
Total cost per treatment/patient – PM patients	£105,124.97	
Key: EM, extensive metaboliser; IM, intermediate metaboliser; PM, poor metaboliser.		

Table 60: Costs per treatment/patient per year associated with the comparators in the cost-consequence model

Items	Value: imiglucerase	Value: velaglucerase	Source
Cost of the comparator per treatment/patient	£199,976	£263,203	See cost calculations above
Costs of infusing in hospital + cost of home with nurse support	£1751	£1751	(0.48*114+0.04*309.45)*26.09
Homecare costs	£12,587	£12,587	£199,976*0.073*0.96 – (0.48*114*26.09)
Training cost	£0.00	£0.00	Assumption
Other costs (monitoring, tests, etc.)	£0.00	£0.00	Assumption
Total cost per treatment/patient	£214,314	£277,540	
Key: ERT, enzyme replacement therapy; IV, intravenous.			

Health-state costs

12.3.7 If the cost-consequence model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in Section 12.1.6. Provide a rationale for the choice of values used in the cost-consequence model.

Resource use costs

Patients in more severe stages of disease were expected to require greater levels of medical resource use. Table 61 shows the frequency of resource requirements and the proportion of patients assumed to use these costs. These figures were derived from the UK guidelines[40], published literature and clinical expert opinion from a clinician caring for patients with GD1 at a specialist centre in the UK.[129] The main published source used for this definition of the resource use profiles is a survey of UK patients with Gaucher disease (n=132).[42] The survey published an estimate for annual costs; however, it did not report costs by disease severity, separate out ERT administration related costs, or capture routine monitoring costs. Resource profiles for some services were estimated from this study, and so were discussed with the KOL and taken into consideration when each of the state specific profiles were developed. In general, the KOL considered the survey cost estimates did not reflect the current management patterns which revolve around a specialist centre, and so some of the values were revised based on KOL advice, except for some outpatient services (e.g. therapist visits) where the KOL felt the estimates were more appropriate.

The costs incurred are divided across four categories; medical services, specialist centre based care and hospital-based care, which make up the direct medical services use in the model, and social service use.

Medical services

These services reflect the costs associated with general practitioner (GP) visits and therapists (counsellor, psychologist, physiotherapist and occupational therapist). The number of GP visits (e.g. for the purpose of referrals, and pain management) is assumed to increase with disease severity and physical therapy and occupational therapy visits are assumed to be associated with skeletal complications. Other services (e.g. counsellor, psychologist, and other therapists) were derived from data published in Wyatt *et al.* (2012) [42] and were assumed not to vary by health state. Unit costs were all obtained from the Personal Social Services Research Unit (PSSRU).[134]

Specialist centre based care

The costs include specialist visits, support from a nurse at the centre and monitoring tests (i.e. haematological, organ volume, bone marrow burden, and bone density). The specialist centre based care costs were derived based on feedback from the KOL who cares for patients with GD1 at a specialist centre in the UK. All patients are assumed to attend a centre for face-to-face consultations with a specialist/consultant and for monitoring. In addition, nurses based at the clinic manage the visits to the clinics for tests and also provide ongoing care with regular follow up calls to facilitate patients accessing appropriate services. This can become particularly complex as many patients travel long distances to reach a centre for face-to-face visits, and these calls are assumed to be bi-weekly and increase with the disease severity. The resource use profiles for each state were developed after considering the UK guidelines for routine monitoring and considering feedback on current management practices from the KOL.

Multiple monitoring tests are planned for each clinic visit, and the typical tests are primarily based on UK guidelines[40], discussed with a specialist and adjusted to reflect their current practice patterns for each health state. Based on the guidelines[40], bone marrow burden is conducted every 5 years. Bone density monitoring frequency increases when osteoporosis is present. The testing frequency for abdominal imaging for spleen and liver size is assumed to increase with increasing DS3 score.

Hospital-based care

Acute care costs include hospital visits (e.g. for orthopaedic-related procedures for joint replacement, fracture avascular necrosis, lytic lesions), and accident and emergency room visits. Unit costs for each of these categories are presented in

Table 62. The cost of a hospital stay for a joint replacement is calculated as a weighted average cost for shoulder, knee and hip replacement procedures. The cost of orthopaedic inpatient stays which were not for joint replacement procedures were calculated as the weighted average of NHS reference costs for pain procedures and musculoskeletal and connective tissue disorders.

Social services

Social services (social worker, home help and housing worker) are assumed to be used by all patients with severe skeletal complications, marked or severe disease. The number of visits per year with a social worker, home care work or housing worker was derived from the survey conducted by Wyatt *et al*. (2012).[42]

Bisphosphonates

Bisphosphonates are included in the model for the management of osteoporosis. The total cost of treatment patients would expect to receive (6 years)[129] is distributed over the time horizon of the model and applied to the proportion of patients suffering osteoporosis in each health state, which is presented in Table 61. The drug unit costs assumed to be used to treat osteoporotic patients are presented in

Table 63, from which a weighted average of £107.22, based on a distribution across the three products, which was elicited from clinical opinion.[129]

Costs applied in model

Table 64 presents the direct medical and social service costs applied in the model per cycle for each of the living health states. Other than the effects of discounting, these costs are assumed to be fixed over time and between treatment arms.

Table 61: Frequency of medical resource use assumed in the model

	DS3 Health State																	
	1		2		3		4		5		6		7		8		9	
Resource use	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**
Medical services																		
GP visits	100	1	100	4	100	4	100	1	100	4	100	4	100	4	100	4	100	4
Counsellor	1	3	1	3	1	3	1	3	1	3	1	3	1	3	1	3	1	3
Other therapist	4	2	4	2	4	2	4	2	4	2	4	2	4	2	4	2	4	2
Psychologist	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
Occupational therapist	0	0	0	0	100	1	0	0	100	1	0	0	100	1	0	0	100	1
Physical therapist	0	0	0	0	100	3	0	0	100	3	0	0	100	3	0	0	100	3
Specialist centre based care																		
Nurse clinic visit	100	2	100	2	100	2	100	2	100	2	100	2	100	2	100	2	100	2
Nurse management calls	100	26	100	26	100	52	100	26	100	52	100	52	100	52	100	52	100	52
Consultant clinic visit	100	2	100	2	100	2	100	2	100	2	100	2	100	2	100	2	100	2
Blood counts and CHITO	100	2	100	2	100	2	100	2	100	2	100	2	100	2	100	2	100	2
Bone marrow burden MRI	100	0.2	100	0.2	100	0.2	100	0.2	100	0.2	100	0.2	100	0.2	100	0.2	100	0.2
Dexa scan	100	0.2	100	0.23	100	0.23	100	0.23	100	0.335	100	0.335	100	0.335	100	0.335	100	0.335
Abdominal imaging	0	0	0	0	100	1	100	1	100	1	100	2	100	2	100	2	100	2
Hospital based acute care																		
Liver/lung disease inpatient stay	0	0	0	0	0	0	0	0	0	0	100	0.5	100	0.5	100	0.5	100	0.5
Orthopaedic inpatient stay (with hip/joint replacement)	0	0	0	0	10	1	0	0	10	1	0	0	10	1	0	0	10	1

	DS3 Health State																	
	1		2		3		4		5		6		7		8		9	
Resource use	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**
Orthopaedic inpatient stay (without joint replacement)	0	0	0	0	90	1	0	0	90	1	0	0	90	1	0	0	90	1
A&E visits	0	0	0	0	5	2	0	0	5	2	0	0	5	2	0	0	5	2
Social services																		
Social worker	0	0	0	0	2	1	0	0	2	1	2	1	2	1	2	1	2	1
Home help/care worker	0	0	0	0	3	145	0	0	3	145	3	145	3	145	3	145	3	145
Housing worker	0	0	0	0	1	5	0	0	1	5	1	5	1	5	1	5	1	5
Treatment of osteoporosis(proportion of patient requiring annual care)																		
Bisphosphonates	0		10		10		10		45		45		45		45		45	

Table 62: Unit costs for medical resource use and data sources

Resource use	Unit cost (2013 GBP [£])	Source of cost estimate	Source of frequency estimate
Medical services			
GP visits (per hour)	£37.00	PSSRU 2015.[135] 10.8b: General practitioner – unit costs. Per patient contact lasting 11.7 minutes, including direct care staff costs, without qualification costs	KOL[129]
Counsellor (per consultation)	£50.00	PSSRU 2014.[134] 2.8: Counselling services in primary medical care. Unit cost per consultation	Wyatt et al.[42]

Resource use	Unit cost (2013 GBP [£])	Source of cost estimate	Source of frequency estimate
Other therapist (per hour)	£44.00	Assumed to be equal to occupational	Wyatt et al.[42]
Psychologist (per hour)	£74.00	PSSRU 2015.[135] 9: Cost per working hour Band 8b. Chapter 18: Clinical Psychologist (Band 8a-b) Face to face cost not reported.	Wyatt et al.[42]
Occupational therapist (per hour)	£44.00	PSSRU 2015.[135] 9.2: 11.5: Cost per working hour Face to face cost not reported.	KOL[129]
Physical therapist (per hour)	£36.00	PSSRU 2015.[135] 9: Cost per working hour Band 5. Chapter 18: Physiotherapist (Band 5). Face to face cost not reported.	KOL[129]
Specialist centre based care			
Nurse clinic visit (1+ hour)	£416.71	NHS Reference costs 2014/15[130] WF01A: Non-consultant led face to face outpatient attendance, follow-up - Clinical Genetics (311)	KOL[129], Deegan 2005[40]
Nurse management calls	£31.01	NHS Reference costs 2014/15 [130] N29AN: Community Health Services - Nursing: Other Specialist Nursing, Adult, Non face to face	KOL[129]
Consultant clinic visit	£433.18	NHS Reference costs 2014/15 [130] WF01A: Consultant led face to face outpatient attendance, follow-up - Clinical Genetics (311)	Deegan 2005[40]
Blood counts and CHITO	£4.20	NHS Reference costs 2014/15[130] Sum of: DAPS04: Clinical Biochemistry. Total. DAPS05: Haematology. Total.	Deegan 2005[40]
Bone marrow burden MRI	£111.90	NHS Reference costs 2014/15[130] Average of IMAGOTH - RA01A: MRI scan, 1 area, no contrast, 19+ years RA04Z: MRI scan, 2-3 areas, no contrast RA07Z: MRI scan, extensive repositioning and /or >1 contrast agent.	KOL[129], Assumption: one received every 5 years

Resource use	Unit cost (2013 GBP [£])	Source of cost estimate	Source of frequency estimate
Dexa scan	£59.44	NHS Reference costs 2014/15[130] DIAGIMOP - RD50Z: Dexa Scan	KOL[129], For disease state 1, 5 yearly. For disease state 2 - 4, 10% every other year; 90% 5 yearly. For disease state 5 - 9, 45% every other year, 55% 5 yearly.
Abdominal imaging	£92.03	NHS Reference costs 2014/15[130] Sum of: DIAGIMOP – RD40Z: Ultrasound Scan, < 20 minutes Consultant led outpatient attendance: WF01B: Non-admitted face to face attendance, first – Diagnostic imaging	KOL[129]
Hospital based acute care			
Liver/lung disease inpatient stay	£1,652.02	NHS Reference costs 2014/15[130]. Liver enlargement and pulmonary arterial hypertension. Weighted average of non-elective long and short stays by number of FCEs:	Patients in more severe health states assumed to be admitted every other year, KOL input[129]
Orthopaedic inpatient stay (with hip/joint replacement)	£3,855.58	NHS Reference costs 2014/15[130]. Sum of: Elective inpatient stay: Weighted average of HN13A-F, HN23A-C, HN53A-C, by number of FCEs – Trauma and Orthopaedics REHABL2 - VC18Z: Rehabilitation for joint replacement	KOL[129], 10% of patients with skeletal complications assumed
Orthopaedic inpatient stay (without joint replacement)	£1,351.78	NHS Reference costs 2014/15[130]. Weighted average of Elective inpatient stays by number of FCEs: WH08A-B Unspecified Pain with CC Score 0-1+, HD23H HD23J	KOL[129], this assumes anyone with a fracture, AVN or lytic lesion is admitted to hospital.
A&E visits	£113.55	NHS Reference costs 2014/15[130]. Accident and emergency services. Weighted average of TA01NA-TA04NA by number of FCEs. All A&E visits not leading to admission.	KOL[129], assumed 5% of patients with skeletal complications
Social services			
Social worker	£179	PSSRU 2013[136] [135]. 11.2: Social worker (adult services) unit costs per hour £79 (including qualifications)	KOL[129]

Resource use	Unit cost (2013 GBP [£])	Source of cost estimate	Source of frequency estimate
Home help/care worker	£24	PSSRU 2015[134, 135]. 11.6: Home care worker. Per hour of weekday face to face contact	KOL[129]
Housing worker	£24	PSSRU 2015[134, 135]. 11.6: Home care worker. Per hour of weekday face to face contact. Assumed same as home help	KOL[129]
Treatment of osteoporosis			
Bisphosphonates	£107.22	MIMS 2015 and eMIT 2015	See table below
Key: AVN, avascular necrosis; A&E, Accident and Emergency; eMIT electronic market information tool, GP, general practitioner; KOL, key opinion leader; MIMS, Monthly Index of Medical Specialists; MRI, magnetic resonance imaging; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.			

Table 63: Treatment of osteoporosis with bisphosphonates

Drug	Form	Strength	Size	Price	BNF Dose	Annual cost	Proportion receiving
Pamidronate disodium	IV	15 mg/ml	6ml vial	£170.45[132]	Osteolytic lesions dose = 90 mg	£170.46	25%
Zoledronic acid - Aclasta® (0.05 mg)	IV	50 mcg/ml	100ml bottle	£253.38[132]	Osteoporosis: 5 mg over at least 15 minutes once a year	£253.38	25%
Alendronic acid	Oral	70 mg	4	£0.21[137]	Osteoporosis: 70 mg once weekly	£1.26	50%
					Weighted average	**£107.22**	
Key: BNF, British National Formulary; IV, intravenous.							

Table 64: Annual resource use costs applied per cycle in the economic model

Disease state	Annual direct medical service costs	Annual social services costs	Total costs per health state per year
1. Mild with no clinical symptoms of bone disease	£2,583.05	£0.00	£2,583.05
2. Mild with bone pain	£2,707.01	£0.00	£2,707.01
3. Mild with SSC	£5,371.82	£108.02	£5,479.84
4. Moderate with no SSC	£2,688.03	£0.00	£2,688.03
5. Moderate with SSC	£5,385.57	£108.02	£5,493.59
6. Marked with no SSC	£4,536.95	£108.02	£4,644.97
7. Marked with SSC	£6,303.61	£108.02	£6,411.63
8. Severe with no SSC	£4,536.95	£108.02	£4,644.97
9. Severe with SSC	£6,303.61	£108.02	£6,411.63
Key: SSC, severe skeletal complications.			

Adverse-event costs

12.3.8 Complete table D9 with details of the costs associated with each adverse event included in the cost-consequence model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

A systematic literature review was performed to identify relevant costs and resource use associated with the adverse events considered in patients with Gaucher disease. The search was conducted in Medline, Medline In-process, EMBASE, The Cochrane Library (NHS EED and HTA database) and EconLit and the search strategies are shown in Section 17.4 (Appendix 4). The searches were conducted between the 15th and 20th October 2015.

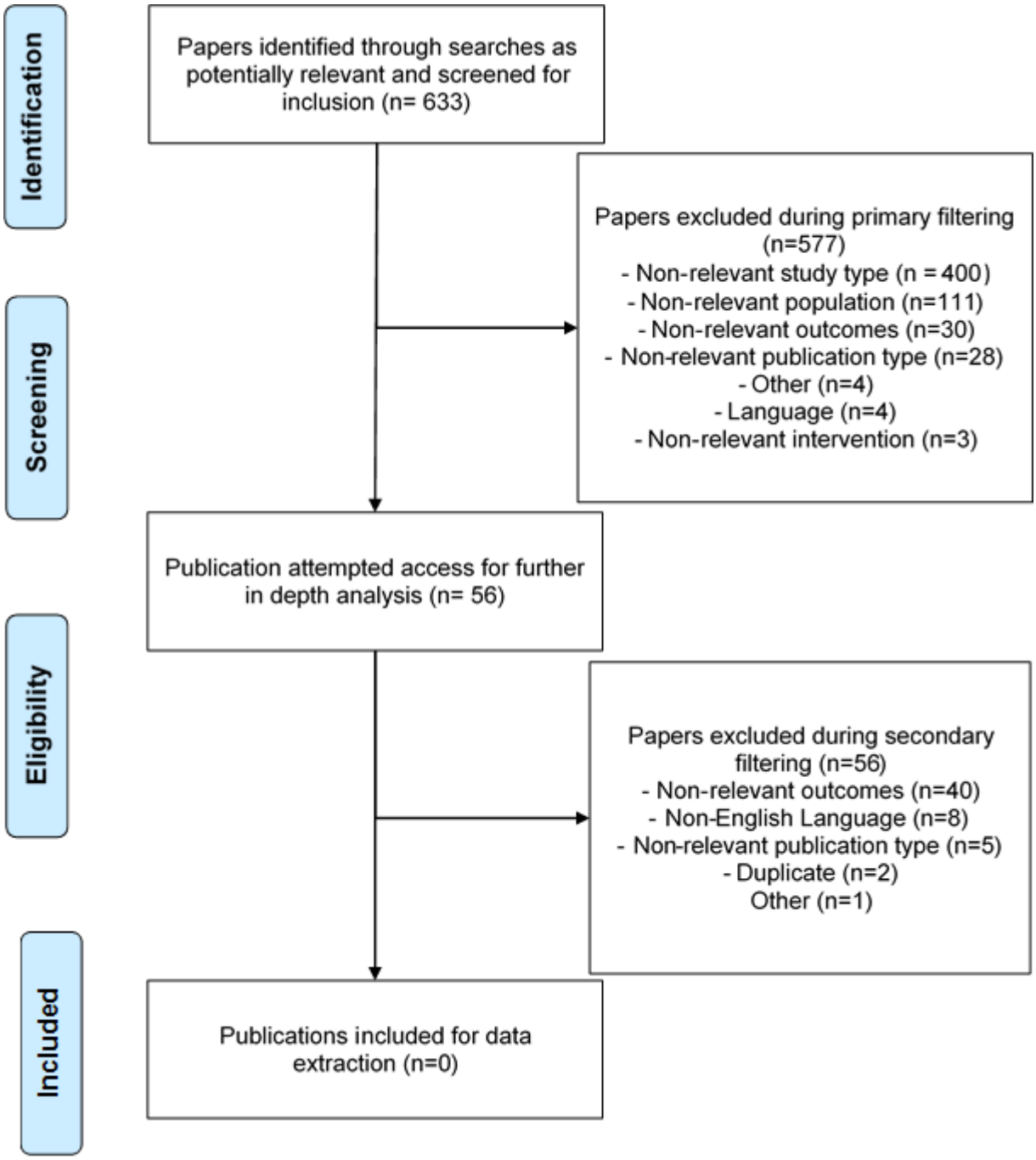
In primary screening, records identified were assessed by their title and abstract for relevance against their inclusion and exclusion criteria, shown in Table 65. Assessment of the full text articles of those carried through from primary screening determined the final eligibility of the identified studies.

Table 65: Inclusion and exclusion criteria for cost and resource use search of relevant adverse events

Inclusion criteria		
Category	**Criteria**	**Rationale**
Study type	Primary studies, economic evaluations reporting cost and/or resource use outcomes, costing studies of trial patients	Both these study types may report relevant values.
Population	Studies will include adult patients with Gaucher disease	The aim was to restrict the search to the relevant population.
Interventions/comparators	No restriction by treatment.	Any costs were to be included if they were relevant adverse events, regardless of treatment status
Outcomes	Any outcomes quantifying the costs and/or resource use requirements of the listed adverse events, as incurred by the NHS in the UK and Ireland	These are the appropriate methods for obtaining relevant costs and resource use
Language	Studies must be available in English.	
Exclusion criteria		
Category	**Criteria**	**Rationale**
Publication type	Systematic and non-systematic reviews, letters and comment articles	These study types are not appropriate.
Publication date	Studies published before 1 January 1990	The first Gaucher disease therapy, imiglucerase, only became available in 1997 when it was approved by the EMA
Key: EMA, European Medicines Agency; NHS, National Health Service.		

The process of study identification and screening is presented diagrammatically in Figure 25. The initial electronic searches identified 633 records, of which 577 were excluded during primary screening. Of the 56 remaining papers, all 56 studies were excluded, with the most common reason for exclusion being irrelevant outcomes (n=40). The adverse event cost and resource use systematic search identified no studies.

Figure 25: PRISMA diagram of the systematic search of cost and resource use studies relating to adverse events in Gaucher disease



Overall, no costs associated with the adverse events (AEs) are included in the model. This is justified as the rates of AEs applied are those for all grades of event, and the majority of these are assumed not to be so severe as to warrant additional resource use.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, Personal Social Services (PSS) costs, and patient and carer costs). If none, please state.

No additional costs are included in the model. The social services costs associated with patients in each health state have been described previously alongside the medical resource use costs in Section 12.3.7.

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No additional sources of cost savings that were not possible to quantify are relevant to the decision problem.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost-consequence analysis.

Structural and data source assumptions are tested by means of scenario sensitivity analyses. The alternative assumptions tested in the model are presented in Table 66, which also includes the setting in the base case analysis.

Table 66: Scenario analyses performed

Parameter/assumption	Base case	Scenarios
Time horizon	70 years	1 year
Differential efficacy of eliglustat	Treatment-specific transition probabilities in first year (ERT stable patients only)	Equal transitions applied using trial data
		Equal transitions applied using registry data
Treatment discontinuation	Treatment with imiglucerase following discontinuation	Discontinuation rates set to zero (reflective of the ENGAGE trial)
IV administration utility decrement	Decrement applied for IV treatments	Decrement set to zero
Percentage discount of velaglucerase	0%	20%
		40%
		60%
		80%

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was undertaken as an analysis of extremes, in which parameters of the model was tested individually, using an upper and lower bound value. Details of the distributions used to do this have been presented earlier in Table 52, and the upper and lower bounds tested in the DSA are presented for each parameter in Table 67. Where distributions or transitions must sum to one, or there is covariance between parameters, the other components alter proportionately to accommodate the upper and lower bound of each individual parameter.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed for the comparison of eliglustat to each of the comparator technologies included in the analysis. The model was run 1,000 times with randomly sampled parameter values to assess the uncertainty in the overall estimates of the costs and QALY outcomes for ach comparator. The parameter distributions presented in Table 52 were used to sample values for each model run. Plots of the mean costs and QALYs from 1:1000 simulations are presented within Section 19 to show how the results stabilise, indicating 1,000 iterations are sufficient.

12.4.3 Complete table D10.1, D10.2 and/or D10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table 67 presents the upper and lower bound values of parameters in the model used for one-way deterministic sensitivity analysis. Table 52 presents the parameter distributions used to derive these bounds; the upper and lower bounds are defined as the 95% confidence intervals given the distribution type and parameters. The distributions presented in Table 52 are also used to vary parameter values in the probabilistic sensitivity analysis. Multi-way sensitivity analysis was not conducted.

Due to their number, the parameter values for the AE incidence rates and Year 1 trial-based transition probabilities are included in an additional appendix in Section 19.6. The long term, registry-based transition probabilities are not varied themselves, rather the parameters of the regression from which they are derived are varied as per the coefficients presented in Table 67.

Table 67: Parameter estimate bounds included in the deterministic sensitivity analysis

Parameter	Point estimate	Lower bound	Upper bound
Patient weight	67.5	64.81	70.19
Treatment discontinuation rate – eliglustat	0.02	0.01	0.03
Treatment discontinuation rate – imiglucerase, velaglucerase	0.02	0.01	0.03
Treatment discontinuation duration – all treatments	3.00	1.82	4.18
Duration of AE risk – all treatments	36.00	21.89	50.11
ENCORE DS3 distribution at baseline: 1	0.77	0.75	0.79
ENCORE DS3 distribution at baseline: 2	0.13	0.08	0.18
ENCORE DS3 distribution at baseline: 4	0.10	0.06	0.15
ENGAGE DS3 distribution at baseline: 1	0.18	0.08	0.27
ENGAGE DS3 distribution at baseline: 4	0.78	0.75	0.81
ENGAGE DS3 distribution at baseline: 6	0.05	0.01	0.13
Haematology day unit	£534	£345.58	£762.77
Direct medical resource use cost: 1	£2,583.05	£1,672.52	£3,691.64
Direct medical resource use cost: 2	£2,707.01	£1,754.84	£3,873.33
Direct medical resource use cost: 3	£5,371.82	£3,474.19	£7,668.33
Direct medical resource use cost: 4	£2,688.03	£1,740.62	£3,841.94
Direct medical resource use cost: 5	£5,385.57	£3,483.08	£7,687.97

Parameter	Point estimate	Lower bound	Upper bound
Direct medical resource use cost: 6	£4,536.95	£2,939.08	£6,487.23
Direct medical resource use cost: 7	£6,303.61	£4,077.19	£8,999.29
Direct medical resource use cost: 8	£4,536.95	£2,39.08	£6,487.23
Direct medical resource use cost: 9	£6,304.61	£4,077.19	£8,999.29
Social services cost: 3	£108.02	£69.91	£154.30
Social services cost: 5	£108.02	£69.91	£154.30
Social services cost: 6	£108.02	£69.91	£154.30
Social services cost: 7	£108.02	£69.91	£154.30
Social services cost: 8	£108.02	£69.91	£154.30
Social services cost: 9	£108.02	£69.91	£154.30
Health state utility: 1	0.764	0.611	0.917
Health state utility: 2	0.666	0.533	0.799
Health state utility: 3	0.683	0.546	0.820
Health state utility: 4	0.686	0.549	0.823
Health state utility: 5	0.606	0.485	0.727
Health state utility: 6	0.642	0.514	0.770
Health state utility: 7	0.561	0.449	0.673
Health state utility: 8	0.596	0.477	0.715
Health state utility: 9	0.515	0.412	0.618
SRT utility increment	0.23	0.184	0.276
Disutility – AE: Back pain	-0.0187	-0.0121	-0.0267
Disutility – AE: Abdominal pain	-0.0006	-0.0004	-0.0008
Disutility – AE: Joint pain	-0.0012	-0.0008	-0.0017
Disutility – AE: Infusion reaction	-0.0110	-0.0071	-0.0157
Disutility – AE: URTI	-0.0001	-0.0001	-0.0001
Disutility – AE: Dizziness	-0.0004	-0.0003	-0.0006
Long-term transition regression coefficients			
Equation 1: 2.health_lag	1.305	1.044	1.566
Equation 1: 3.health_lag	0.840	0.672	1.008
Equation 1: 4.health_lag	2.581	2.065	3.097
Equation 1: 5.health_lag	1.253	1.003	1.504
Equation 1: 6.health_lag	4.504	3.603	5.405
Equation 1: 7.health_lag	3.617	2.894	4.341
Equation 1: 8.health_lag	4.213	3.371	5.056
Equation 1: 9.health_lag	6.072	4.858	7.287
Equation 1: 2.yr_ert	0.293	0.234	0.351

Parameter	Point estimate	Lower bound	Upper bound
Equation 1: 3.yr_ert	0.315	0.252	0.378
Equation 1: 2.baseline_ds3	-0.150	-0.120	-0.180
Equation 1: 3.baseline_ds3	0.873	0.699	1.048
Equation 1: 4.baseline_ds3	1.349	1.079	1.619
Equation 1: spleen_intact	-1.089	-0.871	-1.307
Equation 1: k1	0.740	0.592	0.889
Equation 1: k2	1.662	1.330	1.994
Equation 1: k3	1.727	1.381	2.072
Equation 1: k4	5.054	4.043	6.065
Equation 1: k5	5.835	4.668	7.002
Equation 1: k6	6.577	5.261	7.892
Equation 1: k7	8.808	7.046	10.569
Equation 1: k8	9.066	7.253	10.879
Equation 2: 2.health_lag	1.452	1.162	1.743
Equation 2: 3.health_lag	0.643	0.515	0.772
Equation 2: 4.health_lag	3.019	2.416	3.623
Equation 2: 5.health_lag	0.879	0.703	1.054
Equation 2: 6.health_lag	5.021	4.017	6.025
Equation 2: 7.health_lag	3.919	3.135	4.703
Equation 2: 8.health_lag	Not available		
Equation 2: 9.health_lag	4.521	3.617	5.425
Equation 2: 2.baseline_ds3_yr3	0.401	0.321	0.481
Equation 2: 3.baseline_ds3_yr3	0.832	0.666	0.999
Equation 2: 4.baseline_ds3_yr3	1.940	1.552	2.328
Equation 2: spleen_intact	-1.036	-0.829	-1.243
Equation 2: k1	0.342	0.273	0.410
Equation 2: k2	1.525	1.220	1.830
Equation 2: k3	1.573	1.258	1.887
Equation 2: k4	5.036	4.029	6.043
Equation 2: k5	5.944	4.755	7.133
Equation 2: k6	6.978	5.583	8.374
Equation 2: k7	9.395	7.516	11.275
Equation 2: k8	10.096	8.077	12.116

Key: AE, adverse event; DS3, disease severity scoring system; URTI, upper respiratory tract infection.

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

None of the parameters listed in Table 67 above were omitted from the sensitivity analyses conducted; however, some of the parameters listed in Table 52 in Section 12.2.6 were not varied in sensitivity analyses, and justifications for these are provided below.

Discount rates for cost and QALY outcomes – these were fixed at 3.5%, as these values are a requirement of the NICE reference case and are assumed constant.

The ages of patients at baseline – these values were chosen to best reflect UK clinical reality, and changes in these ages would not be expected to substantially affect the model outcomes, as mortality and long-term efficacy are assumed to be equal between eliglustat and comparator arms.

Dosing information – the dosing of patients was assumed to be known and fixed. For imiglucerase and velaglucerase, where there is some variation in dosing for individual patients, this was tested as scenario analysis instead, as presented in Section 12.4.1.

Gaucher disease and general population mortality – These parameters were not altered in sensitivity analyses as they do not accurately reflect the underlying parameter uncertainty, and the assumption of equal survival for all modelled treatment means that they do not affect the incremental outcomes of eliglustat relative to the comparator treatments, as both arms of the model are affected proportionately by changes in patient survival. For simplicity, and to avoid unnecessary “noise” in sensitivity analyses, these parameters have been assumed to be fixed.

12.5 Results of de novo cost-consequence analysis

Clinical outcomes from the model

12.5.1 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table 68 and Table 69 present the clinical outcomes of the economic model for the ERT stable and treatment naïve populations, respectively. As per the a priori assumption that

patient survival would not be affected by treatment, there were no incremental life-years associated with eliglustat treatment. Eliglustat was associated with a QALY gain of 2.29 compared with the ERT comparators in patients who were stable on ERT. The QALY gain in the treatment naïve patient population was 2.14. The clinical outcomes are equal for IM and EM and PM patients, as metaboliser status only determines the dose of eliglustat and drug costs.

The model does not generate clinical outcomes that are readily comparable to the outcomes of the key sources of trial data. The therapeutic goals from the clinical trials are not explicitly modelled, and the distribution of patients across the DS3 health states in the model cannot be compared to the DS3 observations of the trial, except to those which it uses as direct inputs.

However, the model predicts life expectancies (starting age plus mean life years) of 75.52 years and 74.28 years for the ERT stable and treatment naïve populations, respectively, accounting for the average age at baseline. Weinreb 2008 reports a life expectancy estimate of 68 from birth. The results of the model are not inconsistent, as these represent the life expectancy of patients conditional on them surviving to the baseline age in the model; the mean life expectancy of patients who survive to ages of 32 and 38 would be greater than the average life expectancy estimated at birth, due to the higher mortality in those with a particularly severe diagnosis.

Table 68: Summary of clinical outcomes of the model – ERT/stable population

Technologies	Total LYG	Incremental LYG	Total QALYs	Incremental QALYs
Switching from imiglucerase				
Eliglustat	37.52		16.80	
Imiglucerase	37.52	0.00	14.52	2.28
Switching from velaglucerase				
Eliglustat	37.52		16.80	
Velaglucerase	37.52	0.00	14.52	2.28
Weighted average comparison				
Weighted eliglustat	37.52		16.80	
Weighted comparator	37.52	0.00	14.52	2.28
Key: ERT, enzyme replacement therapy; LYG, life years gained; QALYs, quality-adjusted life years.				

Table 69: Summary of clinical outcomes of the model – treatment naïve population

Technologies	Total LYG	Incremental LYG	Total QALYs	Incremental QALYs
Switching from imiglucerase				
Eliglustat	42.28		18.06	
Imiglucerase	42.28	0.00	15.63	2.43
Switching from velaglucerase				
Eliglustat	42.28		18.06	
Velaglucerase	42.28	0.00	15.62	2.45
Weighted average comparison				
Weighted eliglustat	42.28		18.06	
Weighted comparator	42.28	0.00	15.62	2.44
Key: LYG, life years gained; QALYs, quality-adjusted life years.				

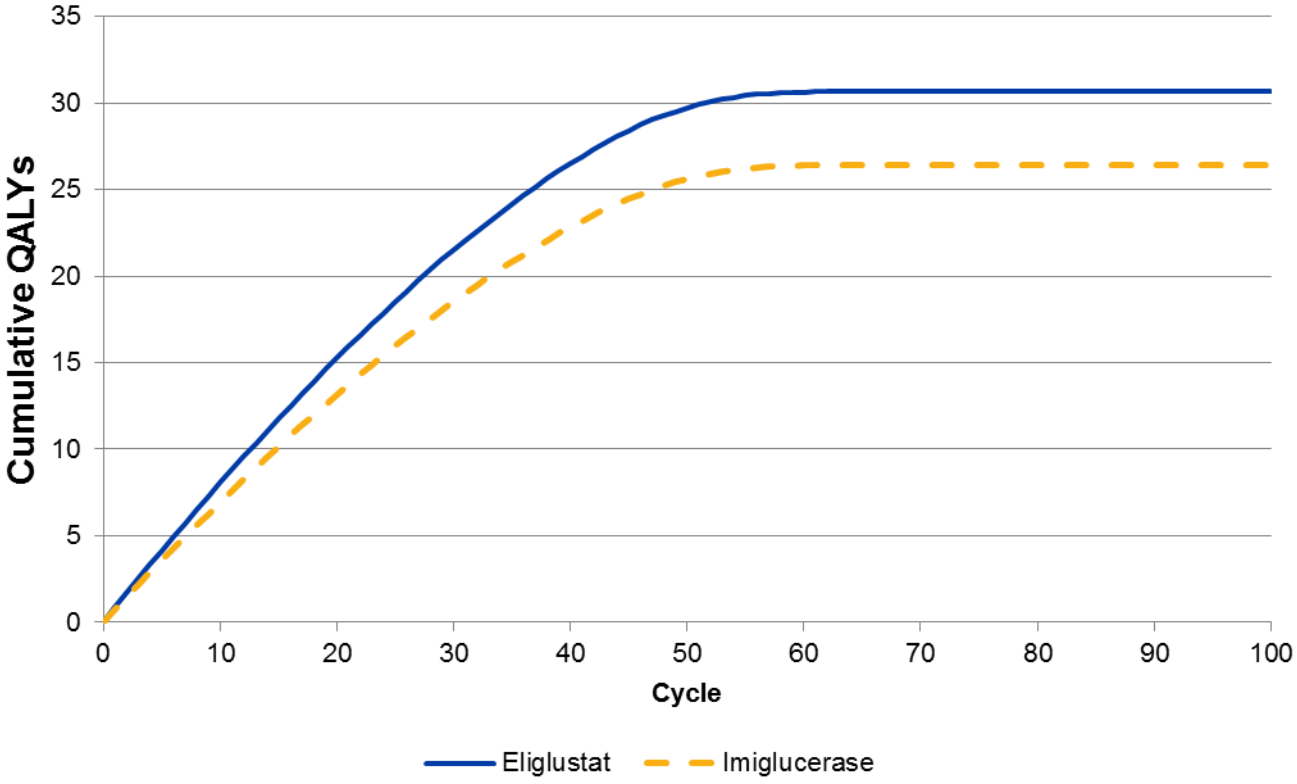
12.5.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

As the model results are generated as a weighted average of 18 different patient cohorts (baseline DS3 states 1-9 with and without splenectomy), Markov traces cannot be generated.

12.5.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

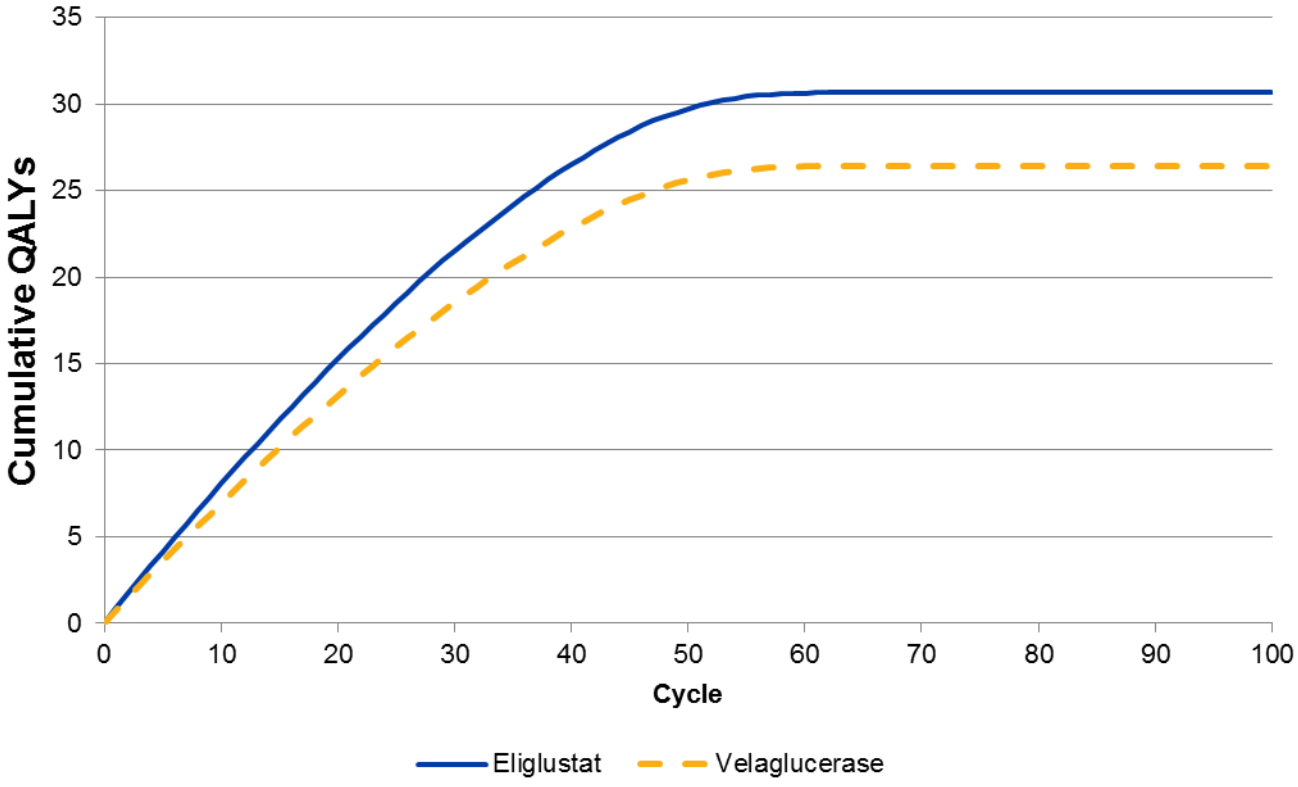
The weighted accumulations of QALYs over the modelled time horizon for each comparison in each population are shown in the following Figure 26 to Figure 29. These are applicable for patients who are IM and EM, as well as those who are PM, as clinical outcomes are assumed to be the same.

Figure 26: Accumulation of undiscounted QALYs over 70 year time horizon - ERT stable population: Eliglustat versus imiglucerase



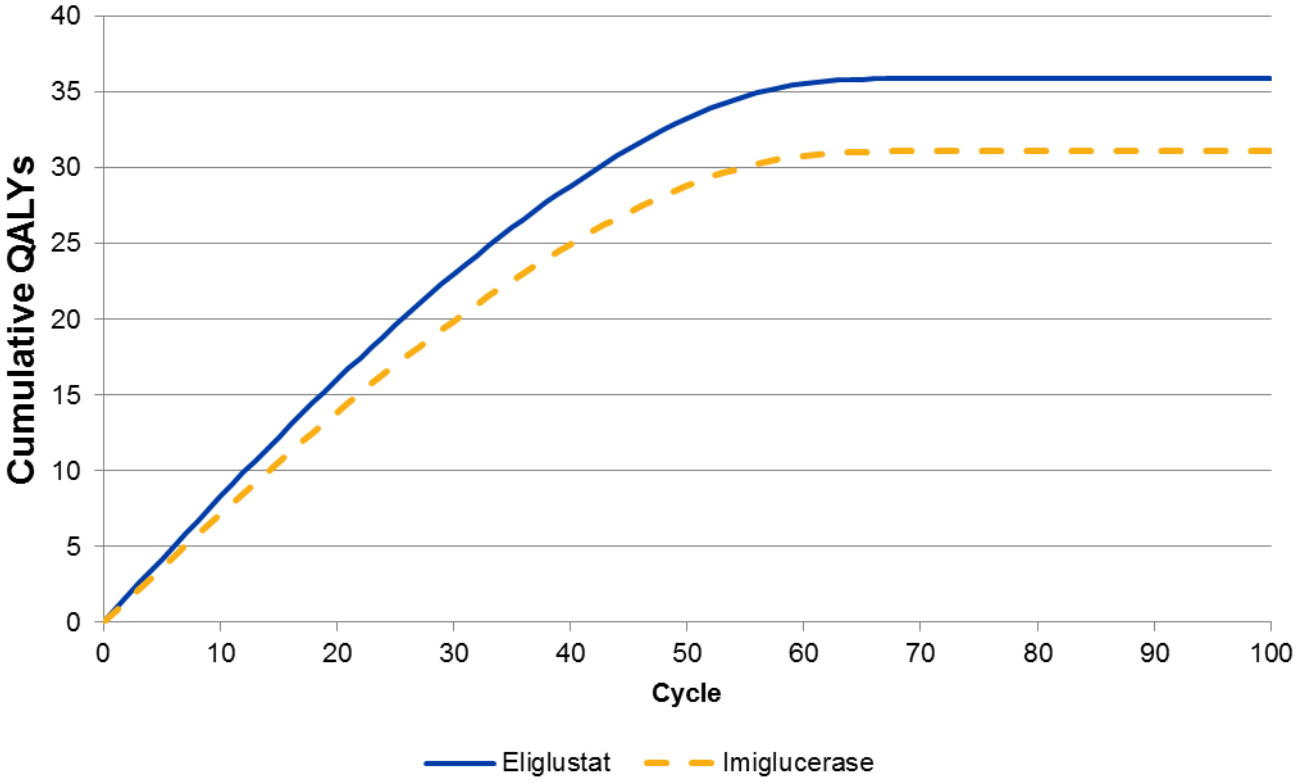
Key: ERT, enzyme replacement therapy; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

Figure 27: Accumulation of undiscounted QALYs over 70 year time horizon - ERT stable population: Eliglustat versus velaglucerase



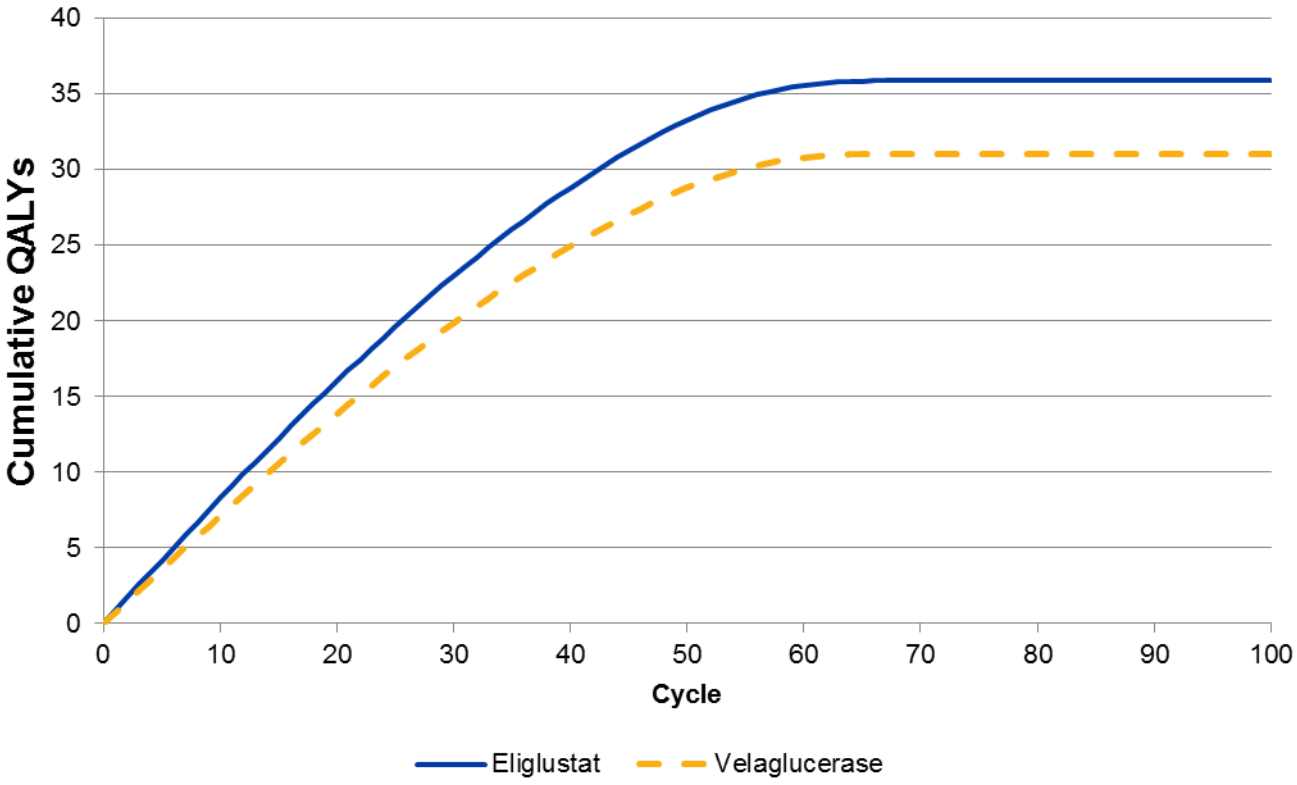
Key: ERT, enzyme replacement therapy; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

Figure 28: Accumulation of undiscounted QALYs over 70 year time horizon - treatment naive population: Eliglustat versus imiglucerase



Key: QALYs, quality-adjusted life years

Figure 29: Accumulation of undiscounted QALYs over 70 year time horizon – treatment naïve population: Eliglustat versus velaglucerase



Key: QALYs, quality-adjusted life years.

12.5.4 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table 70 and Table 71 show the disaggregated life years (LYs) for each of the comparators considered in the analysis. The health state LYs are equal across the arms for the treatment naïve population, as equal efficacy is assumed. For the ERT stable population, the LYs are distributed differently due to the treatment-specific transition probabilities that are applied in the first cycle, but the total LYs is equal across the cohorts, as treatment-specific transitions are not available for this population.

Table 70: Disaggregated life years – ERT stable patient population

Health state LYs	Versus imiglucerase		Versus velaglucerase	
	Eliglustat	**Imiglucerase**	**Eliglustat**	**Velaglucerase**
DS3: 1	19.63	19.65	19.63	19.65
DS3: 2	6.37	6.46	6.37	6.46
DS3: 3	0.29	0.26	0.29	0.26
DS3: 4	9.87	9.82	9.87	9.82
DS3: 5	0.71	0.68	0.71	0.68
DS3: 6	0.30	0.30	0.30	0.30
DS3: 7	0.17	0.17	0.17	0.17
DS3: 8	0.18	0.18	0.18	0.18
DS3: 9	0.01	0.01	0.01	0.01
Total	**37.52**	**37.52**	**37.52**	**37.52**

Key: DS3, disease severity scoring system; ERT, enzyme replacement therapy; LY, life years.

Table 71: Disaggregated life years – Treatment naïve patient population

Health state LYs	Versus imiglucerase		Versus velaglucerase	
	Eliglustat	**Imiglucerase**	**Eliglustat**	**Velaglucerase**
DS3: 1	28.71	28.71	28.71	28.71
DS3: 2	5.16	5.16	5.16	5.16
DS3: 3	0.30	0.30	0.30	0.30
DS3: 4	7.64	7.64	7.64	7.64
DS3: 5	0.24	0.24	0.24	0.24
DS3: 6	0.11	0.11	0.11	0.11
DS3: 7	0.09	0.09	0.09	0.09
DS3: 8	0.00	0.00	0.00	0.00
DS3: 9	0.01	0.01	0.01	0.01
Total	**42.28**	**42.28**	**42.28**	**42.28**

Key: DS3, disease severity scoring system; LY, life years.

Table 72 and Table 73 present the disaggregated, discounted QALYs for the ERT stable and treatment naïve patient populations, respectively. In the ERT stable patients, there are lower health state QALYs for eliglustat than for the comparator drugs, but this is offset by utility increments for the oral administration of eliglustat compared to the IV administration of imiglucerase and velaglucerase.

Table 72: Disaggregated discounted QALYs – ERT stable patient population

Health state LYs	Versus imiglucerase		Versus velaglucerase	
	Eliglustat	**Imiglucerase**	**Eliglustat**	**Velaglucerase**
DS3: 1	8.27	8.29	8.27	8.29
DS3: 2	2.22	2.28	2.22	2.28
DS3: 3	0.12	0.10	0.12	0.10
DS3: 4	3.48	3.45	3.48	3.45
DS3: 5	0.25	0.22	0.25	0.22
DS3: 6	0.10	0.10	0.10	0.10
DS3: 7	0.05	0.05	0.05	0.05
DS3: 8	0.04	0.04	0.04	0.04
DS3: 9	0.00	0.00	0.00	0.00
IV disutility	2.29	0.00	2.29	0.00
Adverse events	-0.01	0.00	-0.01	0.00
Total	**16.81**	**14.52**	**16.81**	**14.52**

Key: DS3, disease severity scoring system; ERT, enzyme replacement therapy; IV, intravenous; LYs, life years; QALYs, quality-adjusted life years.

Table 73: Disaggregated discounted QALYs – Treatment naïve patient population

Health state Lys	Versus imiglucerase		Versus velaglucerase	
	Eliglustat	**Imiglucerase**	**Eliglustat**	**Velaglucerase**
DS3: 1	10.69	10.69	10.69	10.69
DS3: 2	1.70	1.70	1.70	1.70
DS3: 3	0.10	0.10	0.10	0.10
DS3: 4	3.01	3.01	3.01	3.01
DS3: 5	0.08	0.08	0.08	0.08
DS3: 6	0.04	0.04	0.04	0.04
DS3: 7	0.03	0.03	0.03	0.03
DS3: 8	0.00	0.00	0.00	0.00
DS3: 9	0.00	0.00	0.00	0.00
IV disutility	2.43	0.00	2.43	0.00
Adverse events	0.00	-0.01	0.00	-0.02
Total	**18.06**	**15.63**	**18.06**	**15.62**

Key: DS3, disease severity scoring system; IV, intravenous; Lys, life years; QALYs, quality-adjusted life years.

12.5.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 74 and Table 75 present the disaggregated discounted incremental QALYs from the model. Table 76 and Table 78 present the disaggregated discounted costs by the category of expected pharmaceutical and resource use requirements.

Table 74: Summary of discounted QALY gain by health state – ERT stable population

Health state	Versus imiglucerase			Versus velaglucerase		
	Eliglustat	**Imiglucerase**	**Absolute increment versus imiglucerase**	**Eliglustat**	**Velaglucerase**	**Absolute increment versus velaglucerase**
DS3: 1	8.27	8.29	-0.02	8.27	8.29	-0.02
DS3: 2	2.22	2.28	-0.06	2.22	2.28	-0.06
DS3: 3	0.12	0.10	0.02	0.12	0.10	0.02
DS3: 4	3.48	3.45	0.03	3.48	3.45	0.03
DS3: 5	0.25	0.22	0.02	0.25	0.22	0.02
DS3: 6	0.10	0.10	0.00	0.10	0.10	0.00
DS3: 7	0.05	0.05	0.00	0.05	0.05	0.00
DS3: 8	0.04	0.04	0.00	0.04	0.04	0.00
DS3: 9	0.00	0.00	0.00	0.00	0.00	0.00
IV disutility	2.29	0.00	2.29	2.29	0.00	2.29
Adverse events	-0.01	0.00	-0.01	-0.01	0.00	-0.01
Total	**16.81**	**14.52**	**2.28**	**16.81**	**14.52**	**2.28**

Key: DS3, disease severity scoring system; ERT, enzyme replacement therapy; IV, intravenous; QALY, quality-adjusted life year.

Table 75: Summary of discounted QALY gain by health state – treatment naïve population

Health state	Versus imiglucerase			Versus velaglucerase		
	Eliglustat	**Imiglucerase**	**Absolute increment versus imiglucerase**	**Eliglustat**	**Velaglucerase**	**Absolute increment versus velaglucerase**
DS3: 1	10.69	10.69	0.00	10.69	10.69	0.00
DS3: 2	1.70	1.70	0.00	1.70	1.70	0.00
DS3: 3	0.10	0.10	0.00	0.10	0.10	0.00
DS3: 4	3.01	3.01	0.00	3.01	3.01	0.00
DS3: 5	0.08	0.08	0.00	0.08	0.08	0.00
DS3: 6	0.04	0.04	0.00	0.04	0.04	0.00
DS3: 7	0.03	0.03	0.00	0.03	0.03	0.00
DS3: 8	0.00	0.00	0.00	0.00	0.00	0.00
DS3: 9	0.00	0.00	0.00	0.00	0.00	0.00
IV disutility	2.43	0.00	2.43	2.43	0.00	2.43
Adverse events	0.00	-0.01	0.00	0.00	-0.02	0.02
Total	**18.06**	**15.63**	**2.43**	**18.06**	**15.62**	**2.45**

Key: DS3, disease severity scoring system; IV, intravenous; QALY, quality-adjusted life year.

Table 76: Summary of discounted costs by category – ERT stable population, IM and EM

Health state	Versus imiglucerase			Versus velaglucerase		
	Eliglustat	**Imiglucerase**	**Absolute increment versus imiglucerase**	**Eliglustat**	**Velaglucerase**	**Absolute increment versus velaglucerase**
Treatment costs	£ 4,142,824	£ 4,023,067	£ 119,757	£ 4,207,735	£ 5,295,042	-£ 1,087,307
Testing costs	£ 0	£ 0	£ 0	£ 0	£ 0	£ 0
Delivery and drug administration costs	£ 10,961	£ 278,305	-£ 267,344	£ 10,961	£ 278,305	-£ 267,344
Adverse event costs	£ 0	£ 0	£ 0	£ 0	£ 0	£ 0
Direct medical resource use costs	£ 55,301	£ 55,115	£ 186	£ 55,301	£ 55,115	£ 186
Social services resource use costs	£ 96	£ 89	£ 7	£ 96	£ 89	£ 7
Total	**£ 4,209,182**	**£ 4,356,576**	**-£ 147,394**	**£ 4,274,093**	**£ 5,628,550**	**-£ 1,354,457**

Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser.

NB: the treatment costs of eliglustat differ based on the comparison, as patients are assumed to be treated with the other comparator following discontinuation.

Table 77: Summary of discounted costs by category – ERT stable population, PM

Health state	Versus imiglucerase			Versus velaglucerase		
	Eliglustat	**Imiglucerase**	**Absolute increment versus imiglucerase**	**Eliglustat**	**Velaglucerase**	**Absolute increment versus velaglucerase**
Treatment costs	£ 2,174,063	£ 4,023,067	-£ 1,849,004	£ 2,238,974	£ 5,295,042	-£ 3,056,068
Testing costs	£ 0	£ 0	£ 0	£ 0	£ 0	£ 0
Admin costs	£ 10,961	£ 278,305	-£ 267,344	£ 10,961	£ 278,305	-£ 267,344
Adverse event costs	£ 0	£ 0	£ 0	£ 0	£ 0	£ 0
Direct medical resource use costs	£ 55,301	£ 55,115	£ 186	£ 55,301	£ 55,115	£ 186
Social services resource use costs	£ 96	£ 89	£ 7	£ 96	£ 89	£ 7
Total	**£ 2,240,422**	**£ 4,356,576**	**-£ 2,116,154**	**£ 2,305,332**	**£ 5,628,550**	**-£ 3,323,218**

Key: ERT, enzyme replacement therapy; PM, poor metaboliser.

Table 78: Summary of discounted costs by category – treatment naïve population, IM and EM

Health state	Versus imiglucerase			Versus velaglucerase		
	Eliglustat	**Imiglucerase**	**Absolute increment versus imiglucerase**	**Eliglustat**	**Velaglucerase**	**Absolute increment versus velaglucerase**
Treatment costs	£ 4,388,685	£ 4,330,992	£ 57,693	£ 4,457,820	£ 5,540,195	-£ 1,082,375
Testing costs	£ 0	£ 0	£ 0	£ 0	£ 0	£ 0
Admin costs	£ 11,619	£ 281,611	-£ 269,992	£ 11,619	£ 281,611	-£ 269,992
Adverse event costs	£ 0	£ 0	£ 0	£ 0	£ 0	£ 0
Direct medical resource use costs	£ 56,901	£ 56,901	£ 0	£ 56,901	£ 56,901	£ 0
Social services resource use costs	£ 42	£ 42	£ 0	£ 42	£ 42	£ 0
Total	**£ 4,457,247**	**£ 4,669,546**	**-£ 212,299**	**£ 4,526,382**	**£ 5,878,749**	**-£ 1,352,367**

Key: EM, extensive metaboliser; IM, intermediate metaboliser.

Table 79: Summary of discounted costs by category – treatment naïve population, PM

Health state	Versus imiglucerase			Versus velaglucerase		
	Eliglustat	**Imiglucerase**	**Absolute increment versus imiglucerase**	**Eliglustat**	**Velaglucerase**	**Absolute increment versus velaglucerase**
Treatment costs	£ 2,303,674	£ 4,330,992	-£ 2,027,318	£ 2,372,809	£ 5,540,195	-£ 3,167,387
Testing costs	£ 0	£ 0	£ 0	£ 0	£ 0	£ 0
Admin costs	£ 11,619	£ 281,611	-£ 269,992	£ 11,619	£ 281,611	-£ 269,992
Adverse event costs	£ 0	£ 0	£ 0	£ 0	£ 0	£ 0
Direct medical resource use costs	£ 56,901	£ 56,901	£ 0	£ 56,901	£ 56,901	£ 0
Social services resource use costs	£ 42	£ 42	£ 0	£ 42	£ 42	£ 0
Total	**£ 2,372,236**	**£ 4,669,546**	**-£ 2,297,310**	**£ 2,441,371**	**£ 5,878,749**	**-£ 3,437,379**

Key: PM, poor metaboliser.

Base-case analysis

12.5.6 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table D11.

Table 80 presents the incremental costs of eliglustat for the ERT stable population, in which treatment-specific transitions are applied for the first year, followed by long-term transitions derived from the DS3 score study, assuming equal efficacy over this period. Table 82 presents the incremental costs of eliglustat for the treatment naïve population. In the treatment naïve base case, both eliglustat and the comparator treatments are modelled using DS3 transitions from the eliglustat arm of the ENGAGE trial. These tables also include a comparison of eliglustat to a weighted comparator arm, estimated based on the model outcomes for each comparator and their respective market shares in 2013; 118 patients were receiving imiglucerase (48%) and 126 receiving velaglucerase(52%).[138]

Table 80: Base-case results – ERT stable patient population, IM and EM

Technologies	Total costs (£)	Incremental costs (£)
Switching from imiglucerase		
Eliglustat	£4,209,182	
Imiglucerase	£4,356,576	-£147,394
Switching from velaglucerase		
Eliglustat	£4,238,212	
Velaglucerase	£5,527,175	-£1,288,963
Weighted average comparison (XX% imiglucerase and XX% velaglucerase)		
Weighted eliglustat	£4,242,702	
Weighted comparator	£5,013,415	-£770,713
Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser.		

Table 81: Base-case results – ERT stable patient population, PM

Technologies	Total costs (£)	Incremental costs (£)
Switching from imiglucerase		
Eliglustat	£2,240,422	
Imiglucerase	£4,356,576	-£2,116,154
Switching from velaglucerase		
Eliglustat	£2,305,332	
Velaglucerase	£5,628,550	-£3,323,218
Weighted average comparison (48% imiglucerase and 52% velaglucerase)		
Weighted eliglustat	£2,273,941	
Weighted comparator	£5,013,415	-£2,739,474
Key: ERT, enzyme replacement therapy; PM, poor metaboliser.		

Table 82: Base-case results – treatment naïve patient population, IM and EM

Technologies	Total costs (£)	Incremental costs (£)
Initiating on imiglucerase		
Eliglustat	£4,457,247	
Imiglucerase	£4,669,546	-£212,299
Initiating on velaglucerase		
Eliglustat	£4,526,382	
Velaglucerase	£5,878,749	-£1,352,367
Weighted average comparison (48% imiglucerase and 52% velaglucerase)		
Weighted eliglustat	£4,492,948	
Weighted comparator	£5,293,971	-£801,023
Key: EM, extensive metaboliser; IM, intermediate metaboliser.		

Table 83: Base-case results – treatment naïve patient population, PM

Technologies	Total costs (£)	Incremental costs (£)
Initiating on imiglucerase		
Eliglustat	£2,372,236	
Imiglucerase	£4,669,546	-£2,297,310
Initiating on velaglucerase		
Eliglustat	£2,441,371	
Velaglucerase	£5,878,749	-£3,437,379
Weighted average comparison (48% imiglucerase and 52% velaglucerase)		
Weighted eliglustat	£2,407,937	
Weighted comparator	£5,293,971	-£2,886,034
Key: PM, poor metaboliser.		

12.5.7 Report the total difference in costs between the technology and comparator(s).

The total differences in discounted costs for each comparison included in the model, over the 70 year time horizon, are presented in Table 84. Calculating based on the list price of eliglustat estimates a negative incremental cost for each comparison, i.e. eliglustat treatment results in a lower cost over the modelled time horizon. The incremental cost of each comparison is closely linked to the cost per year of treatment of the drugs, although the comparisons are also affected by the costs of discontinuation, as patients incur the costs of follow-on treatment after discontinuation. The model assumes that ERT stable in the ERT arm do not experience AEs or disconuiation. For the ERT stable patient population. For the treatment naïve population the model assumes that when the comparator considered is imiglucerase, patients that discontinue from imiglucerase receive velaglurase, and alternatively when velaglucerase is the comparator, discontinuing patients receive imigluercase. Within the eliglustat arm, when patients discontinue they are assumed to receive the main comparator treatment (i.e. if imiglucerase is the comparator, then discontinuing eliglustat patients are assumed to receive imiglucerase).

Table 84: Summary of cost differences estimates by cost-effectiveness model

Comparison	Estimated cost difference over 70 years
ERT stable patients, IM and EM	
Patients switching from imiglucerase	-£147,394
Patients switching from velaglucerase	-£1,288,963
ERT stable patients, PM	
Patients switching from imiglucerase	-£2,116,154
Patients switching from velaglucerase	-£3,323,218
Treatment naïve patients, IM and EM	
Patients who would otherwise initiate on imiglucerase	-£212,299
Patients who would otherwise initiate on velaglucerase	-£1,352,367
Treatment naïve patients, PM	
Patients who would otherwise initiate on imiglucerase	-£2,297,310
Patients who would otherwise initiate on velaglucerase	-£3,437,379
Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; PM, poor metaboliser.	

12.5.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table D12.

The costs of the modelled treatment by category of cost are presented above in Section 12.5.5.

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table D13.

Table 85 and Table 87 present the discounted cost outcomes of the model disaggregated by health state for the ERT stable and treatment naïve populations, respectively.

Table 85: Summary of discounted costs by health state - ERT stable population, IM and EM

Health state	Versus imiglucerase			Versus velaglucerase		
	Eliglustat	**Imiglucerase**	**Absolute increment versus imiglucerase**	**Eliglustat**	**Velaglucerase**	**Absolute increment versus velaglucerase**
DS3: 1	£ 2,263,074	£ 2,347,651	-£ 84,577	£ 2,297,148	£ 3,033,597	-£ 736,449
DS3: 2	£ 696,239	£ 740,502	-£ 44,263	£ 707,375	£ 956,741	-£ 249,366
DS3: 3	£ 37,934	£ 32,530	£ 5,403	£ 38,404	£ 41,910	-£ 3,506
DS3: 4	£ 1,060,972	£ 1,088,127	-£ 27,155	£ 1,077,989	£ 1,405,906	-£ 327,917
DS3: 5	£ 86,289	£ 81,105	£ 5,184	£ 87,458	£ 104,488	-£ 17,030
DS3: 6	£ 32,185	£ 33,183	-£ 999	£ 32,707	£ 42,787	-£ 10,081
DS3: 7	£ 17,682	£ 18,224	-£ 543	£ 17,966	£ 23,457	-£ 5,491
DS3: 8	£ 13,916	£ 14,333	-£ 417	£ 14,140	£ 18,482	-£ 4,341
DS3: 9	£ 892	£ 919	-£ 27	£ 906	£ 1,183	-£ 277
Total	**£ 4,209,182**	**£ 4,356,576**	**-£ 147,394**	**£ 4,274,093**	**£ 5,628,550**	**-£ 1,354,457**

Key: DS3; disease severity scoring system; EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser.

Table 86: Summary of discounted costs by health state - ERT stable population, PM

Health state	Versus imiglucerase			Versus velaglucerase		
	Eliglustat	**Imiglucerase**	**Absolute increment versus imiglucerase**	**Eliglustat**	**Velaglucerase**	**Absolute increment versus velaglucerase**
DS3: 1	£ 1,202,343	£ 2,347,651	-£ 1,145,308	£ 1,236,417	£ 3,033,597	-£ 1,797,180
DS3: 2	£ 371,146	£ 740,502	-£ 369,357	£ 382,281	£ 956,741	-£ 574,460
DS3: 3	£ 20,248	£ 32,530	-£ 12,282	£ 20,718	£ 41,910	-£ 21,192
DS3: 4	£ 565,604	£ 1,088,127	-£ 522,523	£ 582,621	£ 1,405,906	-£ 823,285
DS3: 5	£ 46,221	£ 81,105	-£ 34,883	£ 47,391	£ 104,488	-£ 57,097
DS3: 6	£ 17,313	£ 33,183	-£ 15,870	£ 17,835	£ 42,787	-£ 24,952
DS3: 7	£ 9,580	£ 18,224	-£ 8,645	£ 9,864	£ 23,457	-£ 13,593
DS3: 8	£ 7,483	£ 14,333	-£ 6,850	£ 7,707	£ 18,482	-£ 10,774
DS3: 9	£ 483	£ 919	-£ 436	£ 497	£ 1,183	-£ 686
Total	**£ 2,240,422**	**£ 4,356,576**	**-£ 2,116,154**	**£ 2,305,332**	**£ 5,628,550**	**-£ 3,323,218**

Key: DS3; disease severity scoring system; ERT, Enzyme replacement therapy; PM, poor metaboliser.

Table 87: Summary of discounted costs by health state – treatment naïve population, IM and EM

Health state	Versus imiglucerase			Versus velaglucerase		
	Eliglustat	**Imiglucerase**	**Absolute increment versus imiglucerase**	**Eliglustat**	**Velaglucerase**	**Absolute increment versus velaglucerase**
DS3: 1	£ 2,924,244	£ 3,064,803	-£ 140,560	£ 2,970,988	£ 3,855,752	-£ 884,764
DS3: 2	£ 534,568	£ 560,336	-£ 25,767	£ 543,207	£ 704,646	-£ 161,439
DS3: 3	£ 31,476	£ 32,971	-£ 1,495	£ 31,976	£ 41,362	-£ 9,386
DS3: 4	£ 916,875	£ 958,977	-£ 42,102	£ 929,338	£ 1,211,169	-£ 281,831
DS3: 5	£ 26,368	£ 27,617	-£ 1,250	£ 26,783	£ 34,652	-£ 7,869
DS3: 6	£ 12,151	£ 12,729	-£ 578	£ 12,343	£ 15,983	-£ 3,640
DS3: 7	£ 10,302	£ 10,788	-£ 486	£ 10,464	£ 13,524	-£ 3,061
DS3: 8	£ 285	£ 299	-£ 14	£ 290	£ 375	-£ 85
DS3: 9	£ 979	£ 1,026	-£ 46	£ 995	£ 1,286	-£ 291
Total	**£ 4,457,247**	**£ 4,669,546**	**-£ 212,299**	**£ 4,526,382**	**£ 5,878,749**	**-£ 1,352,367**

Key: DS3; disease severity scoring system; EM, extensive metaboliser; IM, intermediate metaboliser.

Table 88: Summary of discounted costs by health state – treatment naïve population, PM

Health state	Versus imiglucerase			Versus velaglucerase		
	Eliglustat	**Imiglucerase**	**Absolute increment versus imiglucerase**	**Eliglustat**	**Velaglucerase**	**Absolute increment versus velaglucerase**
DS3: 1	£ 1,557,938	£ 3,064,803	-£ 1,506,865	£ 1,604,682	£ 3,855,752	-£ 2,251,070
DS3: 2	£ 285,104	£ 560,336	-£ 275,232	£ 293,742	£ 704,646	-£ 410,904
DS3: 3	£ 16,976	£ 32,971	-£ 15,995	£ 17,476	£ 41,362	-£ 23,886
DS3: 4	£ 485,214	£ 958,977	-£ 473,763	£ 497,677	£ 1,211,169	-£ 713,492
DS3: 5	£ 14,217	£ 27,617	-£ 13,401	£ 14,632	£ 34,652	-£ 20,020
DS3: 6	£ 6,529	£ 12,729	-£ 6,200	£ 6,721	£ 15,983	-£ 9,262
DS3: 7	£ 5,575	£ 10,788	-£ 5,213	£ 5,737	£ 13,524	-£ 7,787
DS3: 8	£ 153	£ 299	-£ 146	£ 158	£ 375	-£ 217
DS3: 9	£ 530	£ 1,026	-£ 496	£ 545	£ 1,286	-£ 740
Total	**£ 2,372,236**	**£ 4,669,546**	**-£ 2,297,310**	**£ 2,441,371**	**£ 5,878,749**	**-£ 3,437,379**

Key: DS3; disease severity scoring system; PM, poor metaboliser.

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table D14.

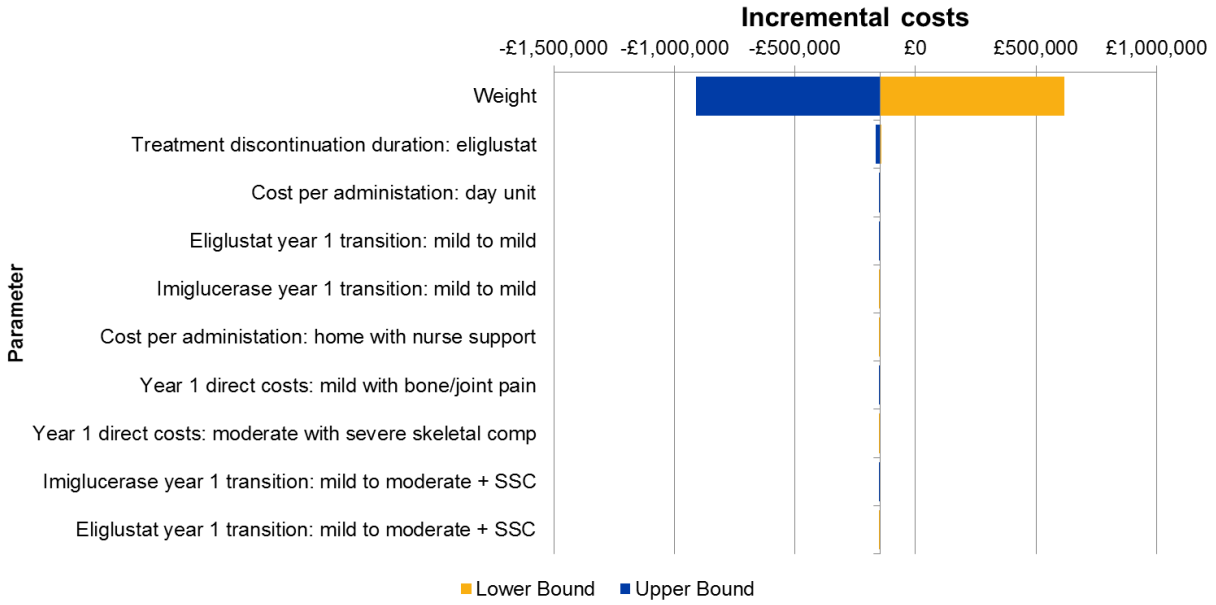
Costs of adverse events are not included in the model.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

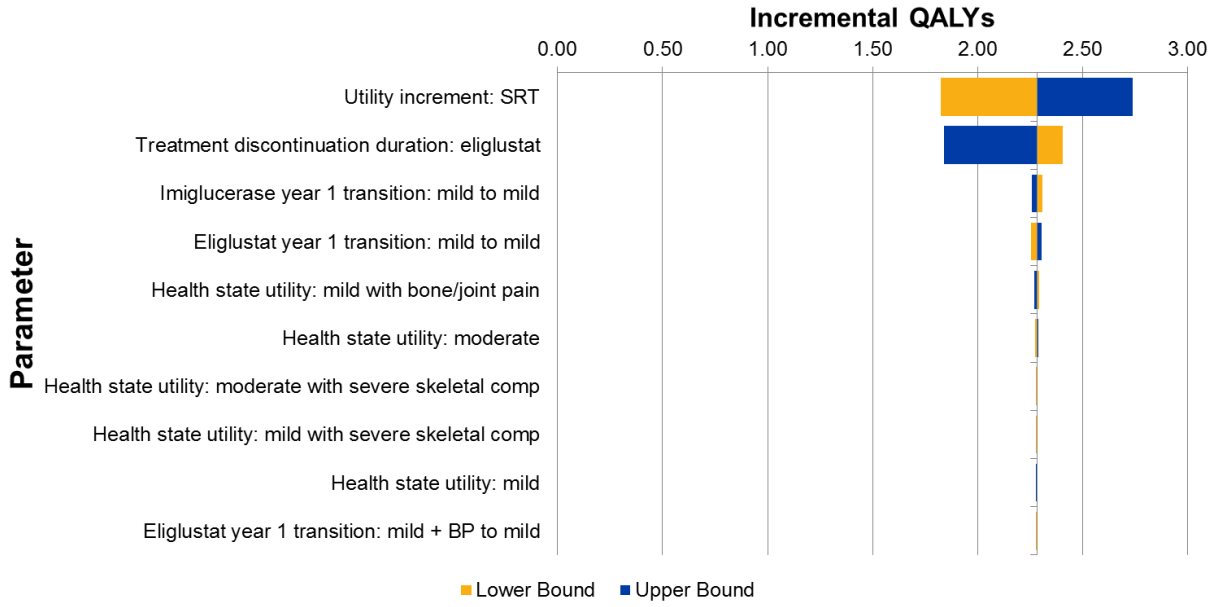
Figure 30 through to Figure 45 show the impact of the 10 most influential parameters on cost and QALY outcomes for eliglustat incremental to imiglucerase and velaglucerase. These influential parameters are identified as the 10 parameters that cause the greatest difference in cost or QALY outcomes between their upper and lower bound values.

Figure 30: Tornado diagram of incremental cost – ERT stable, versus imiglucerase, IM/EM patients



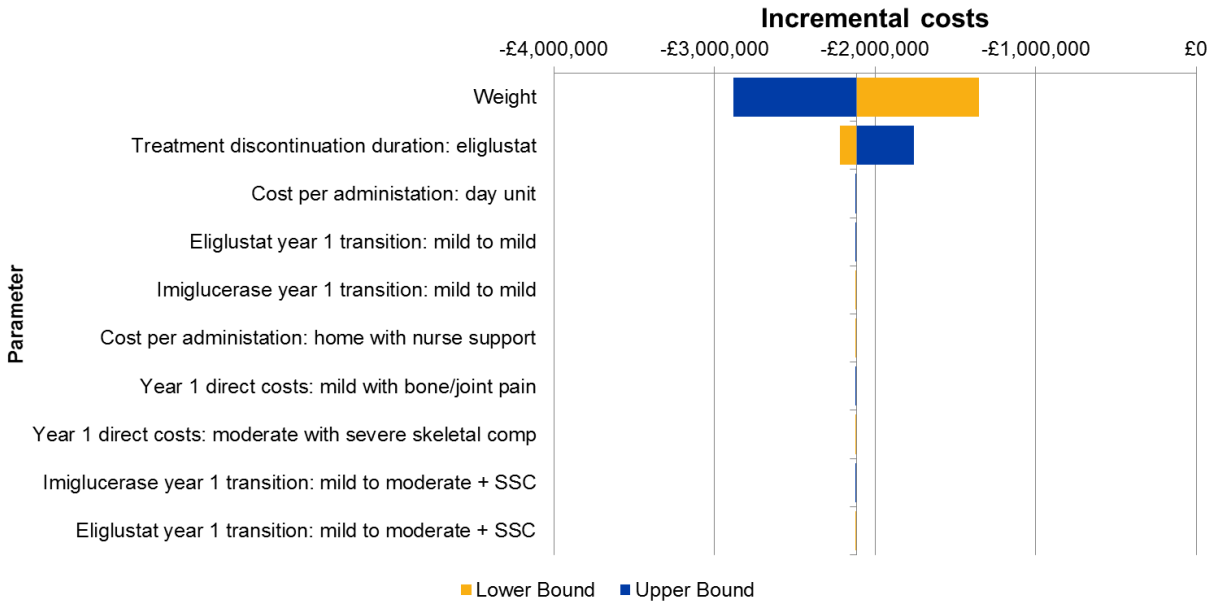
Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; SSC, severe skeletal complications.

Figure 31: Tornado diagram of incremental QALYs – ERT stable, versus imiglucerase, IM/EM patients



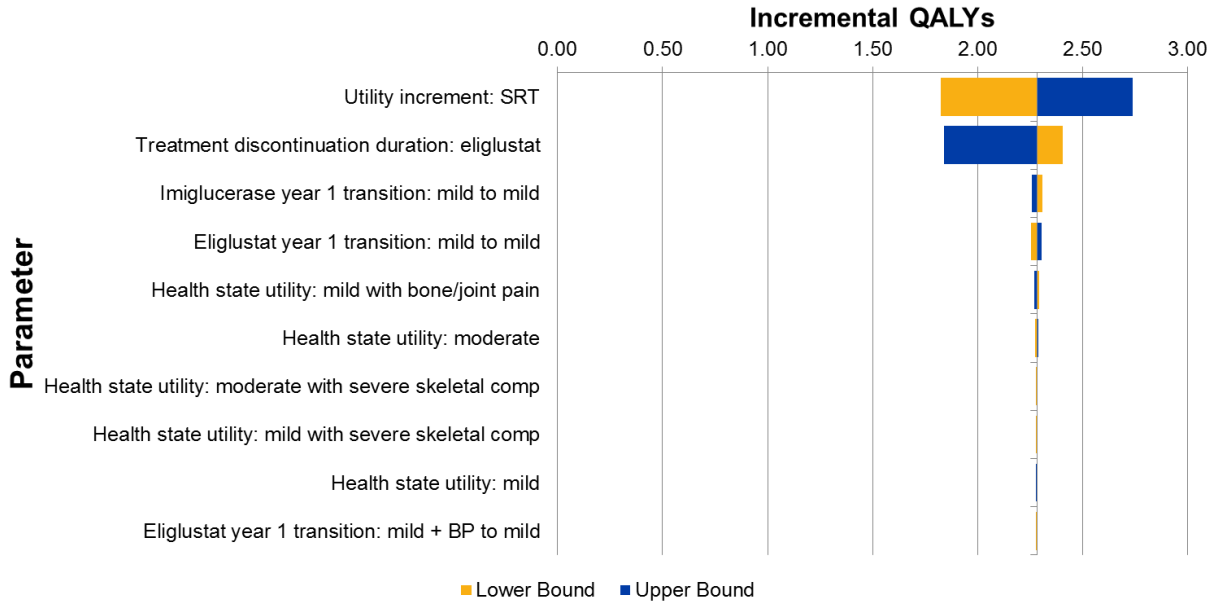
Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

Figure 32: Tornado diagram of incremental cost – ERT stable, versus imiglucerase, PM patients



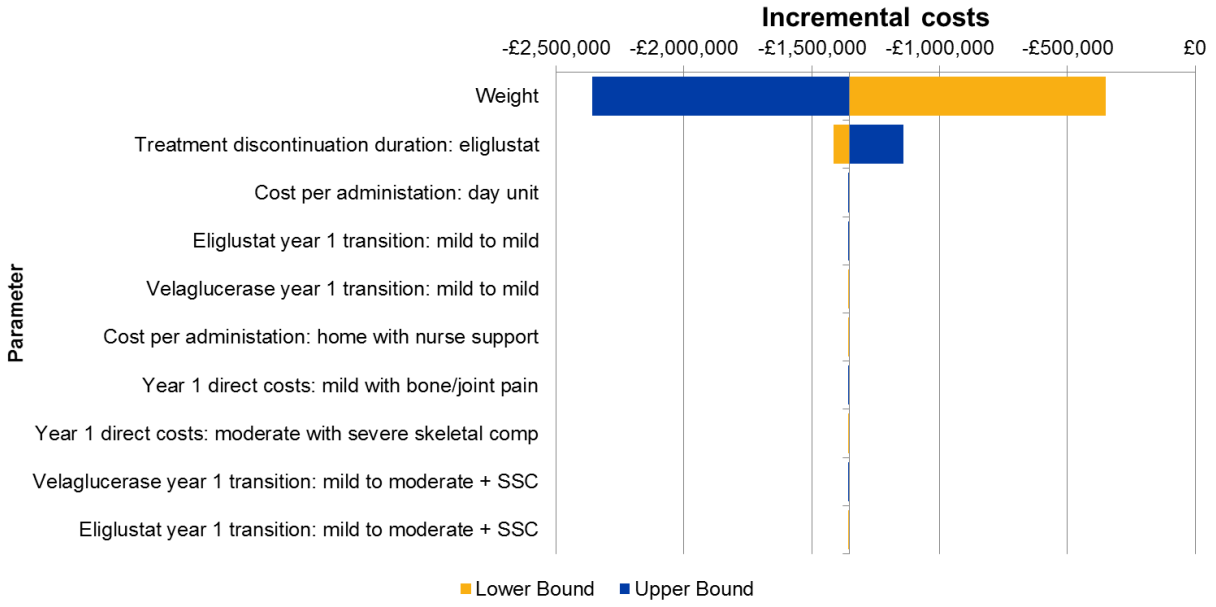
Key: ERT, enzyme replacement therapy; PM, poor metaboliser; SSC, severe skeletal complications.

Figure 33: Tornado diagram of incremental QALYs – ERT stable, versus imiglucerase, PM patients



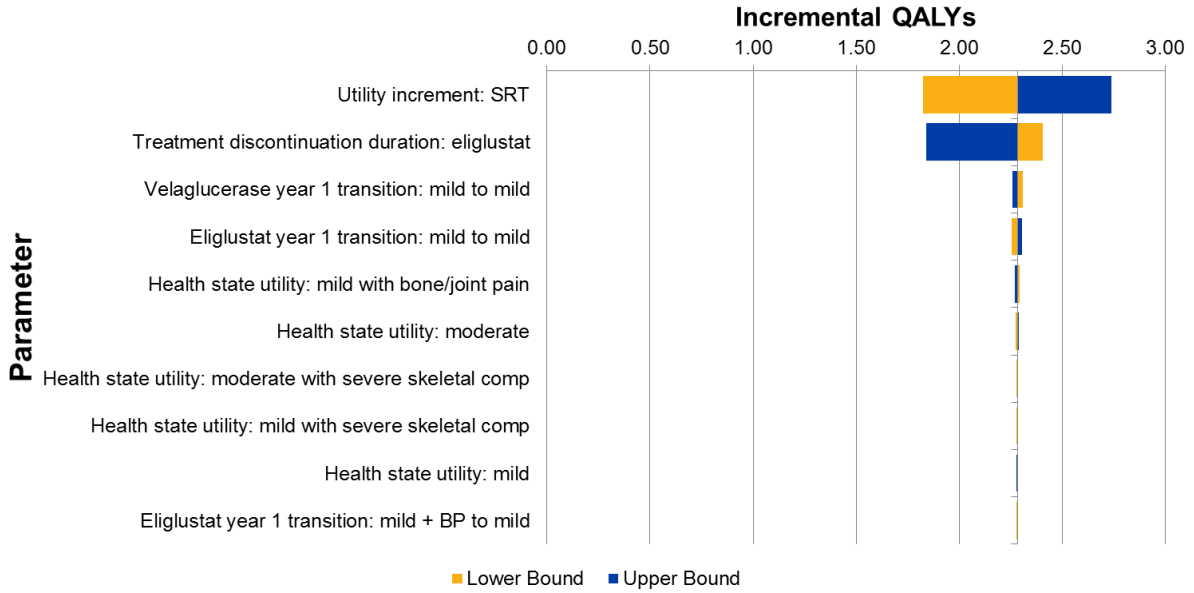
Key: ERT, enzyme replacement therapy; PM, poor metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

Figure 34: Tornado diagram of incremental cost – ERT stable, versus velaglucerase, IM/EM patients



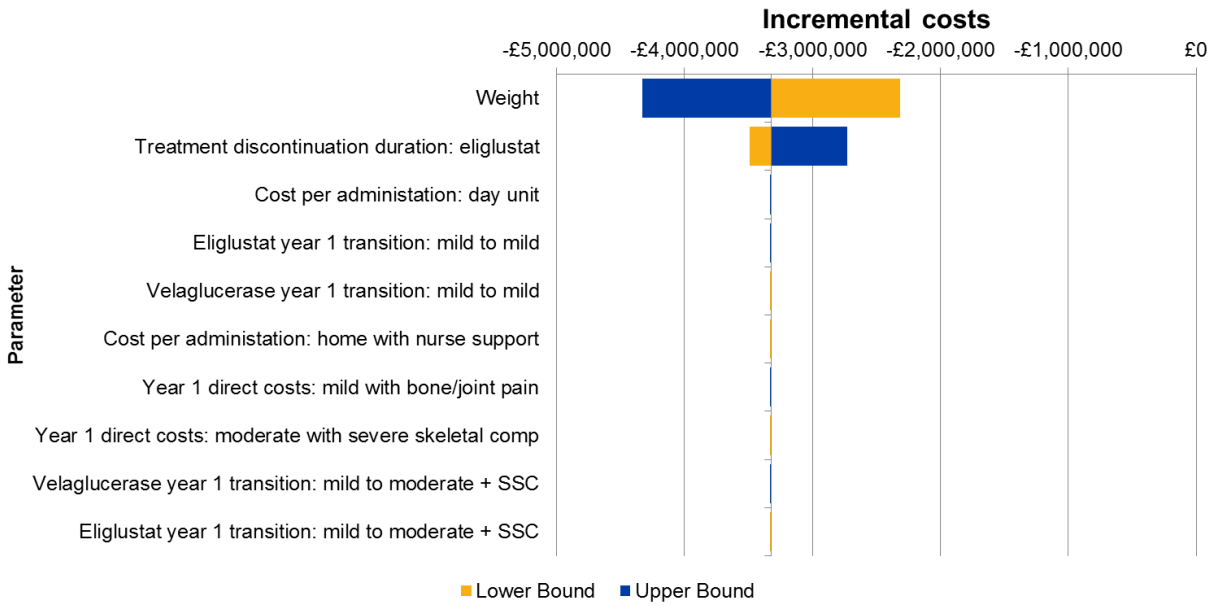
Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; SSC, severe skeletal complications.

Figure 35: Tornado diagram of incremental QALYs – ERT stable, versus velaglucerase, IM/EM patients



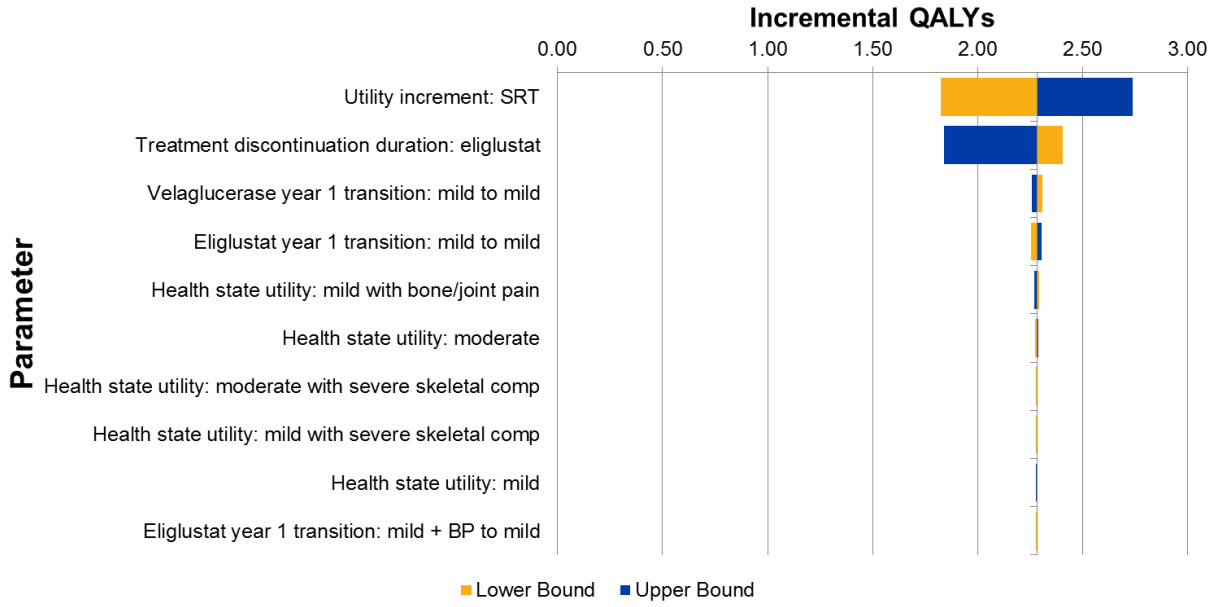
Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

Figure 36: Tornado diagram of incremental cost – ERT stable, versus velaglucerase, PM patients



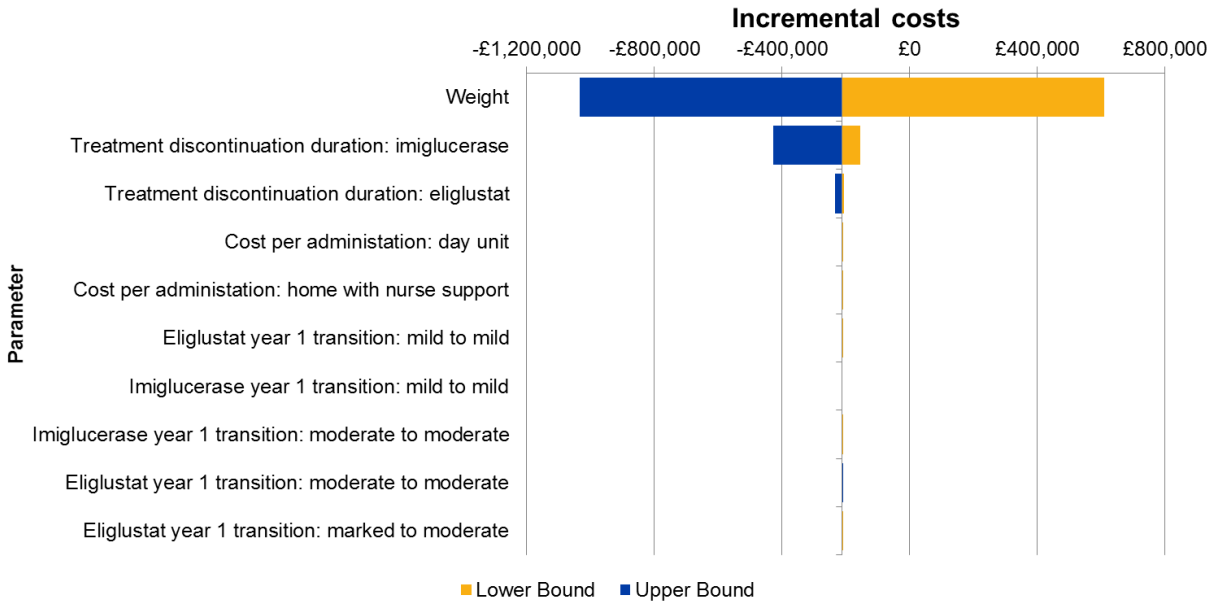
Key: ERT, enzyme replacement therapy; PM, intermediate metaboliser; SSC, severe skeletal complications.

Figure 37: Tornado diagram of incremental QALYs – ERT stable, versus velaglucerase, PM patients



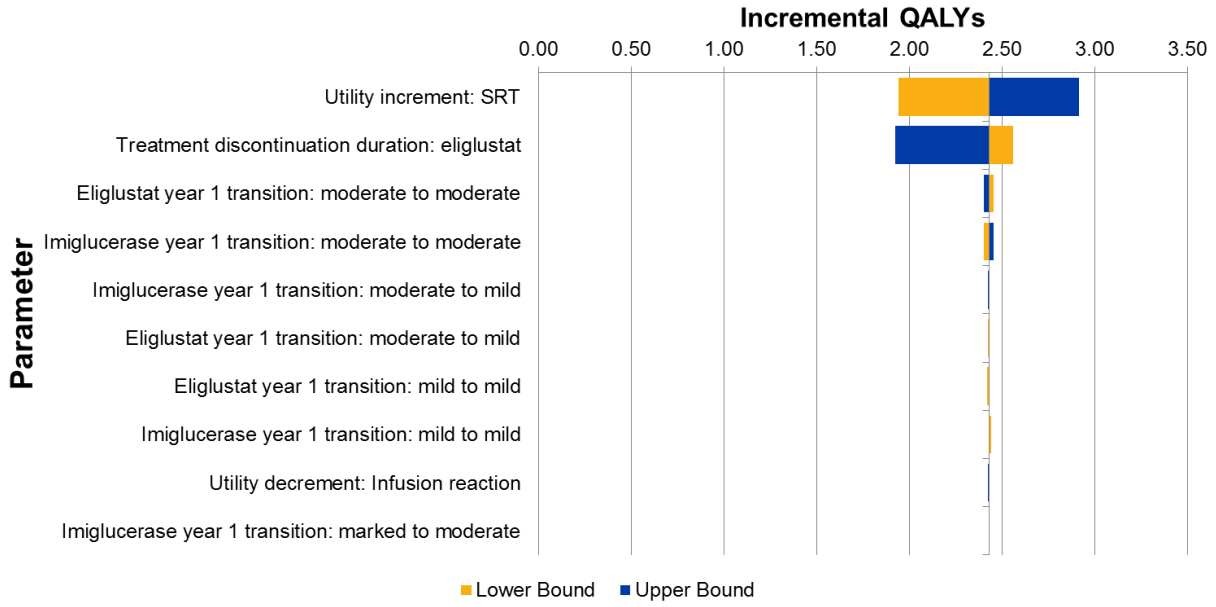
Key: ERT, enzyme replacement therapy; PM, poor metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

Figure 38: Tornado diagram of incremental cost – treatment naïve, versus imiglucerase, IM/EM patients



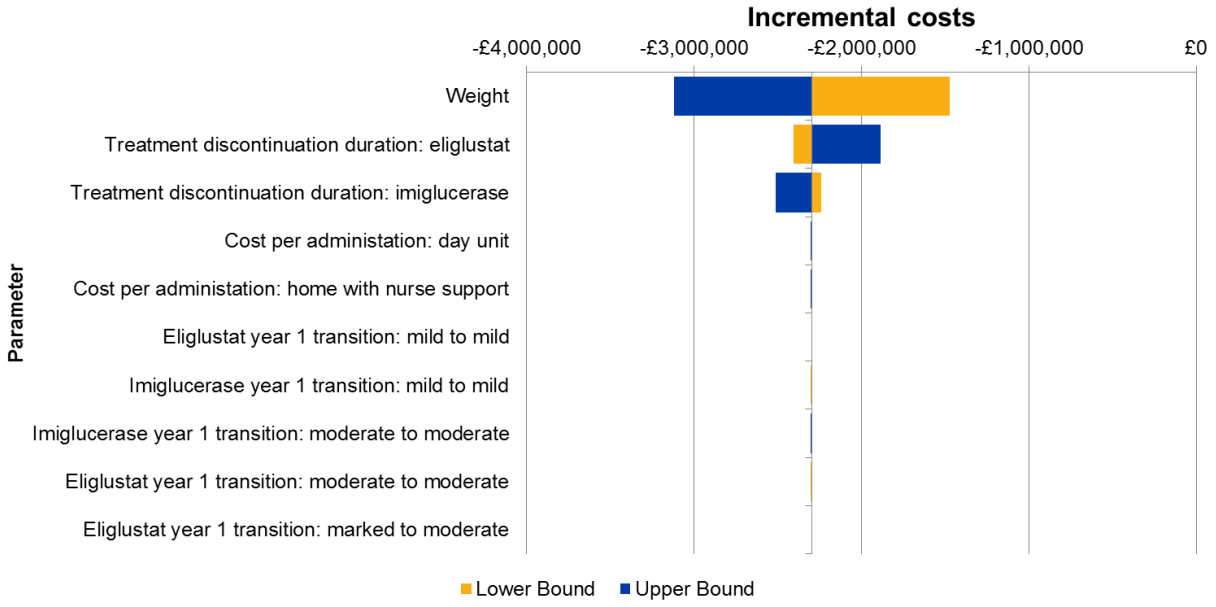
Key: EM, extensive metaboliser; IM, intermediate metaboliser.

Figure 39: Tornado diagram of incremental QALYs – treatment naïve, versus imiglucerase, IM/EM patients



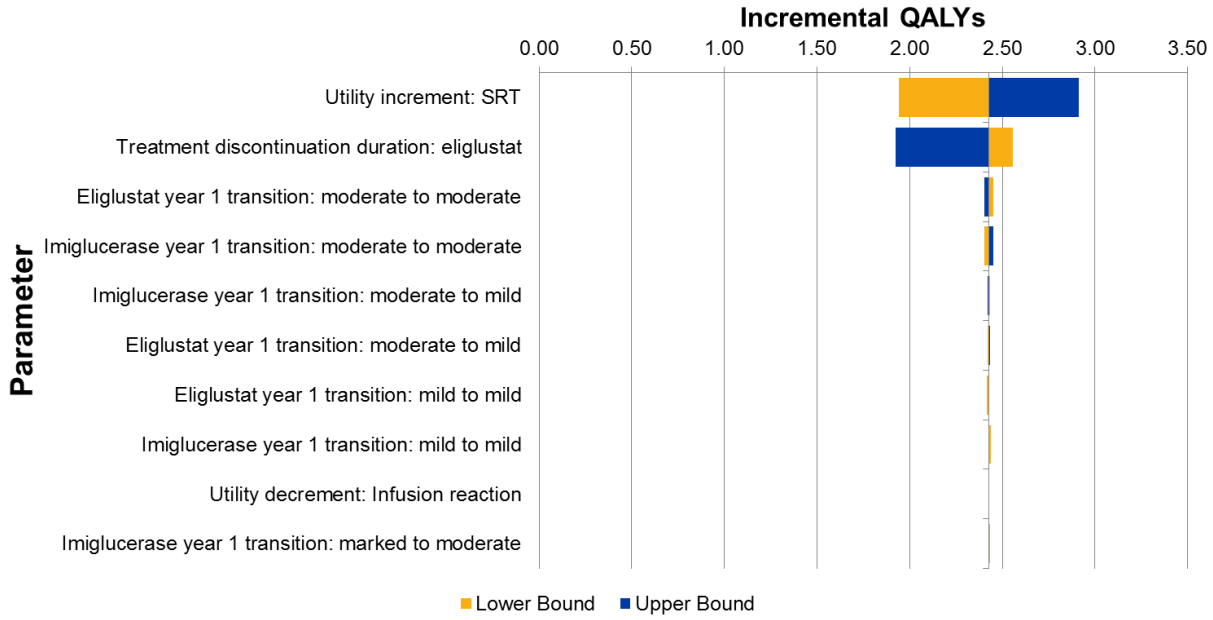
Key: EM, extensive metaboliser; IM, intermediate metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

Figure 40: Tornado diagram of incremental cost – treatment naïve, versus imiglucerase, PM patients



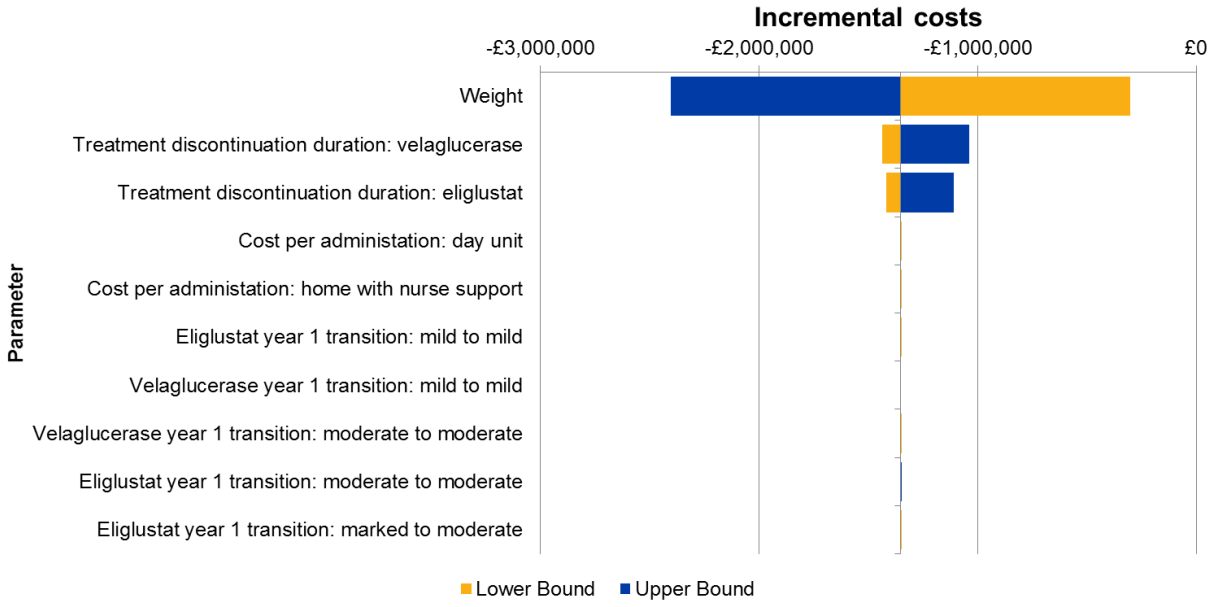
Key: PM, poor metaboliser.

Figure 41: Tornado diagram of incremental QALYs – treatment naïve, versus imiglucerase, PM patients



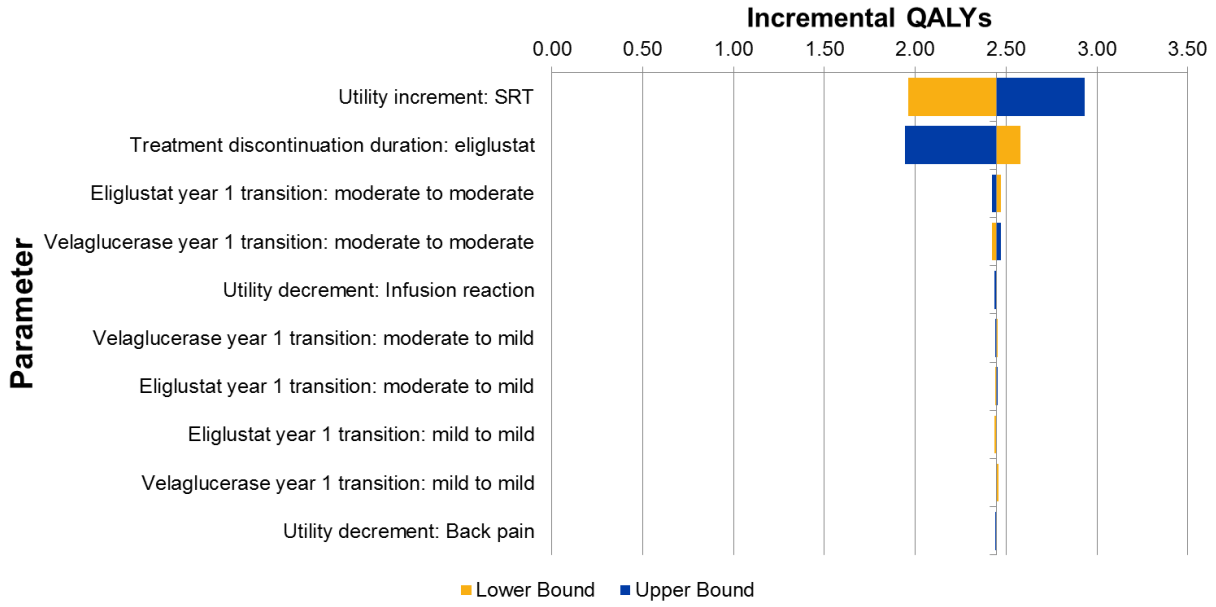
Key: PM, poor metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

Figure 42: Tornado diagram of incremental cost – treatment naïve, versus velaglucerase, IM/EM patients



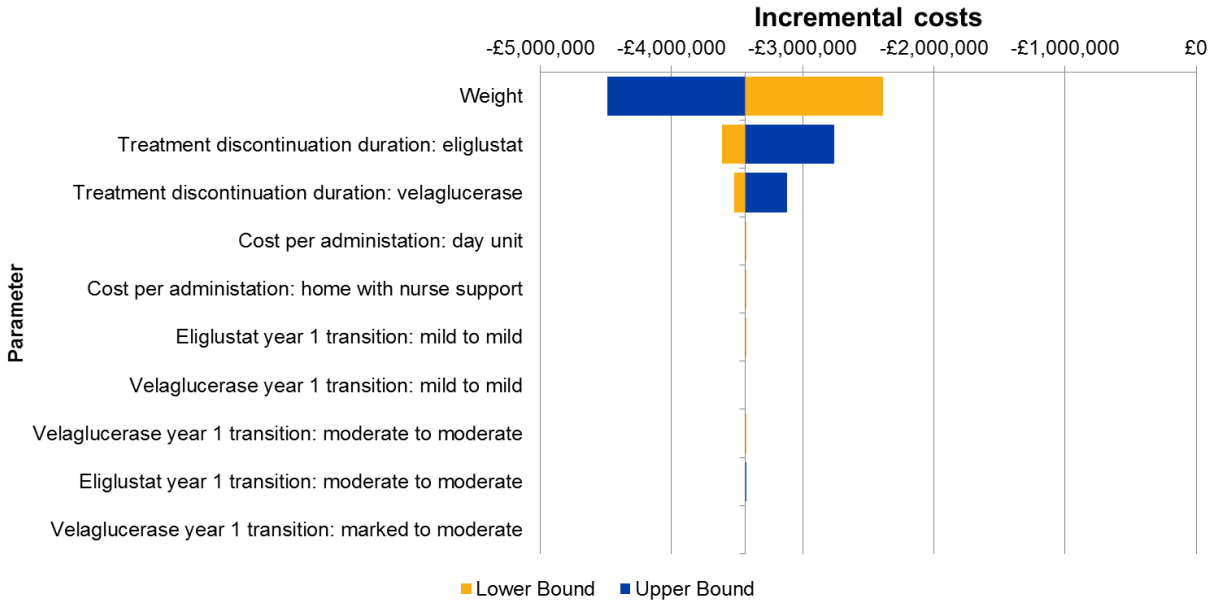
Key: EM, extensive metaboliser; IM, intermediate metaboliser.

Figure 43: Tornado diagram of incremental QALYs – treatment naïve, versus velaglucerase, IM/EM patients



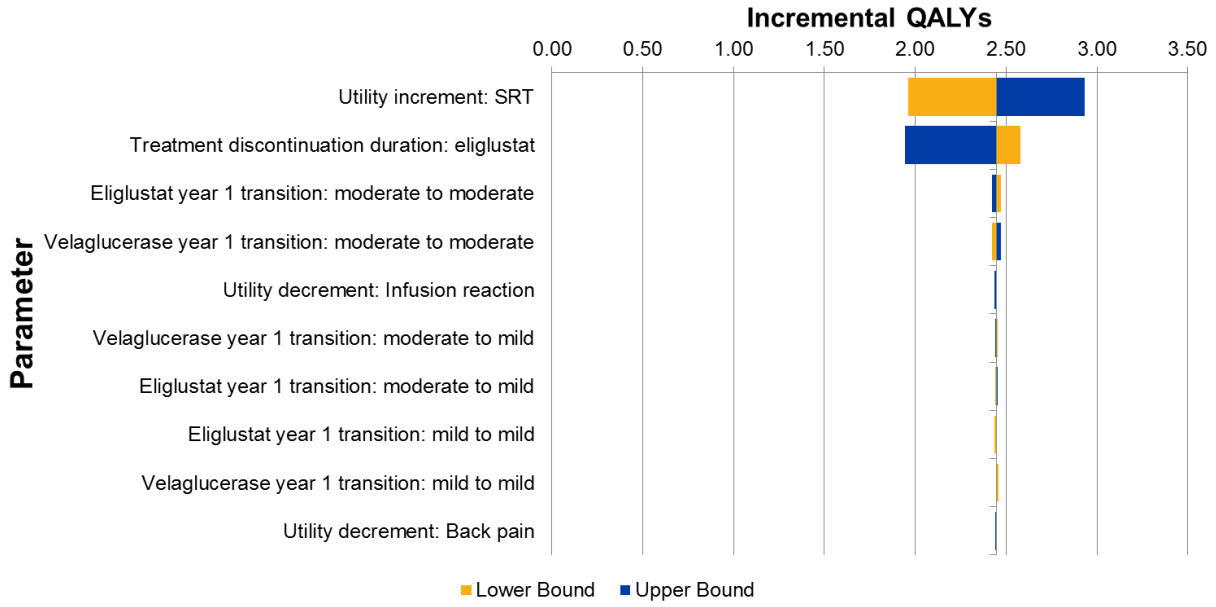
Key: EM, extensive metaboliser; IM, intermediate metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

Figure 44: Tornado diagram of incremental cost – treatment naïve, versus velaglucerase, PM patients



Key: PM, poor metaboliser.

Figure 45: Tornado diagram of incremental QALYs – treatment naïve, versus velaglucerase, PM patients



Key: PM, poor metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.

No multi-way sensitivity analyses were conducted.

12.5.13 Present results of the probabilistic sensitivity analysis described in table D10.3.

PSA was performed for both the ERT stable and treatment naïve populations, each with 1000 simulations, and the mean results of these runs are presented in Table 89 and Table 91.

Table 89: Mean results of PSA - ERT stable population, IM and EM

Technologies	Mean costs	Mean life years	Mean QALYs
Switching from imiglucerase			
Eliglustat	£4,202,686	37.52	16.81
Imiglucerase	£4,364,692	37.52	14.51
Switching from velaglucerase			
Eliglustat	£4,202,686	37.52	16.81
Velaglucerase	£5,597,680	37.52	14.51

Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; ICER, incremental cost-effectiveness ratio; IM, intermediate metaboliser; LYG, life years gained; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Table 90: Mean results of PSA - ERT stable population, PM

Technologies	Mean costs	Mean life years	Mean QALYs
Switching from imiglucerase			
Eliglustat	£2,217,148	37.52	16.82
Imiglucerase	£4,386,008	37.52	14.53
Switching from velaglucerase			
Eliglustat	£2,217,148	37.52	16.82
Velaglucerase	£5,662,169	37.52	14.53
Key: ERT, enzyme replacement therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PM, poor metaboliser; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.			

Table 91: Mean results of PSA – treatment naïve population, IM and EM

Technologies	Mean costs	Mean life years	Mean QALYs
Initiating on imiglucerase			
Eliglustat	£4,556,105	42.28	18.18
Imiglucerase	£4,649,604	42.28	15.70
Initiating on velaglucerase			
Eliglustat	£4,556,105	42.28	18.18
Velaglucerase	£5,851,396	42.28	15.68
Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; ICER, incremental cost-effectiveness ratio; IM, intermediate metaboliser; LYG, life years gained; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.			

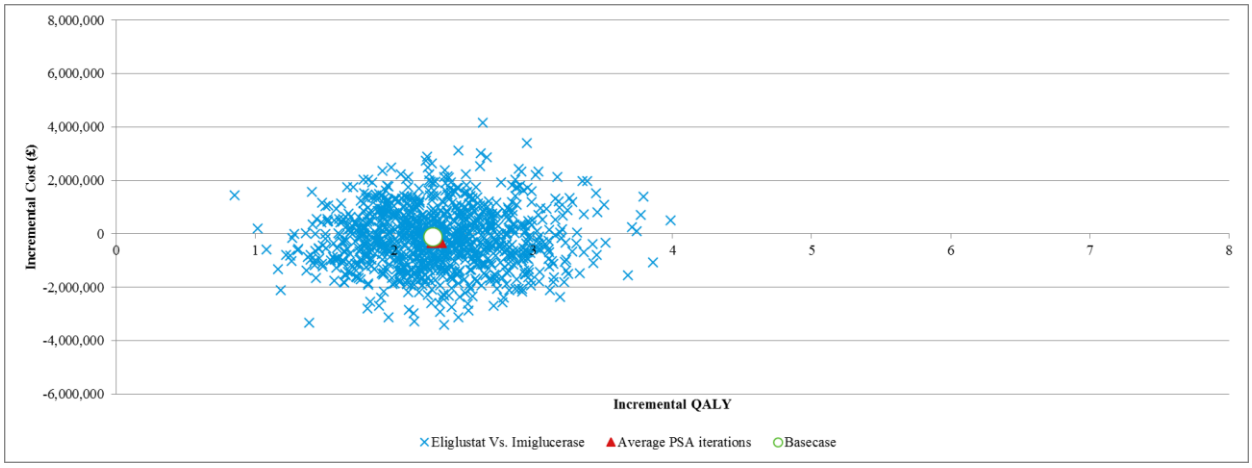
Table 92: Mean results of PSA – treatment naïve population, PM

Technologies	Mean costs	Mean life years	Mean QALYs
Initiating on imiglucerase			
Eliglustat	£2,355,071	42.28	18.06
Imiglucerase	£4,732,185	42.28	15.63
Initiating on velaglucerase			
Eliglustat	£2,355,071	42.28	18.06
Velaglucerase	£5,867,135	42.28	15.61
Key: ERT, enzyme replacement therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PM, poor metaboliser; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.			

The probabilistic results of the model are presented graphically in Figure 46 to Figure 53. These demonstrate the uncertainty in cost and QALY outcomes for each treatment independently. The primary influence in determining the magnitude of the cost and QALY

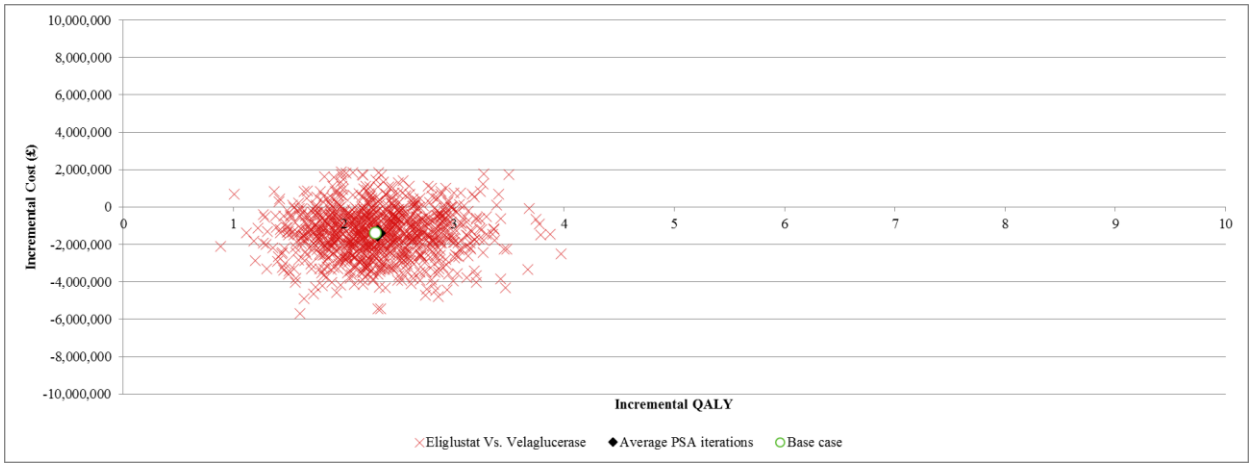
outcomes was the uncertainty regarding life expectancy, causing notable positive correlation between costs and QALYs for both eliglustat and the comparator treatments.

Figure 46: Scatterplot of PSA output: ERT stable population – IM/EM patients switching from imiglucerase



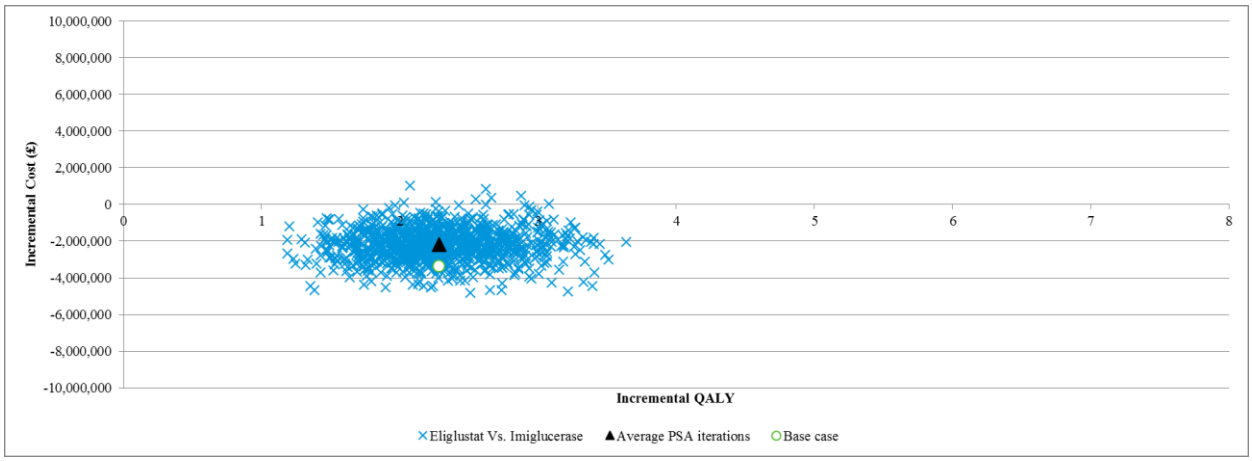
Key: ERT, enzyme replacement therapy; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 47: Scatterplot of PSA output: ERT stable population – IM/EM patients switching from velaglucerase



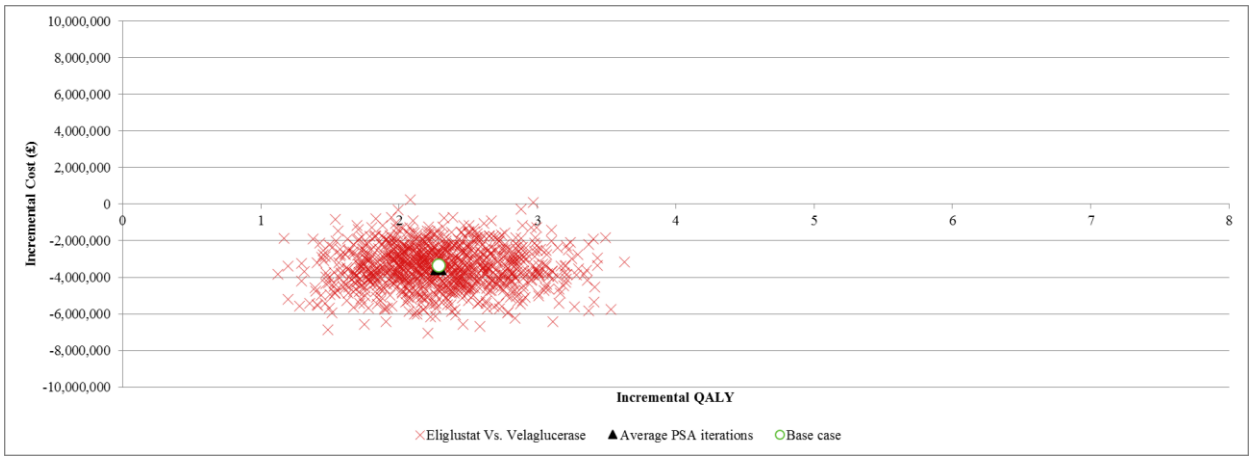
Key: ERT, enzyme replacement therapy; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 48: Scatterplot of PSA output: ERT stable population– PM patients switching from imiglucerase



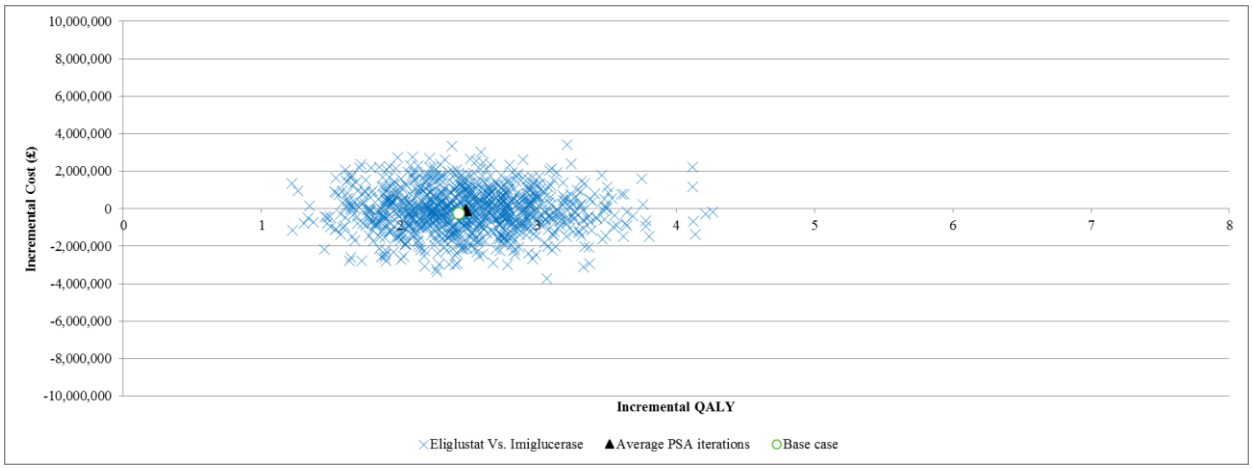
Key: ERT, enzyme replacement therapy; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 49: Scatterplot of PSA output: ERT stable population– PM patients switching from velaglucerase



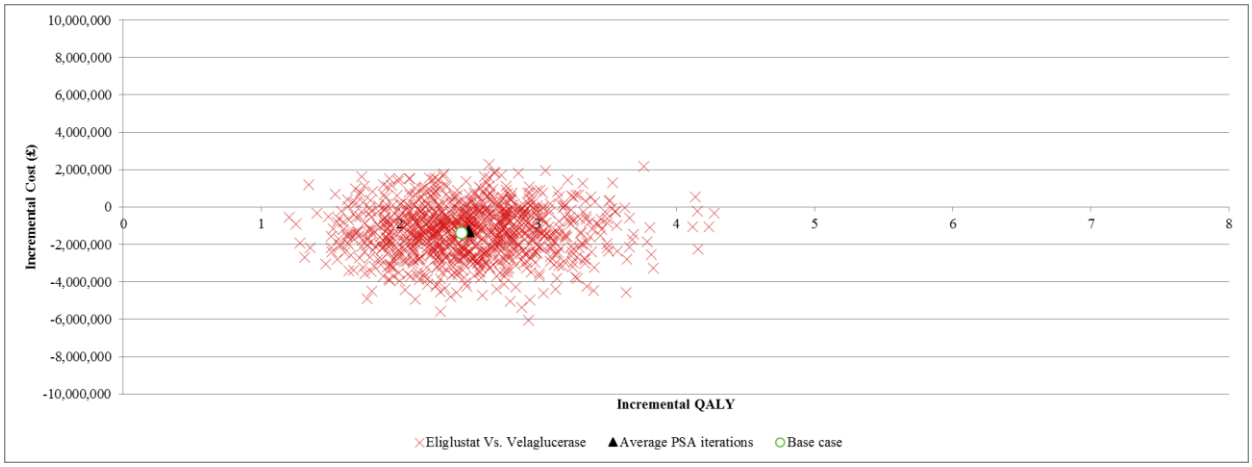
Key: ERT, enzyme replacement therapy; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 50: Scatterplot of PSA output: treatment naïve population – IM/EM patients eliglustat versus imiglucerase



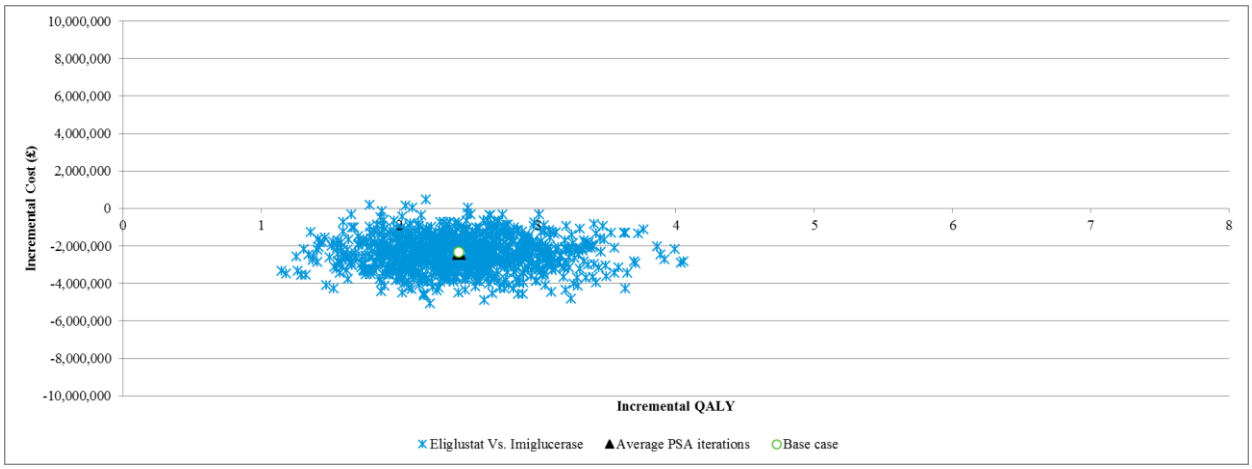
Key: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 51: Scatterplot of PSA output: treatment naïve population – IM/EM patients eliglustat versus velaglucerase



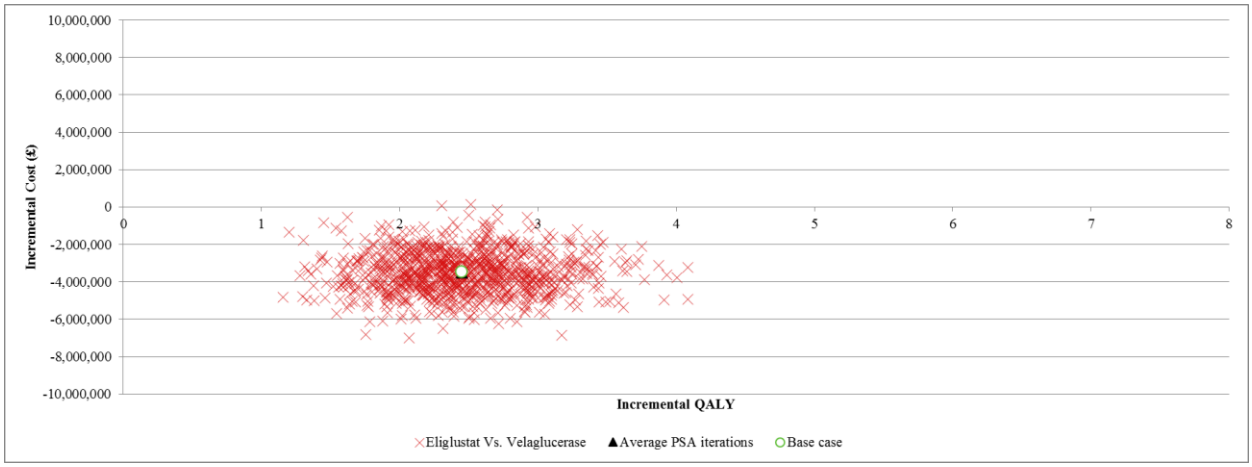
Key: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 52: Scatterplot of PSA output: treatment naïve population – PM patients eliglustat versus imiglucerase



Key: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 53: Scatterplot of PSA output: treatment naïve population – PM patients eliglustt versus velaglucerase



Key: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

12.5.14 What were the main findings of each of the sensitivity analyses?

The one-way sensitivity analyses performed identify the key parameters of the model which determine estimates of the incremental outcomes of eliglustat above those of each of the comparator treatments.

These were primarily parameters associated with the detriments to HRQL and cost that accompany treatment with IV ERT, either as a primary treatment, or as follow-on treatment after discontinuation. Incremental costs were most heavily influenced by patient weight, as this determines the dosing and costs of the ERT comparators. Other influential parameters

were those used to model overall survival of patients, which had some of the largest impacts on cost and QALY outcomes. In the comparisons to IV ERTs, the number of doses that patients were assumed to receive per month resulted in uncertainty regarding the costs of treating patients with imiglucerase and velaglucerase. Direct costs encountered were also very influential.

The probabilistic sensitivity analyses conducted to assess the combined parameter uncertainty of the model, demonstrate that overall stability of the model outputs is high, with the average results fairly close to the average result of 1,000 iterations.

12.5.15 What are the key drivers of the cost results?

The main driver of the model is the pharmacological and resource use costs of treatment provision. With the list price of eliglustat, all of the comparisons made estimated cost increases with eliglustat over the 70 year time horizon. The treatment costs of ERTs are driven by the average weight of patients, which dictates the number of units required for each infusion. The weight assumed is 67.5kg, a higher weight would result in a larger cost, and conversely, a lower weight, a lower cost. The cost outcomes of the model were also sensitive to discontinuation rates, especially in the treatment naïve population, as patients incur the costs of follow-on treatment with ERT following discontinuation.

Miscellaneous results

Describe any additional results that have not been specifically requested in this template. If none, please state.

Table 93 presents the results of the scenario analyses performed, in which the incremental costs relate to eliglustat versus the each comparator technology. Results are not presented for the scenario which assumes equal efficacy for the treatment naïve population, as the analysis for this population assumes equal efficacy in the base case

Table 93: Scenario analysis results

Parameter	Scenario	Technology	ERT stable population		Treatment naïve population	
			Cost	Inc. cost	Cost	Inc. cost
Base case results						
N/A		Eliglustat	£4,209,182		£4,457,247	
		Imiglucerase	£4,356,576	-£147,394	£4,669,546	-£212,299
		Eliglustat	£4,274,093		£4,526,382	
		Velaglucerase	£5,628,550	-£1,354,457	£5,878,749	-£1,352,367
Time horizon						
Time horizon of model (Base case: 70 years)	1 year (versus imiglucerase)	Eliglustat	£209,551		£209,291	
		Imiglucerase	£216,600	-£7,049	£217,423	-£8,132
	1 year (versus velaglucerase)	Eliglustat	£210,735		£210,475	
		Velaglucerase	£279,826	-£69,091	£278,282	-£67,807
Differential efficacy of eliglustat						
Application of different transition probabilities (Base case: trial based transitions for 1 year)	Equal efficacy using trial data (versus imiglucerase)	Eliglustat	£4,209,113		N/A	N/A
		Imiglucerase	£4,356,700	-£147,587	N/A	N/A
	Equal efficacy using trial data (versus velaglucerase)	Eliglustat	£4,274,023		N/A	N/A
		Velaglucerase	£5,628,674	-£1,354,651	N/A	N/A
	Equal efficacy using registry data only (versus imiglucerase)	Eliglustat	£4,208,914		£4,457,365	
		Imiglucerase	£4,356,501	-£147,587	£4,669,664	-£212,299
	Equal efficacy using registry data only (versus velaglucerase)	Eliglustat	£4,273,824		£4,526,499	
		Velaglucerase	£5,628,475	-£1,354,651	£5,878,867	-£1,352,367

Parameter	Scenario	Technology	ERT stable population		Treatment naïve population	
			Cost	Inc. cost	Cost	Inc. cost
Discontinuation						
Discontinuation rates for all treatments (Base case: included, see Section 12.5.1)	Rates set to zero (versus imiglucerase)	Eliglustat	£4,214,318		£4,462,717	
		Imiglucerase	£4,356,576	-£142,258	£4,613,624	-£150,907
	Rates set to zero (versus velaglucerase)	Eliglustat	£4,214,318		£4,462,717	
		Velaglucerase	£5,628,550	-£1,414,232	£5,961,096	-£1,498,379
IV administration utility decrement						
Utility decrement associated with IV administration of ERT (Base case: included, see Section 10.1.3)	No utility decrement (versus imiglucerase)	Eliglustat	£4,209,182		£4,457,491	
		Imiglucerase	£4,356,576	-£147,394	£4,669,598	-£212,107
	No utility decrement (versus velaglucerase)	Eliglustat	£4,274,093		£4,526,625	
		Velaglucerase	£5,628,550	-£1,354,457	£5,878,801	-£1,352,175
Velaglucerase PAS discount						
Percentage discount offered in velaglucerase list price (Base case: 0%, see Section 12.3.6)	20%	Eliglustat	£4,220,050		£4,469,066	
		Velaglucerase	£4,569,542	-£349,492	£4,814,494	-£345,428
	40%	Eliglustat	£4,166,008		£4,411,506	
		Velaglucerase	£3,510,534	£655,474	£3,750,188	£661,319
	60%	Eliglustat	£4,111,965		£4,353,947	
		Velaglucerase	£2,451,525	£1,660,440	£2,685,881	£1,668,066
	80%	Eliglustat	£4,057,922		£4,296,388	
		Velaglucerase	£1,392,517	£2,665,406	£1,621,575	£2,674,813

Key: ERT, enzyme replacement therapy; IV, intravenous; N/A, not applicable; PAS, patient access scheme; SRT, substrate reduction therapy.

12.6 Subgroup analysis

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

The analyses considered four patient populations; those who were stable on ERT at baseline and those who were treatment naïve at baseline, each separated into those that were IM or EM and those that were PM. These populations were identified and assessed as they are the patient populations in which comparative efficacy data for eliglustat is available.

No sub-groups within these have been explicitly considered in the economic analyses, and it is not expected that any subgroup of patients would any greater incremental effects from treatment than the Gaucher disease population as a whole. Diminishing numbers of patients also limits the statistical analysis of further subgroups.

12.6.2 Define the characteristics of patients in the subgroup(s).

N/A

12.6.3 Describe how the subgroups were included in the cost-consequence analysis.

N/A

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in Section 12.5.6 (base-case analysis).

N/A

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

The results of the model presented in Section 12.5 include patients who are IM and EM and patients who are PM. These have been reported separately to reflect the lower dose of eliglustat recommended for PM patients. No adjustments of treatment efficacy have been made, and this difference in dosing affects only the treatment costs of eliglustat.

Subgroups based on patient genotype could not be considered in the analyses due to data limitations. As has been concluded by previous economic evaluations in Gaucher disease[37], there are not sufficient data to base assumptions of differential treatment effects amongst patients with the main groups of mutations that exist within the wider disease population.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

Model inputs and structure were validated by the means of consultations with clinical experts in the field of Gaucher disease. Technical validation of the model was ensured by the use of internal methodological checklists, based on the Drummond checklist recommended for use when assessing economic evaluations.[139]

The model has been quality control checked and reviewed by BresMed who were not directly involved in the construction of this model. This check involved extensive testing of the model using an internal checklist which aimed to identify technical errors within the model, and highlight structural uncertainties.

The results of the economic model cannot be compared to the previous economic evaluations of ERT identified in the literatures searches, as these compared ERT against untreated patients or standard care. However, the total cost of imiglucerase treatment estimated by the model (treatment naïve population; the population for which the patient's life years is most similar) is comparable to the total cost reported by van Dussen et al. (£4,669,546 compared with €5,716,473 [£4,498,710 applying an exchange rate of 0.788 to three decimal places]).[119]

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-consequence analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Although there are no published economic analyses of eliglustat for comparison, the model built to assess eliglustat here is consistent with prior analyses in Gaucher disease in general. The results of the model have determined that the cost-effectiveness of treatment is largely dictated by the pharmaceutical costs incurred, a conclusion that has also been drawn in previously published analysis is this disease area.

Previous analyses have not had the breadth of evidence that has been available for the analyses that have been undertaken here. The clinical trial data available for eliglustat have allowed the modelling of disease severity, encompassing the symptomatic burdens that drive disease progression, and to use this to capture the impact on patient HRQL based on directly measured responses taken from a large trial of Gaucher disease patients.

12.8.2 Is the cost-consequence analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

The cost-effectiveness model built is generalisable to all GD1 patients in the UK.

The similarity of the trial population to Gaucher disease patients in England is discussed in Section 9.9.4. There is evidence that patients in the ENGAGE trial are similar in terms of disease severity and DS3 distribution at baseline to patients initiating treatment in the UK[21], and that patients in the ENCORE trial are comparable to treatment-experienced patients in international registry data.[110, 113]

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

A perennial weakness of cost-effectiveness analysis of orphan technologies is the availability of robust clinical evidence with which to parameterise an economic model. Although this has been a limitation of the economic evaluation of eliglustat, the evidence

base is more comprehensive than previous assessments of interventions in Gaucher disease.

The model is also limited by the absence of head-to-head data for eliglustat against the comparators cited. Whilst RCT data are available for eliglustat from two studies, of which one study was a head-to-head trial with 160 patients (ENCORE), which can be uncommon in orphan disease, this evidence does not incorporate all comparators considered with limited direct evidence that incorporates velaglucerase. This weak evidence base and data available for the comparators cited means that a full network meta-analysis is not possible. Furthermore head-to-head evidence is not available for both populations considered and only presents eliglustat versus imiglucerase within the ERT stable population. Due to this paucity of evidence it is necessary for the model to assume comparable efficacy between the comparators, and between eliglustat and the comparators in the treatment-naïve population. However, the ENCORE trial demonstrated non-inferiority of eliglustat compared with imiglucerase, and it is recognised that there is equivalent efficacy between imiglucerase and velaglucerase. It is therefore appropriate to assume equal efficacy in the absence of head-to-head data. This is further supported by the ITC presented in Section 9.8. The model also uses data from the ITT population from the trials, and this is applied to both patient groups defined by metaboliser status (IM/EM and PM). The model therefore functions on the assumption that the efficacy and clinical outcomes are not substantially affected by metaboliser status.

The model makes use of a wealth of HRQL data, which differentiate between groups of patients by symptom severity and have the capacity to quantify the impact over time and through disease progression

The model is sensitive to the ERT dosing in the comparator arm..

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The analyses that have been conducted and reported here fully assess the uncertainties within the evidence base and the results presented are complete to the extent of the data that are available. Only further data collection, particularly with regard to treatment efficacy and HRQL evidence could enhance the certainty of these results.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

The budget impact calculations estimate the difference in costs over 5 years if eliglustat were to be introduced as a treatment option. These costs are based on theSmPC licensed dose of eliglustat and the dosing of ERTs used in the ENCORE clinical trial.

The parameters presented in Table 94 are used to calculate the numbers of patients treated under the current treatment pattern, and the proposed provision of treatment with eliglustat included. The cost outcomes of the cost-effectiveness model are used to estimate the total expenditure of each cohort and determine the incremental budget impact of making eliglustat available in England. The model results for the IM and EM patients are used, as these contributed the majority of patients in the trial data, and likely therefore, the patient population.

The prevalence of GD1 for the UK (XXX) was obtained from Genzyme market share data. These were reweighted using ONS 2014 mid-population estimates to calculate XXX GD1 patients within England. Of these, 86% (XXX) are estimated to be aged 18 or older and therefore eligible for treatment with eliglustat.[42] Of the XXX estimated patients 91% were assumed to be ERT stable.

The number of patients stable on imiglucerase and velaglucerase in 2013 obtained from the market data is used to distribute the patients across the comparators at the start of the budget impact model. To estimate the number of patients in the first year of the budget impact model (2017), the prevalence from 2015 is inflated, assuming a 0.4% rise between 2015 and 2017, and a 0.4% rise per annum thereafter, based on market analysis. This reflects improvements in the diagnosis of the disease, and the uptake of treatment in previously untreated prevalent patients.

The calculations also consider newly diagnosed patients that are due to initiate treatment each year. This is estimated based on Genzyme market analysis to be X patients within the UK per year. When reweighted by ONS data, X English patients are anticipated to

begin treatment with eliglustat per year. Both groups of newly diagnosed and ERT stable patients are pooled together and initiate treatment on either imiglucerase or velaglucerase (under the current market shares) or eliglustat (in the proposed market breakdown). Newly diagnosed patients are split by the ERT market shares in 2013, and it is assumed that XX% and XX% of new patients receive imiglucerase and velaglucerase, respectively.

The numbers of patients switching from ERT to eliglustat each year are based on Genzyme market analysis.[140] All newly diagnosed patients are assumed to initiate on eliglustat rather than imiglucerase/velaglucerase.

CMU guidance scenario

As guidance from the Commercial Medicines Unit (CMU) states preference for velaglucerase over imiglucerase on the grounds of cost[34] (based on a confidential discount) is available for velaglucerase), an alternative scenario is presented in the budget impact analysis in which the calculations assume that 100% of new patients receive, or would have received, velaglucerase as first line treatment.

Table 94: Parameters used to calculate population treated with eliglustat

Population parameters	Estimate	Source
Population of England	54,316,618	Office of National Statistics. MYE1: Population Estimates Summary for the UK, mid-2014. Published 26 June 2015[41]
Population of England and Wales	57,408,654	
Population of the UK	64,596,752	
Type 1 Gaucher disease patients in 2015 in the UK	238	Genzyme. Data on file[138].
Type 1 Gaucher disease patients in 2015 in UK (weighted based on ONS population figures)	200	Genzyme data on file[138] weighted by ONS statistics[41]
Proportion of type 1 GD patients over the age of 18	86%	Wyatt et al.[42]
Increase in prevalence per year	0.04%	Assumption. Increase in GD1 diagnoses in adult prevalent population
Market shares		
Patients stable on imiglucerase in UK in 2013	XXX	Genzyme. Data on file[138]
Patients stable on velaglucerase in UK in 2013	XXX	
Proportion of total GD1 patients receiving imiglucerase	XX%	
Proportion of total GD1 patients receiving	XX%	

Population parameters	Estimate	Source
velaglucerase		
Incident patients at birth		
Number of GD1 patients due to initiate treatment in 2017	X	Assumption.
Key: GD, Gaucher disease.		

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

The numbers of patients that are expected to switch from being stable on ERT to eliglustat each year are presented in Table 95.

The expected treatment of patients under the current market shares is presented in Table 96 and the changes in treatment that are expected to result from the implementation of eliglustat are presented in Table 97. The number of patients receiving eliglustat is split by the population (either stable on ERT or treatment naïve), and by which comparator drug they would have otherwise received. This allows the model to apply the relevant cost outcomes from the cost-effectiveness model to estimate the total costs across the population.

The respective patient numbers for the scenario in which 100% of new patients receive, or would receive, velaglucerase, are presented in Table 98 and Table 99.

The rate at which patients who are stable on ERT switch to receive eliglustat is based on internal market analyses.[140] These rates are split by 2013 ERT market share data rates which are presented in Table 94 (XX% imiglucerase patients and XX% velaglucerase). The availability of eliglustat is not expected to impact on the incidence or prevalence of GD1.

Table 95: Anticipated patients newly initiated on eliglustat

Uptake	2017	2018	2019	2020	2021	Source
Patients newly initiated on eliglustat (i.e. patients switched from ERT stable plus treatment naïve) in the UK per year	XX	XX	XX	XX	XX	Genzyme. Data on file[140]
Patients newly initiated on eliglustat (i.e. patients switched from ERT stable plus treatment naïve) in England per year	XX	XX	XX	XX	XX	Adjusted for English patients only[41]
Key: ERT, enzyme replacement therapy.						

Table 96: Current market shares (absence of eliglustat) 2017-2021

Treatment	2017	2018	2019	2020	2021
Stable on imiglucerase	XX	XX	XX	XX	XX
Stable on velaglucerase	XX	XX	XX	XX	XX
Initiating on imiglucerase	X	X	X	X	X
Initiating on velaglucerase	X	X	X	X	X
Cumulative total patients	XXX	XXX	XXX	XXX	XXX

Table 97: Proposed market shares (including eliglustat) 2017-2021

Treatment	2017	2018	2019	2020	2021
Imiglucerase	XX	XX	XX	XX	XX
Velaglucerase	XX	XX	XX	XX	XX
Eliglustat:					
Switching from imiglucerase (ERT stable)	XX	XX	XX	XX	XX
Switching from velaglucerase (ERT stable)	XX	XX	XX	XX	XX
Naïve patients initiating in place of imiglucerase	XX	XX	XX	XX	XX
Naïve patients initiating in place of velaglucerase	XX	XX	XX	XX	XX
Total patients per year initiating on eliglustat	XX	XX	XX	XX	XX
Cumulative total patients	XX	XX	XX	XX	XX
Key: ERT, enzyme replacement therapy.					

Table 98: Current market shares (absence of eliglustat) 2017-2021, assuming 100% of treatment naïve patients receive velaglucerase

Treatment	2017	2018	2019	2020	2021
Stable on imiglucerase	XX	XX	XX	XX	XX
Stable on velaglucerase	XX	XX	XX	XX	XX
Initiating on imiglucerase	XX	XX	XX	XX	XX
Initiating on velaglucerase	XX	XX	XX	XX	XX
Cumulative total patients	XX	XX	XX	XX	XX

Table 99: Proposed market shares (including eliglustat) 2016-2020, assuming 100% of treatment naïve patients receive velaglucerase

Treatment	2017	2018	2019	2020	2021
Imiglucerase	XX	XX	XX	XX	XX
Velaglucerase	XX	XX	XX	XX	XX
Eliglustat:					
Switching from imiglucerase (ERT stable)	XX	XX	XX	XX	XX
Switching from velaglucerase (ERT stable)	XX	XX	XX	XX	XX
Initiating in place of imiglucerase	XX	XX	XX	XX	XX
Initiating in place of velaglucerase	XX	XX	XX	XX	XX
Total patients per year initiating on eliglustat	XX	XX	XX	XX	XX
Cumulative total patients	XX	XX	XX	XX	XX
Key: ERT, enzyme replacement therapy.					

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

The costs included in the budget impact analysis are those included in the cost-effectiveness model built to assess eliglustat. The cost outputs of the model are used to estimate the total costs of the modelled market shares and estimate the incremental budget impact of introducing eliglustat as a treatment option.

The costs included are described in the previous sections, but broadly include: drug acquisition costs, administration costs, medical resource and social services resource use costs. Adverse event costs and genotype testing costs are assumed to be zero, in line with

the assumptions made in the cost-effectiveness model. The cost of genotype testing will be met by Genzyme.

13.4 Describe any estimates of resource savings associated with the use of the technology.

The disaggregated results of the budget impact analysis presented in Section 13.7 demonstrate that there are cost savings with respect to the administration of IV ERT, which are negated if patients switch to oral eliglustat. In the overall budget impact estimate, this is offset against the increases is drug acquisition costs and marginal medical resource use costs.

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

All of the potential for cost-savings to the NHS and PSS has been included in the analyses undertaken. The results of the analysis with this included have been submitted separately.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

Given the life-long and debilitating nature of Gaucher disease, there is significant financial burden on patients' families and carers. It is not clear if or how this would be affected if patients were to switch from existing treatments to eliglustat. There is the potential for saving in avoiding travel costs (and disruption to work) incurred for those patients expected to visit clinics for ERT infusions; however, any expected saving cannot be reliably quantified.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

The total expenditures of the current market share and the proposed market share, with eliglustat included, are presented in Table 100 and Table 101**, respectively. The total estimated incremental costs of eliglustat are presented in Table 102 which are based on the relevant market share estimates presented in Section 13.6. The budget impact per year is presented in Figure 54, and the cumulative impact over 5 years is shown in**

Figure 55. The budget impact of introducing eliglustat at its anticipated list price equates to approximately 10-12% increases in expenditure per year.

Table 100: Estimated expenditure 2017-2021; current market share

Cost category	Year				
	2017	2018	2019	2020	2021
Treatment costs	XX	XX	XX	XX	XX
Testing costs	XX	XX	XX	XX	XX
Administration costs	XX	XX	XX	XX	XX
Adverse event costs	XX	XX	XX	XX	XX
Direct medical resource use costs	XX	XX	XX	XX	XX
Social services resource use costs	XX	XX	XX	XX	XX
Total	XX	XX	XX	XX	XX

Table 101: Estimated expenditure 2017-2021; proposed market share

Cost category	Year				
	2017	2018	2019	2020	2021
Treatment costs	XX	XX	XX	XX	XX
Testing costs	XX	XX	XX	XX	XX
Administration costs	XX	XX	XX	XX	XX
Adverse event costs	XX	XX	XX	XX	XX
Direct medical resource use costs	XX	XX	XX	XX	XX
Social services resource use costs	XX	XX	XX	XX	XX
Total	XX	XX	XX	XX	XX

Table 102: Estimated budget impact 2017-2021

Cost category	Year				
	2017	2018	2019	2020	2021
Treatment costs	XX	XX	XX	XX	XX
Testing costs	XX	XX	XX	XX	XX
Administration costs	XX	XX	XX	XX	XX
Adverse event costs	XX	XX	XX	XX	XX
Direct medical resource use costs	XX	XX	XX	XX	XX
Social services resource use costs	XX	XX	XX	XX	XX
Total	-£1,873,401	-£2,987,521	-£3,622,848	-£4,242,818	-£4,846,357

Figure 54: Estimated budget impact 2017-2021

Figure 55: Cumulative budget impact estimates 2017-2021

CMU guidance scenario

The results for the analysis run under the assumption that 100% of new patients initiating treatment will be treated with velaglucerase, instead of the 48%/52% split observed in 2013, are presented in Table 103. The budget impact per year and the cumulate budget impact over five years are presented in Figure 56 and

Figure 57, respectively. This analysis reflects the current guidance from the CMU, which indicates a preference for velaglucerase on the grounds of cost. However, this scenario is subject to some uncertainty, as this guidance is in effect only until 2016, at which point new guidance may be issued.

Table 103: Estimated budget impact 2017-2021, assuming 100% velaglucerase uptake in new patients

Cost category	Year				
	2017	**2018**	**2019**	**2020**	**2021**
Treatment costs	XX	XX	XX	XX	XX
Testing costs	XX	XX	XX	XX	XX
Administration costs	XX	XX	XX	XX	XX
Adverse event costs	XX	XX	XX	XX	XX
Direct medical resource use costs	XX	XX	XX	XX	XX
Social services resource use costs	XX	XX	XX	XX	XX
Total	XX	XX	XX	XX	XX

Figure 56: Estimated budget impact 2017-2021, assuming 100% velaglucerase uptake in new patients

Figure 57: Cumulative budget impact estimates 2017-2021, assuming 100% velaglucerase uptake in new patients

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc.).

The estimates of patient numbers are relatively certain given the data that are available, and treatments for the condition have been available for several years. Also due to the small patient population in the UK, patient numbers can be reasonably well estimated.

The estimates of the incremental costs of eliglustat are subject to some uncertainty, as per the results of the economic model, but are well validated and are expected to provide reasonable estimates over the 5 years of the budget impact analysis, especially given the dominance of drug costs in determining the differential costs. However, there is uncertainty over uptake rates, which will be driven both by clinician and patient preference, and NHS purchasing decisions.

It should be noted that the cost output applied in the budget impact analysis does include the effect of mortality from the cost-effectiveness model.

The output is sensitive to assumptions about ERT dosing. The analysis is based on the dosing of ERT in the ENCORE study.

Section E – Impact of the technology beyond direct health benefits and on the delivery of the specialised service

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to Section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

Section 15 is aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

The majority of the cost and health outcomes relevant to the decision problem are expected to be captured within the analyses presented here. The costs of the treatment and management GD1 are primarily borne by the NHS and PSS, and any additional costs incurred on patients and their families and carers are not expected to be substantial.

The cost-effectiveness analysis incorporated patient preference for oral therapy as the impact seen on patient utility, as a HRQL decrement for patients treated with IV ERTs. This impact is likely to fall wider than is captured in these analyses, with benefits for patients' families and carers from avoiding regular infusions and the ability to resume a more normal life. For a small proportion of patients this requires attendance as a day case, and may require additional carer time to accompany patients. However, for the majority of patient who receive infusions at home, there will still likely be some value placed on avoiding these infusions. For patients with mild symptomatic burden and are still in work, there would be productivity losses associated with the administration of IV therapy, which would be mitigated through the use of oral treatment.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

It is not expected that there would be any substantial impact on government bodies other than the NHS and PSS, which bear the costs included in the economic analyses presented here.

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Any costs incurred on patients and their families and carers are expected to fall into one of the following categories:

- Travel costs to and from treatment centres for IV administration of ERT, monitoring consultations or treatment of symptoms.
- Lost earnings for patients or family members caring for patients, and any costs of additional care not covered by the NHS and associated services

These have not been quantified in the analyses presented here, but would be expected to be relatively small compared to scale of costs borne by the NHS and PSS.

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

The impact will be the difference between receiving an oral therapy compared to receiving an infusion based therapy once every two weeks. Some impact on carers might be anticipated, but no data have been identified to quantify this in a meaningful way.

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

As reported in the EPAR, the CHMP felt that a sub-registry to the ICGG Gaucher Registry was necessary to investigate the long-term safety of eliglustat.[71] The CHMP recommended that reports from the sub-registry should be submitted with every periodic safety update report. As such, Genzyme have planned a prospective ICGG sub-registry to characterise the long-term safety profile of eliglustat in real-world clinical practice.[71] In particular, the sub-registry will aim to investigate the safety of eliglustat in long-term treatment, investigate use in patients who are CYP2D6 indeterminate metabolisers or non-genotyped patients, and in patients who are ultra-rapid CYP2D6 metabolisers.[71]

14.6 Describe the anticipated impact of the technology on innovation in the UK.

Eliglustat is the first oral ceramide analogue licenced for the treatment of GD1.[4] It is also the first oral therapy available as first-line treatment, and may result in improvements in the management of the disease in England. Patient preference for oral therapy was clearly demonstrated in the ENCORE trial, in which patients completed questionnaires indicating their preferred route of administration, citing the following reasons: convenience, the capsule form, taking the drug at home, and feeling better after treatment.[72]

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 year

At present our assumption is that there will not be an increase in registry collection over that already carried out on Gaucher disease

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

There are no plans as yet agreed to review the clinical effectiveness of the technology in clinical practice in the UK.

15 Impact of the technology on delivery of the specialised service

15.1 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

It is assumed that eliglustat will require no additional development or staff training above what is already required for the provision of care. The availability would negate the requirement of nurse support that is often required for home infusions of IV ERTs, which are the mainstay of current treatment practice.

Prescription of eliglustat does require laboratory testing to determine rates of the metabolism of eliglustat, in line with its licence in the treatment of poor, intermediate and extensive metabolisers only. Eliglustat is not licenced for use in patients who are ultra-rapid or indeterminate metabolisers. Metaboliser status is predominantly dependent on the activity of the enzyme CYP2D6, which is the primary metaboliser of eliglustat. The test for CYP2D6 status can be conducted at laboratories in the UK with existing NHS contracts, and the cost of these tests will be covered by Genzyme.

15.2 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

It is not expected that additional infrastructure would be required other than genotyping testing for the safe and effective provision of eliglustat, as the treatment facilities are already in place in the UK. However, the use of eliglustat may reduce the burden on staff due to it being an oral treatment compared to the existing IV therapies.

16 References

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4. Shayman JA. Eliglustat tartrate: Glucosylceramide Synthase Inhibitor Treatment of Type 1 Gaucher Disease. *Drugs of the future*. 2010; 35(8):613-20.

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17 Appendices

17.1 Appendix 1: Search strategy for clinical evidence

The following information should be provided:

17.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The following databases were searched to identify the relevant clinical information:

- MEDLINE (via PubMed)
- Embase
- Cochrane Central Register of Controlled Trials (via The Cochrane Library)

17.1.2 The date on which the search was conducted.

Databases were searched on 5 February 2013, and then for the updated searches on 5 January 2014 and 14 August 2015

17.1.3 The date span of the search.

Databases were searched from 1990 to 14 August 2015

17.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

MEDLINE Search via PubMed

5 January 2014

(("gaucher's disease" OR "gaucher disease") OR (gaucher* AND (lysosom* OR intralysosom* OR lipidosis OR glucosidase OR glucocerebrosidase))) NOT (Letter[pt] OR editorial[pt] AND (1990 : 2014[dp])) NOT ((review[pt]) NOT (systematic OR meta-analy*

OR ((indirect OR mixed) AND “treatment comparison”))) Publication date from 1990/01/01 to 2014/1/05; Humans; English

14 August 2015

(((((((("gaucher's disease" OR "gaucher disease") OR (gaucher* AND (lysosom* OR intralysosom* OR lipidosis OR glucosidase OR glucocerebrosidase)))) AND ((#1 NOT (Letter[pt] OR editorial[pt] OR review[pt])))) AND ((#2 NOT (systematic OR meta-analy* OR ((indirect OR mixed) AND “treatment comparison”)))))) AND ((#3) AND ("2013/10/01"[Date - Publication] : "2015/08/14"[Date - Publication]))) AND ((#4) AND Humans[Filter])) AND ((#5) AND English[Language])

EMBASE Search

5 January 2014

'gaucher`s disease':ab,ti OR 'gaucher disease':ab,ti OR (gaucher*:ab,ti AND (lysosom*:ab,ti OR intralysosom*:ab,ti OR lipidosis:ab,ti OR glucosidase:ab,ti OR glucocerebrosidase:ab,ti)) NOT (letter:it OR editorial:it) NOT (review:it NOT ('meta analysis'/exp OR 'meta analysis')) AND [abstracts]/lim AND [1990-2014]/py AND ('patient'/exp/mj OR [humans]/lim) AND [english]/lim

14 August 2015

1 Gaucher$ disease.ti,ab. (5180)

2 (gaucher$ and (lysosom$ or intralysosom$ or lipidosis or glucosidase or glucocerebrosidase)).ti,ab. (2650)

3 1 or 2 (5396)

4 letter/ (862955)

5 editorial/ (511440)

6 "review"/ (2080638)

7 exp meta analysis/ (97354)

8 meta analysis.tw. (86847)

9 7 or 8 (127245)

10 6 not 9 (2039566)

11 or/4-5,10 (3412052)

12 3 not 11 (4735)

13 limit 12 to abstracts (3819)

14 limit 13 to yr="2013 -Current" (810)

15 animal/ (1683594)

16 human/ (16095397)

17 15 not (15 and 16) (1266291)

18 14 not 17 (809)

19 limit 18 to english language (793)

CENTRAL Search via The Cochrane Library

5 January 2014

(("gaucher's disease" OR "gaucher disease") OR (gaucher* AND (lysosom* OR intralysosom* OR lipidosis OR glucosidase OR glucocerebrosidase))) NOT (review NOT (systematic OR meta-analy* OR ((indirect OR mixed) AND “treatment comparison”))) in title abstract keywords from 1990 to 2014

14 August 2015

#1 ("gaucher* disease"):ti,ab,kw

#2 (gaucher* and (lysosom* or intralysosom* or lipidosis or glucosidase or glucocerebrosidase)):ti,ab,kw

#3 #1 or #2

#4 (review not (systematic or meta-analy* or ((indirect or mixed) and "treatment comparison"))):ti,ab,kw

#5 #3 not #4 Publication Year from 2013 to 2015

17.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

The following conference proceedings were also searched:

- The 2012 annual meeting of the European Working Group on Gaucher Disease (EWGGD); there was no 2013 meeting
- The 2012 and 2013 meetings of the American Society of Human Genetics (ASHG)
- The 2012 meeting of the Society for the Study of Inborn Errors of Metabolism (SSIEM); there was no 2013 meeting
- The 2013 annual meeting of the Lysosomal Disease Network (LDN).

17.1.6 The inclusion and exclusion criteria.

Table 104: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Population • Adult or mixed (adult and paediatric) patients with confirmed type 1 Gaucher disease *Interventions* • Alglucerase • Eliglustat • Imiglucerase • Miglustat • Taliglucerase alfa • Velaglucerase alfa • Unspecified ERT *Comparators* • Placebo or best supportive care or any of the interventions or no treatment *Outcomes* • Clinical efficacy • Safety • Patient reported outcomes (PROs) *Study Design: Level 1 screening (titles/abstracts)* • Interventional: – RCTs – Non-randomised, controlled studies – Single-arm trials • Observational: – Prospective studies – Retrospective studies *Study Design: Level 2 screening (full-text)* • RCTs only	*Population* • Subjects with no GD • Studies involving only paediatric patients • Studies involving only GD2 or GD3 patients • Studies of a mix of GD1 and GD2/3 patients whose outcomes were not reported separately • Pregnant women with GD • Studies in which outcomes were not reported separately by ERT or SRT treatment • Any clinical trial involving <5 GD1 patients or observational studies involving <10 GD1 patients* *Interventions* • Any treatment other than ERT or SRT *Comparators* • N/A *Outcomes* • In vitro, animal, foetal, molecular, genetic, PD/PK outcomes • Biopsy findings, plasma or serum levels of antibodies, lipids and proteins *Study Design: Level 1 screening (titles/abstracts)* • Systematic reviews and meta analyses (references were checked for any additional relevant studies) • In vitro studies • Letters to the editor regarding a randomised trial • Case report • Expert opinion • Narrative review • Treatment guidelines (references were checked for any additional relevant studies) *Study Design: Level 2 screening (full-text)* • As for level 1 screening listed above, and • Interventional: – RCTs – Non-randomised, controlled studies – Single-arm trials • Prospective, observational studies only *Additional Restrictions* • Non-English studies • Any observational studies published prior to 1 January 2000**

Inclusion Criteria	Exclusion Criteria
Key: ERT: enzyme replacement therapy; GD1, Gaucher Disease type 1; GD2, Gaucher Disease type 2; GD3, Gaucher Disease type 3; N/A, not applicable; PD/PK, pharmacodynamics/pharmacokinetic; RCT, randomised controlled trial; SRT: substrate reduction therapy. **Notes:** * Most of the rejected publications were case reports or case studies and were rejected at the abstract screening level. Also, almost two thirds of them are published before 2005, before any treatments for GD became available. In addition, a large proportion of them are studies of various genetic diseases, which appear to include only a few GD patients ****** Observational studies published before 2000 were excluded as these only reported imiglucerase or alglucerase due to the availability of only these ERTs for type 1 Gaucher disease.	

17.1.7 The data abstraction strategy.

Data were extracted from all primary publications and supplemented as necessary and appropriate with data from related secondary publications. Each study accepted at the full-text level was reviewed and extracted by one investigator and validated independently by a second investigator. Any discrepancies with regard to the data elements presented and extracted in an article were resolved by a third investigator. Three eliglustat study reports provided by the sponsor have also been included as primary data sources and extracted into the tables/dataset for analysis, while the articles or abstracts related to three eliglustat trials identified via the systematic literature review were listed as related publications without data extraction.

The following elements of interest were captured, if available:

- Study design
- Geographic region
- Number of patients evaluated or randomised
- Treatment groups/dose
- Study population (treatment naïve, prior treatment, mixed)
- Patient baseline information (especially disease severity as reported by the investigator)
- Clinical efficacy outcomes
  - Spleen volume or size

        - Assessment methods such as magnetic resonance imaging (MRI) or computed tomography (CT) scan; mean changes or percent increase or reduction
    - Liver volume or size
        - Assessment methods such as MRI or CT scan; mean changes or percent increase or reduction
    - Haematological test results (haemoglobin level and platelet counts); mean change or percent change
    - Biomarker results (CCL18, chitotriosidase)
    - Skeletal pathology
        - Assessment methods such as radiographs (X-ray), MRI, or bone densitometry (dual-energy X-ray absorptiometry [DXA]), including the spine and bilateral femur
        - Total density measurements as well as T- and Z-scores of BMD score (change from baseline)
        - Bone crises
    - PROs
        - Bone pain (Brief Pain Inventory [BPI])
        - Fatigue (Fatigue Severity Score [FSS])
        - General quality of life (Short Form-36 Health Survey [SF-36] – total, physical, and mental score)
        - Other PROs
- Clinical safety outcomes
    - Any adverse events (AEs) reported (including but not limited to neurological, gastrointestinal [GI], cardiovascular, especially cardiac arrhythmias and syncopal episodes)
    - Treatment discontinuations (total, due to AEs, due to lack of efficacy)
- Outcomes were taken at reported timepoints. For each outcome, it was also noted if the outcomes were reported for patient subgroups (e.g. by disease severity, genotype, age, gender)

17.2 Appendix 2: Search strategy for adverse events

No separate search for adverse event data was conducted as AE data were taken from the identified trials. As such, this section is not applicable and has not been completed.

The following information should be provided.

17.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Not Applicable

17.2.2 The date on which the search was conducted.

Not Applicable

17.2.3 The date span of the search.

Not Applicable

17.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not Applicable

17.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not Applicable

17.2.6 The inclusion and exclusion criteria.

Not Applicable

17.2.7 The data abstraction strategy.

Not Applicable

17.3 Appendix 3: Search strategy for economic evidence

The following information should be provided.

17.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

The following databases were searched:

- Medline,
- Medline In-process,
- EMBASE,
- NHS Economic Evaluations Database (EED),
- Health Technology Assessment (HTA) database, and
- EconLit.

Medline and EMBASE were searched via OVID, and the HTA database and EED were searched via the Cochrane Library.

17.3.2 The date on which the search was conducted.

Initial searches were conducted between 30 May 2014 and 12 June 2014. These were updated with identical searches between 27 July 2015 and 14 August 2015.

17.3.3 The date span of the search.

The search was restricted to papers published after 1 January 1990. This is consistent with the clinical systematic review, and reflects the emergence of SRT and ERT in the late

1990s. No relevant studies would be expected prior to this date. The update searches were restricted to studies published in 2014 to present.

17.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The full strategies used in the electronic searches are presented below. In the updated searches performed in 2015, the only amendment was the restriction of studies to those published 2014 or later, to aid the identification of newly published material.

MEDLINE

1 exp Gaucher Disease/ (3737)
2 Gaucher$ disease.ti,ab. (3764)
3 1 or 2 (4540)
4 Gaucher$.ti,ab. (4126)
5 exp Lysosomes/ or exp lipidoses/ or exp glucosidases/ or exp glucosylceramidase/ (63815)
6 (lysosom$ or intralysosom$ or lipidosis or glucosidase or glucocerebrosidase).ti,ab. (60799)
7 4 and (5 or 6) (3737)
8 3 or 7 (4637)
9 Economics/ (26885)
10 "costs and cost analysis"/ (41675)
11 Cost allocation/ (1941)
12 Cost-benefit analysis/ (59907)
13 Cost control/ (20204)
14 Cost savings/ (8725)
15 Cost of illness/ (17560)
16 Cost sharing/ (1934)
17 "deductibles and coinsurance"/ (1426)
18 Medical savings accounts/ (483)
19 Health care costs/ (27025)
20 Direct service costs/ (1030)
21 Drug costs/ (12130)
22 Employer health costs/ (1066)
23 Hospital costs/ (7732)
24 Health expenditures/ (13650)
25 Capital expenditures/ (1942)
26 Value of life/ (5898)
27 exp economics, hospital/ (19461)
28 exp economics, medical/ (13552)
29 Economics, nursing/ (3899)
30 Economics, pharmaceutical/ (2534)
31 exp "fees and charges"/ (26999)
32 exp budgets/ (12067)
33 (low adj cost).mp. (25163)
34 (high adj cost).mp. (8142)
35 (health?care adj cost$).mp. (4524)
36 (fiscal or funding or financial or finance).tw. (83513)
37 (cost adj estimate$).mp. (1462)
38 (cost adj variable).mp. (33)
39 (unit adj cost$).mp. (1586)
40 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (177914)
41 or/9-40 (475500)
42 Letter/ (841909)
43 Review/ (1876922)
44 Comment/ (586011)

45 animal/ (5310606)
46 human/ (13445733)
47 45 not (45 and 46) (3849457)
48 or/42-44,47 (6624207)
49 8 and 41 (70)
50 49 not 48 (40)
51 limit 50 to yr="1990 -Current" (40)

Embase
1 exp Gaucher disease/ (5805)
2 Gaucher$ disease.ti,ab. (4544)
3 1 or 2 (6312)
4 Gaucher$.ti,ab. (5013)
5 exp lysosome/ or exp lipidosis/ or exp glucosidase/ or exp glucosylceramidase/ (68013)
6 (lysosom$ or intralysosom$ or lipidosis or glucosidase or glucocerebrosidase).ti,ab. (69611)
7 4 and (5 or 6) (4689)
8 3 or 7 (6435)
9 Socioeconomics/ (108829)
10 Cost benefit analysis/ (64344)
11 Cost effectiveness analysis/ (97547)
12 Cost of illness/ (14059)
13 Cost control/ (48383)
14 Economic aspect/ (103048)
15 Financial management/ (100296)
16 Health care cost/ (128778)
17 Health care financing/ (11420)
18 Health economics/ (33542)
19 Hospital cost/ (13769)
20 (fiscal or financial or finance or funding).tw. (104817)
21 Cost minimization analysis/ (2469)
22 (cost adj estimate$).mp. (1986)
23 (cost adj variable$).mp. (156)
24 (unit adj cost$).mp. (2435)
25 or/9-24 (662866)
26 letter.pt. (844943)
27 review.pt. (1951596)
28 animal/ (1566889)
29 human/ (14668058)
30 28 not (28 and 29) (1188713)
31 or/26-27,30 (3918377)
32 8 and 25 (181)
33 32 not 31 (113)
34 limit 33 to yr="1990 -Current" (112)

Cochrane
1 MeSH descriptor: [Gaucher Disease] explode all trees
2 (Gaucher* disease):ti,ab
3 1 or 2
4 Gaucher*:ti,ab
5 MeSH descriptor: [Lysosomes] explode all trees
6 MeSH descriptor: [Lipidoses] explode all trees
7 MeSH descriptor: [Glucosidases] explode all trees
8 MeSH descriptor: [Glucosylceramidase] explode all trees
9 5 or 6 or 7 or 8
10 (lysosom* or intralysosom* or lipidosis or glucosidase or glucocerebrosidase):ti,ab
11 4 and (9 or 10)
12 3 or 11 Publication Date from 1990 to 2014

EconLit
1 Gaucher$ disease.ti,ab. (2)

17.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

A number of conference proceedings were identified to potentially contain relevant studies. The following meetings were identified as relevant, but were not searched, as abstracts are published in journals that are indexed in the electronic databases:

- Lysosomal Disease Network (LDN) WORLD Symposium
- Society for the Study of Inborn Errors of Metabolism (SSIEM)
- International Society for Pharmacoeconomics and Outcome Research (ISPOR) - November

Records of the most recent meetings of the following conferences were searched, as they are not published in indexed journals, and therefore relevant abstracts would not be expected to be identified in the electronic searches:

- EWGGD
- ASHG

Hand searching of these poster and podium presentation abstracts did not identify any additional relevant material.

17.4 Appendix 4: Search strategy for adverse event cost and resource use and utilities

17.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- Cochrane
- EconLIT

The following databases were searched:

- Medline,
- Medline In-process,
- EMBASE,
- Cochrane
- EconLit.

Medline and EMBASE were searched via OVID.

17.4.2 The date on which the search was conducted.

Databases were searched between 15 and 20 October 2015.

17.4.3 The date span of the search.

The search was restricted to papers published after 1 January 1990. This is consistent with the clinical and economic reviews, and reflects the emergence of SRT and ERT in the late 1990s. No relevant studies would be expected prior to this date.

17.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The full strategies used in the electronic searches are presented below.

Utilities associated with adverse events in a Gaucher disease population.

MEDLINE and EMBASE

1	'gaucher disease'/exp
2	gaucher*
3	#1 OR #2
4	'quality of life'/exp
5	qol:ab,ti OR (quality NEXT/2 life):ab,ti
6	'value of life'/exp
7	(value NEXT/2 (money OR monetary)):ab,ti
8	'life quality':ab,ti OR 'life qualities':ab,ti
9	'utility':ab,ti OR 'utilities':ab,ti
10	'disutility':ab,ti OR 'disutilities':ab,ti
11	'well being':ab,ti OR 'wellbeing':ab,ti
12	'quality adjusted life year'/exp
13	'quality adjusted life':ab,ti OR qaly*:ab,ti OR qald*:ab,ti OR qale*:ab,ti OR qtime*:ab,ti
14	'disability adjusted life year':ab,ti OR 'disability adjusted life years':ab,ti OR daly*:ab,ti
15	'questionnaires'/exp

16	'health survey'/exp
17	'health status'/exp
18	'health status indicator'/exp
19	'self report'/exp
20	sf36:ab,ti OR 'sf 36':ab,ti OR 'short form 36':ab,ti OR 'shortform 36':ab,ti OR 'sf thirtysix':ab,ti OR 'sf thirty six':ab,ti OR 'shorform thirtysix':ab,ti OR 'shortform thirty six':ab,ti OR 'short form thirtysix':ab,ti OR 'short form thirty six':ab,ti
21	'sf 6':ab,ti OR sf6:ab,ti OR 'short form 6':ab,ti OR 'shortform 6':ab,ti OR 'sf six':ab,ti OR sfsix:ab,ti OR 'shortform six':ab,ti OR 'short form six':ab,ti
22	sf12:ab,ti OR 'sf 12':ab,ti OR 'short form 12':ab,ti OR 'shortform 12':ab,ti OR 'sf twelve':ab,ti OR sftwelve:ab,ti OR 'shortform twelve':ab,ti OR 'short form twelve':ab,ti
23	sf16:ab,ti OR 'sf 16':ab,ti OR 'short form 16':ab,ti OR 'shortform 16':ab,ti OR 'sf sixteen':ab,ti OR sfsixteen:ab,ti OR 'shortfrom sixteen':ab,ti OR 'short form sixteen':ab,ti
24	'sf20':ab,ti OR 'sf 20':ab,ti OR 'short form 20':ab,ti OR 'shortform 20':ab,ti OR 'sf twenty':ab,ti OR sftwenty:ab,ti OR 'shortform twenty':ab,ti OR 'short form twenty':ab,ti
25	euroqol:ab,ti OR 'euro qol':ab,ti OR 'euroqol 5d':ab,ti OR 'euroqol-5d':ab,ti OR 'euroqol 5-d':ab,ti OR eq5d:ab,ti OR 'eq 5d':ab,ti
26	hql:ab,ti OR hrql OR hqol:ab,ti OR 'h qol':ab,ti OR hrqol:ab,ti OR 'hr qol':ab,ti
27	(health* NEXT/1 year* NEXT/1 equivalent*):ab,ti OR hye:ab,ti OR hyes:ab,ti
28	'health utilities index':ab,ti
29	hui:ab,ti OR hui1:ab,ti OR hui2:ab,ti OR 'hui-2':ab,ti OR hui3:ab,ti OR 'hui-3':ab,ti
30	rosser:ab,ti
31	(quality NEXT/2 (wellbeing OR 'well being')):ab,ti OR qwb:ab,ti
32	(willingness NEXT/2 pay):ab,ti OR wtp:ab,ti
33	(patient NEAR/1 report*):ab,ti
34	'standard gamble':ab,ti OR 'sg':ab,ti OR (standard NEXT/1 gamble*):ab,ti
35	'time trade off':ab,ti OR 'time tradeoff':ab,ti OR tto:ab,ti
36	'fatigue impact scale':ab,ti OR 'fis':ab,ti
37	'visual analogue scale':ab,ti OR 'vas':ab,ti
38	'visual analogue scale 10':ab,ti OR 'vas10':ab,ti OR 'vas 10':ab,ti
39	'grade scale':ab,ti
40	'sickness impact profile':ab,ti OR 'sip':ab,ti
41	'grogono-woodgate health index':ab,ti OR 'grogono-woodgate index':ab,ti OR 'grogono woodgate':ab,ti OR 'gw index':ab,ti
42	'psychological general well being':ab,ti OR 'psychological well being':ab,ti OR 'psychological wellbeing':ab,ti
43	'functional capacity':ab,ti
44	'frailty':ab,ti
45	'activity scales':ab,ti
46	'presenteeism':ab,ti
47	'absenteeism':ab,ti
48	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47
49	#3 AND #48
50	#3 AND #48 AND [1-1-1990]/sd NOT [15-10-2015]/sd

Cochrane	
1	MeSH descriptor: [Gaucher Disease] explode all trees
2	gaucher*
3	#1 OR #2
4	#1 OR #2 [Publication Year from 1990 to 2015]
5	#1 OR #2 [Publication Year from 1990 to 2015] AND HTAD
6	#1 OR #2 [Publication Year from 1990 to 2015] AND NHS EED

Medline in process	
1	"Gaucher disease"[MeSH Terms]
2	gaucher*
3	#1 OR #2
4	((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint))
5	#3 AND #4

EconLit		**Search Options**
S1	MH "Gaucher disease"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
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S5	TI (qol OR (quality N2 life)) OR AB (qol OR (quality N2 life))	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
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S7	TI (value N2 (money OR monetary)) OR AB (value N2 (money OR monetary))	**Expanders** - Also search within the full text of the articles

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S8	TI ("life quality" OR "life qualities") OR AB ("life quality" OR "life qualities")	**Expanders** - Also search within the full text of the articles
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S9	TI ("utility" OR "utilities") OR AB ("utility" OR "utilities")	**Expanders** - Also search within the full text of the articles
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S10	TI ("disutility" OR "disutilities") OR AB ("disutility" OR "disutilities")	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S11	TI ("well being" OR "wellbeing") OR AB ("well being" OR "wellbeing")	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S12	MH "Quality-Adjusted Life Years"	**Expanders** - Also search within the full text of the articles
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S13	TI ("quality adjusted life" OR qaly* OR qald* OR qale* OR qtime*) OR AB ("quality adjusted life" OR qaly* OR qald* OR qale* OR qtime*)	**Expanders** - Also search within the full text of the articles
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S14	TI ("disability adjusted life year" OR "disability adjusted life years" OR daly*) OR AB ("disability adjusted life year" OR "disability adjusted life years" OR daly*)	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S15	MH "Questionnaires"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S16	MH "Health Survey"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S17	MH "Health Status"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S18	MH "Health Status Indicator"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S19	MH "Self Report"	**Expanders** - Also search

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S20	TI (sf36 OR "sf 36" OR "short form 36" OR "shortform 36" OR "sf thirtysix" OR "sf thirty six" OR "shorform thirtysix" OR "shortform thirty six" OR "short form thirtysix" OR "short form thirty six") OR AB (sf36 OR "sf 36" OR "short form 36" OR "shortform 36" OR "sf thirtysix" OR "sf thirty six" OR "shorform thirtysix" OR "shortform thirty six" OR "short form thirtysix" OR "short form thirty six")	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S21	TI ("sf 6" OR sf6 OR "short form 6" OR "shortform 6" OR "sf six" OR sfsix OR "shortform six" OR "short form six") OR AB ("sf 6" OR sf6 OR "short form 6" OR "shortform 6" OR "sf six" OR sfsix OR "shortform six" OR "short form six")	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S22	TI (sf12 OR "sf 12" OR "short form 12" OR "shortform 12" OR "sf twelve" OR sftwelve OR "shortform twelve" OR "short form twelve") OR AB (sf12 OR "sf 12" OR "short form 12" OR "shortform 12" OR "sf twelve" OR sftwelve OR "shortform twelve" OR "short form twelve")	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S23	TI (sf16 OR "sf 16" OR "short form 16" OR "shortform 16" OR "sf sixteen" OR sfsixteen OR "shortfrom sixteen" OR "short form sixteen") OR AB (sf16 OR "sf 16" OR "short form 16" OR "shortform 16" OR "sf sixteen" OR sfsixteen OR "shortfrom sixteen" OR "short form sixteen")	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S24	TI (sf20 OR "sf 20" OR "short form 20" OR "shortform 20" OR "sf twenty" OR sftwenty OR "shortform twenty" OR "short form twenty") OR AB (sf20 OR "sf 20" OR "short form 20" OR "shortform 20" OR "sf twenty" OR sftwenty OR "shortform twenty" OR "short form twenty")	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S25	TI (euroqol OR "euro qol" OR "euroqol 5d" OR "euroqol-5d" OR "euroqol 5-d" OR eq5d OR "eq 5d") OR AB (euroqol OR "euro qol" OR "euroqol 5d" OR "euroqol-5d" OR "euroqol 5-d" OR eq5d OR "eq 5d")	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S26	TI (hql OR hrql OR hqol OR "h qol" OR hrqol OR "hr qol") OR AB (hql OR hrql OR hqol OR "h qol" OR hrqol OR "hr qol")	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S27	TI ((health* N1 year* N1 equivalent*) OR hye OR hyes) OR AB ((health* N1 year* N1 equivalent*) OR hye OR hyes)	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S28	TI "health utilities index" OR AB "health utilities index"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S29	TI (hui OR hui1 OR hui2 OR "hui-2" OR hui3 OR "hui-3") OR AB (hui OR hui1 OR hui2 OR "hui-2" OR hui3 OR "hui-3")	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S30	TI rosser OR AB rosser	**Expanders** - Also search within the full text of the articles

		Search modes - Find all my search terms
S31	TI ((quality N2 (wellbeing OR "well being")) OR qwb) OR AB ((quality N2 (wellbeing OR "well being")) OR qwb)	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S32	TI ((willingness N2 pay) or wtp) OR AB ((willingness N2 pay) or wtp)	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S33	TI (patient N1 report*) OR AB (patient N1 report*)	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S34	TI ("standard gamble" OR sg OR (standard N1 gamble*)) OR AB ("standard gamble" OR sg OR (standard N1 gamble*))	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S35	TI ("time trade off" OR "time tradeoff" OR tto) OR AB ("time trade off" OR "time tradeoff" OR tto)	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S36	TI ("fatigue impact scale" OR fis) OR AB ("fatigue impact scale" OR fis)	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S37	TI ("visual analogue scale" OR vas) OR AB ("visual analogue scale" OR vas)	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S38	TI ("visual analogue scale 10" OR vas10 OR "vas 10") OR AB ("visual analogue scale 10" OR vas10 OR "vas 10")	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S39	TI "grade scale" OR AB "grade scale"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S40	TI ("sickness impact profile" OR sip) OR AB ("sickness impact profile" OR sip)	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S41	TI ("grogono-woodgate health index" OR "grogono-woodgate index" OR "grogono woodgate" OR "gw index") OR AB ("grogono-woodgate health index" OR "grogono-woodgate index" OR "grogono woodgate" OR "gw index")	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S42	TI ("psychological general well being" OR "psychological well being" OR	**Expanders** - Also search

	"psychological wellbeing") OR AB ("psychological general well being" OR "psychological well being" OR "psychological wellbeing")	within the full text of the articles **Search modes** - Find all my search terms
S43	TI "functional capacity" OR AB "functional capacity"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S44	TI frailty OR AB frailty	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S45	TI "activity scales" OR AB "activity scales"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S46	TI presenteeism OR AB presenteeism	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S47	TI absenteeism OR AB absenteeism	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S48	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S49	S3 AND S48	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S50	S3 AND S48	**Limiters** - Date Published: 19900101-20151031 **Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S51	S3 AND S48 Source – Econlit	**Limiters** - Date Published: 19900101-20151031 **Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms

Medline and Embase

1 'gaucher disease'/exp
2 gaucher*
3 #1 OR #2
4 'economics'/exp
5 'costs and cost analysis'/exp
6 'cost allocation'/exp
7 'cost benefit analysis'/exp
8 'cost control'/exp
9 'cost savings'/exp
10 'cost of illness'/exp
11 'cost sharing'/exp
12 'deductibles and coinsurance'/exp
13 'medical savings accounts'/exp
14 'health care costs'/exp
15 'direct service costs'/exp
16 'drug costs'/exp
17 'employer health costs'/exp
18 'hospital costs'/exp
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20 'capital expenditures'/exp
21 'value of life'/exp
22 'economics, medical'/exp
23 'economics, hospital'/exp
24 'economics, nursing'/exp
25 'economics, pharmaceutical'/exp
26 'budget'/exp
27 'fees and charges'/exp
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29 (high NEXT/1 costs):ab,ti
30 (healthcare NEXT/1 cost*):ab,ti
31 fiscal:ab,ti OR funding:ab,ti OR financial:ab,ti OR finance:ab,ti
32 (cost NEXT/1 estimate*):ab,ti

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3	
3	unit NEXT/1 cost*
4	
3	economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti
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3	fee:ab,ti OR fees:ab,ti
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3	(value NEXT/2 (money OR monetary)):ab,ti
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3	'quality adjusted life year'/exp
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4	'disease management'
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4	'physician practice patterns'
4	
4	'health care rationing'
5	
4	((clinical OR critical OR patient) NEXT/1 path*):ab,ti
6	
4	(managed NEXT/2 (care OR clinical OR network)):ab,ti
7	
4	(resource* NEXT/2 allocat*):ab,ti
8	
4 9	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48
5 0	#3 AND #49
5 1	#3 AND #49 AND [1-1-1990]/sd NOT [15-10-2015]/sd

Cochrane

1	MeSH descriptor: [Gaucher Disease] explode all trees
2	gaucher*
3	#1 OR #2
4	#1 OR #2 [Publication Year from 1990 to 2015]
5	#1 OR #2 [Publication Year from 1990 to 2015] AND HTAD
6	#1 OR #2 [Publication Year from 1990 to 2015] AND NHS EED

Medline in process	
1	"Gaucher disease"[MeSH Terms]
2	gaucher*
3	#1 OR #2
4	((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint))
5	#3 AND #4

EconLit		**Search Options**
S1	MH "Gaucher disease"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
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S3	S1 OR S2	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S4	MH "Economics"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S5	MH "Costs and Cost Analysis"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S6	MH "Cost Allocation"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S7	MH "Cost-Benefit Analysis"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S8	MH "Cost Control"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S9	MH "Cost Savings"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S10	MH "Cost of Illness"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S11	MH "Cost Sharing"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S12	MH "Deductibles and Coinsurance"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S13	MH "Medical Savings Accounts"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S14	MH "Health Care Costs"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S15	MH "Direct Service Costs"	**Expanders** - Also search within the full text of the articles

		Search modes - Find all my search terms
S16	MH "Drug Costs"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S17	MH "Employer Health Costs"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S18	MH "Hospital Costs"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S19	MH "Health Expenditures"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S20	MH "Capital Expenditures"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S21	MH "Value of Life"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S22	MH "Economics, Medical"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S23	MH "Economics, Hospital"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S24	MH "Economics, Nursing"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S25	MH "Economics, Pharmaceutical"	**Expanders** - Also search within the full text of the articles
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S26	MH "Budgets"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S27	MH "Fees and Charges"	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S28	TI (low N1 costs) OR AB (low N1 costs)	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S29	TI (high N1 costs) OR AB (high N1 costs)	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S30	TI (healthcare N1 cost*) OR AB (healthcare N1 cost*)	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S31	TI ((fiscal OR funding OR financial OR finance)) OR AB ((fiscal OR funding OR financial OR finance))	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S32	TI (cost N1 estimate*) OR AB (cost N1 estimate*)	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms
S33	TI (cost N1 variable*) OR AB (cost N1 variable*)	**Expanders** - Also search within the full text of the articles
		Search modes - Find all my search terms

S34	unit N1 cost*	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S35	TI (economic* OR pharmacoeconomic* OR price* OR pricing) OR AB (economic* OR pharmacoeconomic* OR price* OR pricing)	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S36	TI (fee OR fees) OR AB (fee OR fees)	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S37	TI (value N2 (money OR monetary)) OR AB (value N2 (money OR monetary))	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S38	MH "Quality-Adjusted Life Years"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S39	TI ("quality adjusted life year" OR "quality adjusted life years" OR qualy*) OR AB ("quality adjusted life year" OR "quality adjusted life years" OR qualy*)	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
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S41	MH "Consumer satisfaction"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S42	MH "Patient Acceptance of Health Care"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S43	MH "Disease Management"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S44	MH "Physician Practice Patterns"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S45	MH "Health Care Rationing"	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S46	TI ((clinical OR critical OR patient) N1 path*) OR AB ((clinical OR critical OR patient) N1 path*)	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S47	TI (managed N2 (care OR clinical OR network)) OR AB (managed N2 (care OR clinical OR network))	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S48	TI resource* N2 allocat* OR AB resource* N2 allocat*	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S49	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S50	S3 AND S49	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms
S51	S3 AND S49	**Limiters** - Date Published: 19900101-20151031

S52	S3 AND S49 Source – Econlit	**Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms **Limiters** - Date Published: 19900101-20151031 **Expanders** - Also search within the full text of the articles **Search modes** - Find all my search terms

17.5 Appendix 5: Describe how the data from the clinical evidence were used in the cost-consequence analysis.

17.5.1 Summary of trial data used in the model

The efficacy of eliglustat and the comparator technologies are implemented as the movement of patients between DS3 health states per cycle, derived from the clinical trials available for eliglustat. The GD-DS3 a validated GD1 specific measure is described in Section 6.1. It consists of three domains: haematological (with 3 items), visceral (with 3 items) and bone (with 5 items).

Data from two randomised controlled trials (RCTs), ENGAGE and ENCORE, were used to derive the starting health-state distributions and from ENGAGE and ENCORE for the transition probabilities for the first annual cycle, which corresponds to treatment response during the first year of therapy.

The ENGAGE study was a double-blinded study in treatment naïve GD1 patients, comparing treatment with eliglustat (50 mg or 100 mg twice daily) to placebo.[52] The trial is described in detail in Section 9.4.1. The primary endpoint of the study was percentage change in spleen volume from baseline at the end of the trial period (39 weeks). Secondary endpoints included haemoglobin levels, platelet counts and liver volume, and tertiary endpoints included Z scores for BMD, bone pain and bone crises. All of these outcomes correspond to items in the GD-DS3 instrument. The trial also included the SF-36 questionnaire as a HRQL endpoint. The placebo arm of the trial was determined not to be relevant to the decision problem and is not used in the model.

The ENCORE trial was an open-label randomised clinical trial[72], in which patients who were stable on treatment at the start of the trial period were randomised to receive eliglustat (50 mg, 100 mg or 150 mg) twice daily or IV administration of imiglucerase every 2 weeks (at doses ranging from 30-130 U/kg per month). The trial is described in greater detail in Section 9.4.1.

The composite primary endpoint of the trial was the proportion of patients that remained stable on treatment at 52 weeks (the duration of the comparative phase of the trial), and included haemoglobin levels, platelet counts, liver volume and spleen volume. Secondary endpoints of the trial included Z scores for BMD, and tertiary endpoints included bone pain and bone crises. These trial outcomes align with items of the GD-DS3, and were used to derive transition probabilities for the model. The trial also included the SF-36 questionnaire as a measure of HRQL.

The three comparators in the model are assumed to have equivalent efficacy, and are based on the same transition probability matrices. In the base case, these transition probabilities are applied for the first cycle, the duration that comparative data are available. Data from the Gaucher DS3 Score Multi-Site Study Group ("DS3 Score Study")[66], were used to derive long-term transition probabilities following the trial data.

The DS3 Score Study was designed to evaluate the ability of the DS3 score to predict disease progression and patterns of treatment response. Data for the DS3 Score Study came from patients that had enrolled in the ICGG Gaucher Registry and consented to participate[66]. DS3 scores were collected from participants and were linked to their clinical data in the ICGG Registry.

The application of the different efficacy sources in the model is described below in Table 105. In combining the data in this way, the model incorporates the extent of comparative efficacy data available, and assumes comparable decline in disease state based on longer-term natural history data available.

HRQL data from the DS3 Score Study, the ENGAGE and ENCORE trials, and the Phase II eliglustat study were pooled in post hoc analyses and used to estimate health-state-specific utilities for the model.

The Phase II trial (Genzyme, 2013), used to estimate HRQL parameters for the model, was an open-label, single-arm trial in which 26 treatment-naïve patients were treated with 50 mg or 100 mg of eliglustat twice daily for 52 weeks. The primary endpoints of the trial were efficacy, safety and pharmacokinetics, but also included a HRQL endpoint in the form of the SF-36 questionnaire.

Table 105: Sources of health state transitions used in the model

Year/cycle	Treatment naïve population		ERT stable population	
	Eliglustat	**ERT Comparators***	**Eliglustat**	**ERT Comparators***
0-1	Eliglustat arm of the ENGAGE trial		Eliglustat arm of ENCORE	Imiglucerase arm of ENCORE
1-2	Results of ordinary logistic regression based on observations from DS3 Score Study		Results of ordinary logistic regression based on observations from DS3 Score Study	
2-3				
3-4+				

Key: ERT, enzyme replacement therapy.
Notes: *The efficacy for imiglucerase and velaglucerase are assumed to be equivalent.

17.5.2 Baseline distributions across health states

The distribution of patients at baseline across the nine living health states was based on the baseline characteristics in the ENGAGE and ENCORE clinical trials. The distribution for the “Treatment Naïve” population is based on the distribution of all patients (in the eliglustat and placebo arms) at the time of randomisation in the ENGAGE trial. The distribution for the “Stable ERT” population is based on the distribution of all patients (in the eliglustat and imiglucerase arms) at the time of randomisation in the ENCORE trial. Standard errors for the fraction of patients in each health state were derived using the binomial formula $\sigma_i = (p_i(1-p_i)/n)^{1/2}$ where p_i is the fraction of patients in health state i and n is the total number of patients in the trial.

Both of these distributions are presented in Table 106. No patients were observed at baseline in health states 2, 3, 5, and 7–9 in the ENGAGE trial and no patients were observed at baseline in health states 3 and 5–9 in the ENCORE trial. This is due to trial protocols that excluded patients with more severe disease.

Table 106: Baseline health state distributions derived from clinical trial data

Health state	Baseline distribution	
	Treatment Naive Population (ENGAGE trial) (N=40)[52] **Mean (SE)**	**Stable ERT Population (ENCORE trial) (N=118)[72]** **Mean (SE)**
1. Mild	0.1750 (0.0601)	0.7712 (0.0387)
2. Mild + bone pain	0.0000 (0.0000)	0.1271 (0.0307)
3. Mild + SSC	0.0000 (0.0000)	0.0000 (0.0000)
4. Moderate	0.7750 (0.0660)	0.1017 (0.0278)
5. Moderate + SSC	0.0000 (0.0000)	0.0000 (0.0000)
6. Marked	0.0500 (0.0345)	0.0000 (0.0000)
7. Marked + SSC	0.0000 (0.0000)	0.0000 (0.0000)
8. Severe	0.0000 (0.0000)	0.0000 (0.0000)
9. Severe + SSC	0.0000 (0.0000)	0.0000 (0.0000)
Key: ERT, enzyme replacement therapy; SSC, severe skeletal complications.		

17.5.3 Short-term transitions

The transition probabilities for the first cycle of the model were derived from the ENGAGE and ENCORE clinical trials and represent patients' responses to treatment during the trial period. For the ENCORE trial this was from randomisation to 52 weeks. For the ENGAGE trial, this was from randomisation to 39 weeks. The movements of patients within this 9 month period are applied for the first year-long cycle of the model.

In the base case, these transition probabilities were derived from the respective trial arms of the ENCORE trial, or the eliglustat arm of the ENGAGE trial.

For the treatment-naïve population, both arms were parameterised using the eliglustat arm of the ENGAGE trial, with the assumption that there is no significant difference in efficacy. This is as there is insufficient data to create a network meta-analysis including the comparators in the model, and the ENGAGE trial was placebo controlled. The limitations of the evidence base in this patient population have been described previously in Section 9.4.

In the ERT stable population, eliglustat is modelled using transition probabilities based on the eliglustat arm of the ENCORE trial, and both comparators (imiglucerase and velaglucerase) were modelled using the imiglucerase arm of the trial. This assumed that both imiglucerase and velaglucerase have equivalent efficacy. This assumption is

supported by available RCT evidence and the ITC undertaken to assess the relative efficacy of treatments (Section 9.8). In sensitivity analyses, a scenario was run in which the treatment efficacy between eliglustat and comparators was assumed to be the same, in which the transition probabilities applied were derived from the pooled data from both arms of the ENCORE trial.

Standard errors for the transition probabilities were derived using the binomial formula $\sigma_{ij} = \left(p_{ij}(1-p_{ij})/n_i\right)^{1/2}$ where p_{ij} is the observed proportion of patients who transition to health state j from health state i and n_i is the number of patients starting in health state i. These transition probabilities are presented in Table 107 to Table 110. As these transitions are based on patient movements in the trial, states for which there were no patients at baseline were assumed to have a 100% chance of remaining in that state, with all other transitions set to zero ($p_{ij} = 0$). In the absence of appropriate data, it was necessary to assume that patients did not move from these states during this period.

Table 107: Transition probabilities for first year of treatment for the treatment naïve population derived from the eliglustat arm of the ENGAGE trial (N=20), mean (SE)

Starting Health State	Ending Health State (SE)								
	Mild	**Mild + Bone Pain**	**Mild + SSC**	**Moderate**	**Moderate + SSC**	**Marked**	**Marked + SSC**	**Severe**	**Severe + SSC**
Mild	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Mild + Bone Pain	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Mild + SSC	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Moderate	0.1765 (0.0925)	0.0000 (0.0000)	0.0000 (0.0000)	0.8235 (0.0925)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Moderate + SSC	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Marked	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Marked + SSC	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Severe	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)
Severe + SSC	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)

Key: SSC, severe skeletal complications.

Table 108: Transition probabilities for first year of treatment for the ERT stable population derived from the pooled eliglustat and imiglucerase arms of the ENCORE trial (N=118), mean (SE)

Starting Health State	Ending Health State								
	Mild	Mild + Bone Pain	Mild + SSC	Moderate	Moderate + SSC	Marked	Marked + SSC	Severe	Severe + SSC
Mild	0.8571 (0.0367)	0.0330 (0.0187)	0.0440 (0.0215)	0.0110 (0.0109)	0.0549 (0.0239)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Mild + Bone Pain	0.6667 (0.1217)	0.2667 (0.1142)	0.0000 (0.0000)	0.0000 (0.0000)	0.0667 (0.0644)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Mild + SSC	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Moderate	0.1667 (0.1076)	0.0833 (0.0798)	0.0000 (0.0000)	0.6667 (0.1361)	0.0833 (0.0798)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Moderate + SSC	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Marked	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Marked + SSC	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Severe	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)
Severe + SSC	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)

Key: SSC, severe skeletal complications.

Table 109: Transition probabilities for first year of treatment for the ERT stable population derived from the eliglustat arm of the ENCORE trial (N=74), mean (SE)

Starting Health State	Ending Health State								
	Mild	**Mild + Bone Pain**	**Mild + SSC**	**Moderate**	**Moderate + SSC**	**Marked**	**Marked + SSC**	**Severe**	**Severe + SSC**
Mild	0.8545 (0.0475)	0.0182 (0.0180)	0.0545 (0.0306)	0.0182 (0.0180)	0.0545 (0.0306)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Mild + Bone Pain	0.6667 (0.1361)	0.2500 (0.1250)	0.0000 (0.0000)	0.0000 (0.0000)	0.0833 (0.0798)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Mild + SSC	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Moderate	0.1429 (0.1323)	0.0000 (0.0000)	0.0000 (0.0000)	0.7143 (0.1707)	0.1429 (0.1323)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Moderate + SSC	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Marked	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Marked + SSC	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Severe	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)
Severe + SSC	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)

Key: SSC, severe skeletal complications.

Table 110: Transition probabilities for first year of treatment for the ERT stable population derived from the imiglucerase arm of the ENCORE trial (N=44), mean (SE)

Starting Health State	Ending Health State								
	Mild	**Mild + Bone Pain**	**Mild + SSC**	**Moderate**	**Moderate + SSC**	**Marked**	**Marked + SSC**	**Severe**	**Severe + SSC**
Mild	0.8611 (0.0576)	0.0556 (0.0382)	0.0278 (0.0274)	0.0000 (0.0000)	0.0556 (0.0382)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Mild + Bone Pain	0.6667 (0.2722)	0.3333 (0.2722)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Mild + SSC	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Moderate	0.2000 (0.1789)	0.2000 (0.1789)	0.0000 (0.0000)	0.6000 (0.2191)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Moderate + SSC	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Marked	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Marked + SSC	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)
Severe	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)	0.0000 (0.0000)
Severe + SSC	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	0.0000 (0.0000)	1.0000 (0.0000)

Key: SSC, severe skeletal complications.

17.5.4 Transitions for Longer-Term Projections

Data from DS3 Score Study were used to estimate the annual transition probabilities for time periods beyond that of the clinical trials. Observations from all of the patients in the DS3 Score Study data were pooled, excluding patients whose clinical assessments were made before starting ERT, who were missing a DS3 score (and hence the health state), or were missing information on when they initiated ERT. Each patient's follow-up time in the DS3 Score Study was divided into years (12-month intervals) starting with each patient's date of ERT initiation. The first 12 months that a patient was using ERT was defined as Year 0, the second 12 months (Months 13 through 24) were defined as Year 1, and so forth.

Patients were observed at multiple time points that may not have exactly corresponded to the 12-month intervals defined above, and 34% of patients had multiple observations in the same year. Because multiple observations from the same patient in the same health state in the same year do not contribute additional information regarding health-state transitions, the number of observation was reduced to 1 observation per patient per year. Where patients had multiple observations within the same health state (i.e. that did not result in a movement between states) within the same 12-month period, all but one were removed. However, if patients were observed multiple times in a given year in different health states, we retained only the observation associated with the worst health state (i.e. the patient transitioned to the worst health state experienced in that year). Pairs of consecutive observations (i.e. Year t and Year $t+1$) were used to estimate the transition probabilities between Years 1-2, 2-3 and 3-4. The transitions in the final year were then repeatedly applied to all cycles beyond 4 years.

A patient's probability of being in a given health state after 1 year was assumed to be a function of the patient's health state in the previous year using the relationship $\Pr(H_t = h) = f(H_{t-1}, T, D, S)$, where H is the health state, h represents the possible values for H (1, 2, …, 9), t indexes the year, T represents the time period (Year 0, Year 1, Year 2, Year 3, and Years ≥ 4), D represents a starting DS3 score value (explained below), and S represents the patient's spleen status (intact vs. splenectomised). As the health state is a categorical variable, the lagged health state variable (H_{t-1}) on the right-hand side of the equation is entered as a set of dummy variables.

Two regression models were built. The first ("Equation 1") is used for the treatment naïve population, and includes coefficients to differentiate transitions for Years 1, 2, 3 and 4+. The second ("Equation 2") only included observations from Years ≥4 and included a term for patients' DS3 score as of Year 3. This equation is used for the ERT stable population and does not include terms for individual years. This was based on the assumption that these patients were stable on ERT and would follow constant progression risks.

Two functional forms were assessed to estimate the models; a multinomial logistic model and an ordered logistic model. The most general approach, the multinomial logistic, did not converge due to too few observations for some transitions, so the ordered logistic model specification was chosen.

The coding of the health state variable represented an inherent ordering of increasing disease severity and this was confirmed by examining the mean DS3 scores by health state and conferring with a leading clinician involved in the DS3 Scoring Study.[129] The underlying assumption of proportional odds between categories of the dependent variable may not hold in this instance. However, due to the sparseness of the available data, the less restrictive multinomial logistic model could not be used.

The estimated ordered logistic regression coefficients (Table 111 for Equation 1 and Table 112 for Equation 2; generated using Stata 11.2[141]) were then used to predict the annual transition probabilities from health state i to health state j for the appropriate annual cycles in the model. The regressions were run twice to produce transition matrices with and without splenectomy, a weighted average of which is used to populate the movements of ERT stable patients in the model, based on the prevalence of splenectomy at baseline. All transition probabilities were computed conditional on a starting distribution of DS3 scores specified in the model. Standard errors for the model coefficients were adjusted for multiple observations per patient using data clustering; the transition probabilities were computed in the model itself using the following formulas.

$$\Pr(H = 1) = \frac{1}{1+\exp(X\beta - k_1)} \quad \text{for Health State 1}$$

$$\Pr(H = h) = \frac{1}{1+\exp(X\beta - k_h)} - \frac{1}{1+\exp(X\beta - k_{h-1})} \quad \text{for Health States } h = 2, \ldots, 8$$

$$\Pr(H = 9) = 1 - \frac{1}{1+\exp(X\beta - k_8)} \quad \text{for Health State 9}$$

Because there were no observations of patients transitioning into Health State 8 (marked without SSC) in Equation 1 (Years 1-3), the probability of that transition was set to zero for Years 1 to 3.

Table 111: Ordered logistic regression results (annual health-state transitions using DS3 Score Study data) for the treatment naïve population (Equation 1)

	Coefficient	Standard error	95% CI
Health state in previous year (vs. mild)			
Mild + bone pain	1.30***	0.24	0.83–1.78
Mild + SSC	0.84*	0.45	−0.05–1.73
Moderate	2.58***	0.31	1.98–3.18
Moderate + SSC	1.25***	0.38	0.51–2.00
Marked	4.50***	0.47	3.59–5.42
Marked + SSC	3.62***	0.46	2.71–4.52
Severe	4.21***	0.70	2.85–5.58
Severe + SSC	6.07***	1.37	3.38–8.76
Year (vs. Year 1)			
Year 2	0.29	0.36	−0.41–1.00
Year 3+	0.32	0.31	−0.28–0.91
Baseline DS3 category (vs. mild)			
Moderate	-0.15	0.28	−0.69–0.39
Marked	0.87***	0.27	0.34–1.41
Severe	1.35***	0.41	0.54–2.15
Not splenectomised (vs. splenectomised)	−1.09	0.25	−1.58–0.60
Ordered logit cutpoints			
Cutpoint 1	0.74	0.46	−0.15–1.63
Cutpoint 2	1.66	0.46	0.75–2.57
Cutpoint 3	1.73	0.47	0.81–2.64
Cutpoint 4	5.05	0.52	4.04–6.07
Cutpoint 5	5.84	0.52	4.81–6.86
Cutpoint 6	6.58	0.63	5.34–7.82
Cutpoint 7	8.81	0.64	7.56–10.06
Cutpoint 8	9.07	0.65	7.79–10.34
No. of patients	**130**		
No. of observations	**970**		

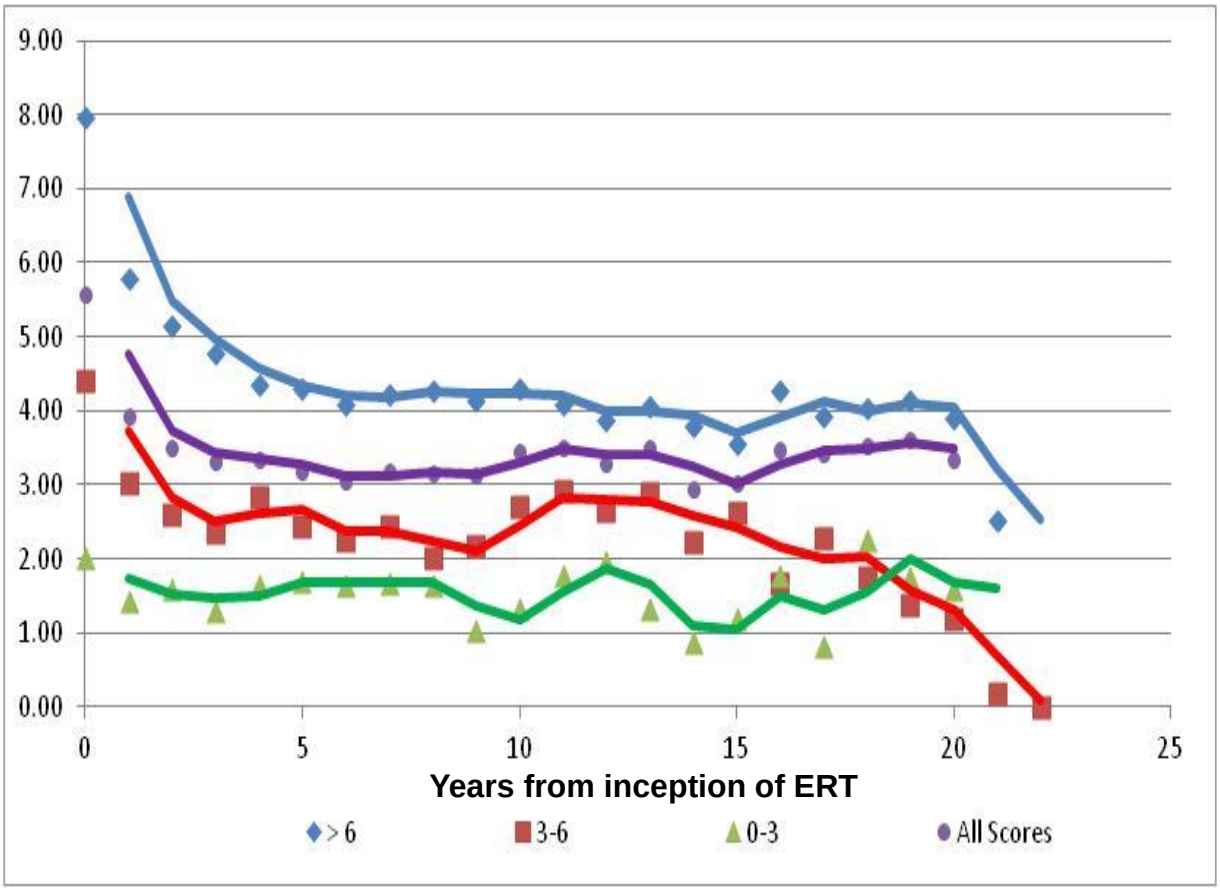
	Coefficient	Standard error	95% CI
Key: CI=confidence interval; SSC=severe skeletal complications. **Notes:** Standard errors account for multiple observations per patient. Year 1 captures transitions from Year 0 to Year 1, Year 2 captures transitions from Year 1 to Year 2, and Year 3+ captures all annual transitions for Year t to Year $t+1$ for $t \geq 2$. *** p<0.01, ** p<0.05, * p<0.10.			

Table 112: Ordered logistic regression results (annual health-state transitions using DS3 Score Study data) for Years ≥4 (Equation 2)

	Coefficient	Standard error	95% CI
Health state in previous year (vs. mild)			
Mild + bone pain	**1.45*** **	**0.32**	**0.82–2.08**
Mild + SSC	**0.64**	**0.66**	**−0.65–1.94**
Moderate	**3.02*** **	**0.35**	**2.34–3.70**
Moderate + SSC	**0.88** **	**0.43**	**0.03–1.72**
Marked	**5.02*** **	**1.48**	**2.12–7.92**
Marked + SSC	**3.92*** **	**0.56**	**2.82–5.02**
Severe + SSC	**4.52*** **	**1.53**	**1.53–7.51**
Year 3 DS3 category (vs. mild)			
Moderate	0.40*	0.24	−0.08–0.88
Marked	0.83**	0.38	0.09–1.58
Severe	1.94	1.72	−1.43–5.31
Not splenectomised (vs. splenectomised)	−1.04***	0.32	−1.66–0.41
Ordered logit cutpoints			
Cutpoint 1	0.34	0.37	−0.39–1.07
Cutpoint 2	1.52	0.42	0.71–2.34
Cutpoint 3	1.57	0.42	0.75–2.39
Cutpoint 4	5.04	0.54	3.98–6.10
Cutpoint 5	5.94	0.52	4.93–6.96
Cutpoint 6	6.98	0.83	5.35–8.61
Cutpoint 7	9.40	0.84	7.75–11.04
Cutpoint 8	10.10	0.63	8.85–11.34
No. of patients	92		
No. of observations	594		
Key: CI=confidence interval; SSC=severe skeletal complications **Notes**: Standard errors account for multiple observations per patient. Results are for annual transitions for Year *t* to Year *t*+1 for *t* ≥ 3. *** p<0.01, ** p<0.05, * p<0.10.			

After 4 years in the treatment naïve population and 1 year in the ERT stable population, the transition probabilities were assumed constant, based on diminished sample sizes and the assumption that the natural history of the disease would stabilise after this period on treatment. As the data from the DS3 Score Study below shows DS3 scores stabilise on average between 1 to 5 years after initiating treatment and remain relatively constant between Years 5 to 20. This is an analysis based on the data presented from the DS3 Score Study shown in Figure 58.[113] This is consistent with applying the same transition probabilities within the model from Year 4 onwards.

Figure 58: Average GD1-DS3 state over time from ERT initiation



Key: DS3, disease severity scoring system; ERT, enzyme replacement therapy; GD-1, Gaucher disease type 1.

17.5.5 Application of transition probabilities

As DS3 health state at baseline and splenectomy status are both included in the regression models used to predict the long-term transition probabilities, the patient characteristics as they are defined in the model generate a set of averaged transitions, which are then applied to all patients in the deterministic model. To address this, the model

is run using a Visual Basic for Applications (VBA) macro, modelling each possible combination of baseline DS3 state and splenectomy status separately, such that the appropriate transitions are applied to each cohort. Weighted results are then generated using the patient characteristics defined in the model.

17.5.6 Mortality

Mortality data in the model were derived from two sources: Gaucher disease mortality (all-cause mortality from a cohort of GD1 patients), and general population mortality risks. Throughout the model, the greatest mortality risk from the two sources is applied per cycle.

Gaucher disease mortality was taken from a published analysis of the ICGG registry data on GD1 mortality for those on ERT.[35] Table 113 presents the data retrieved from the ICGG registry. These were used to generate simulated patient level (SPL) data, to which parametric curves were fit.

The data in Table 113 were used to derive the incidence rate (IR) for each time range, with the assumption that hazards were constant within each range, but could change between ranges. This is expected to be appropriate given that the age ranges defined are narrow. Although these registry data are expected to be the most appropriate source of Gaucher disease mortality data, the registry does include some data for previously untreated patients from before effective treatments became available. The estimates of mortality rates resulting from this will include some pollution from this effect, but, as the model assumes equal mortality rates across all of the comparators, it is not expected that this will bias the results towards any individual treatment in the model.

Table 113: Type 1 Gaucher disease mortality data from the ICGG registry published

Age	No. of deaths	Person-years of follow-up	Deaths per 100 person-years
0 to <1	0	3	0.00
1 to <5	2	221	0.90
5 to <10	4	869	0.46
10 to <15	2	1230	0.16
15 to <20	2	1257	0.16
20 to <25	5	1143	0.44
25 to <30	0	1055	0.00
30 to <35	1	1040	0.10
35 to <40	7	1072	0.65

Age	No. of deaths	Person-years of follow-up	Deaths per 100 person-years
40 to <45	4	1064	0.38
45 to <50	7	1146	0.61
50 to <55	7	1035	0.68
55 to <60	8	781	1.02
60 to <65	7	520	1.35
65 to <70	8	423	1.89
70 to <75	12	327	3.67
75 to <80	12	175	6.86
80 to <85	2	96	2.08
85 to <90	10	46	21.74
≥90	2	6	33.33

Key: ICGG, International Collaborative Gaucher Group.
Source: Weinreb *et al.* 2008[35]

The survival probabilities were estimated using the following equations:

IR = hazard rate = $\frac{d[-ln(S(t))]}{dt}$, with S (t_0) = 1,

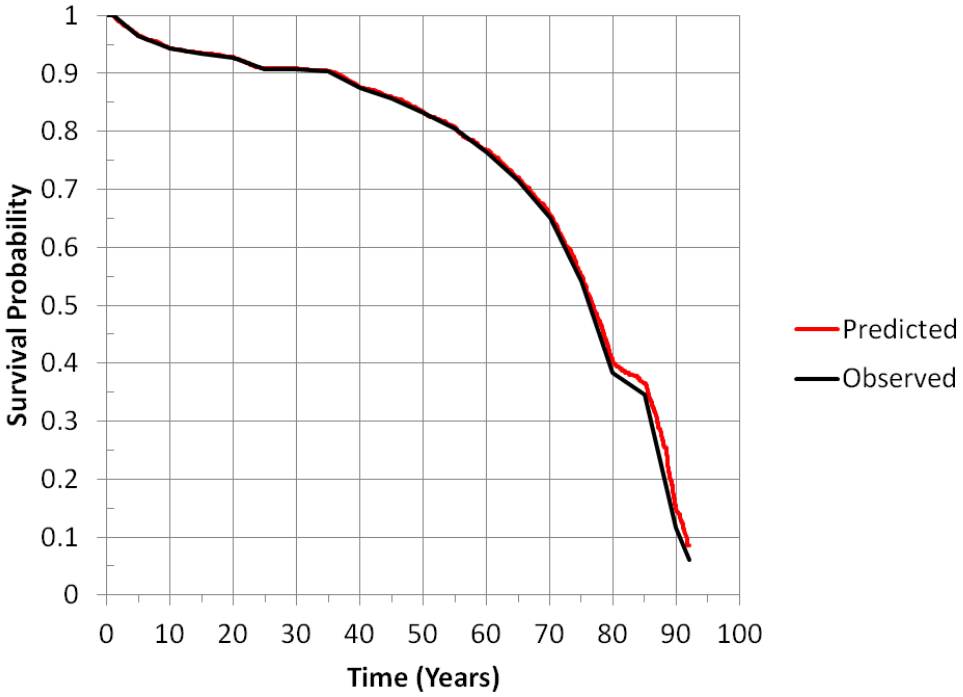
Hazard rate $_{0\text{-}1}$ = $\frac{[-\ln(S(t1))]-[-\ln(S(t0))]}{t1-t0}$

Solving for S (t_1),

S (t_1) = $e^{[\ln(S(t0))-hazard\ rate_{0-1}*(t1-t0)]}$

Using the generated probabilities, SPL data were sampled using the methods reported by Tierney *et al.* (2007)[142], assuming no prior knowledge of the number at risk at each time point. This generated a dataset of 2,876 individual patient survival times, with a censoring indicator variable. The resulting data are presented in the form of a Kaplan–Meier plot in Figure 59.

Figure 59: Observed vs. predicted survival for Gaucher disease Type 1 using Tierney method



A range of parametric curves were fit to these data to assess goodness of fit; exponential, Weibull, Gompertz, log-logistic and log-normal. Goodness of fit was examined using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), and by estimating the median survival from each curve to assess the clinical plausibility of the fits. The data used to determine the best-fitting curve are presented in Table 114. Diagnostic plots for each curve are presented in Figure 60; no diagnostic plot is available for the generalised gamma distribution. The predicted long-term survival for each curve is plotted in Figure 61.

Table 114: Goodness of fit statistics for Gaucher disease mortality curve fits

	Predicted Median, years	AIC	BIC
Weibull	75.5	4493.008	4504.932
Log-normal	88.4	5210.725	5222.649
Log-logistic	82.8	4795.833	4807.757
Exponential	86.4	5011.194	5017.156
Generalised gamma	68.3	3860.368	3878.254
Gompertz	75.2	4492.008	4503.932
Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.			

Figure 60: Diagnostic plots for Gaucher disease mortality parametric curve fits

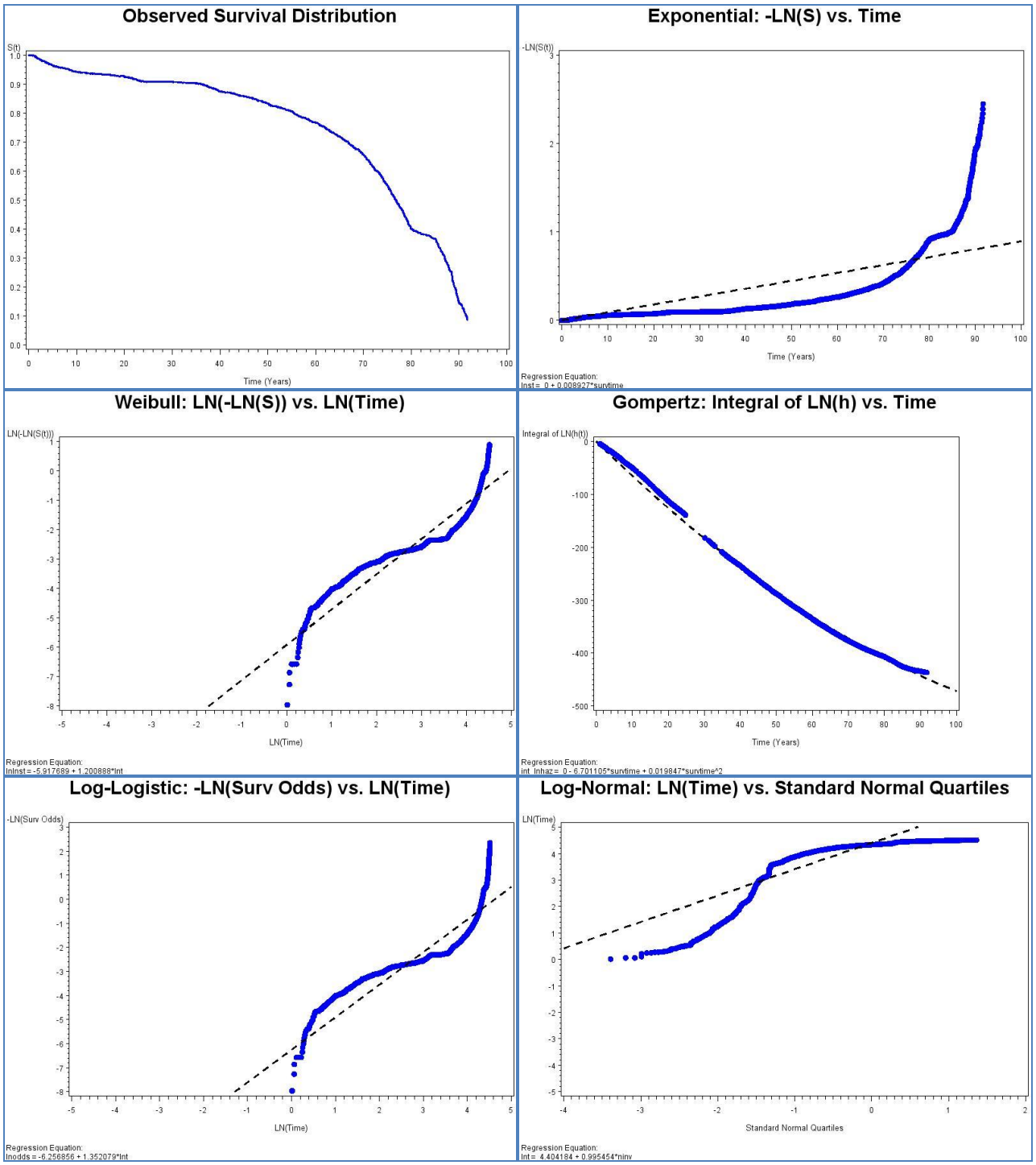
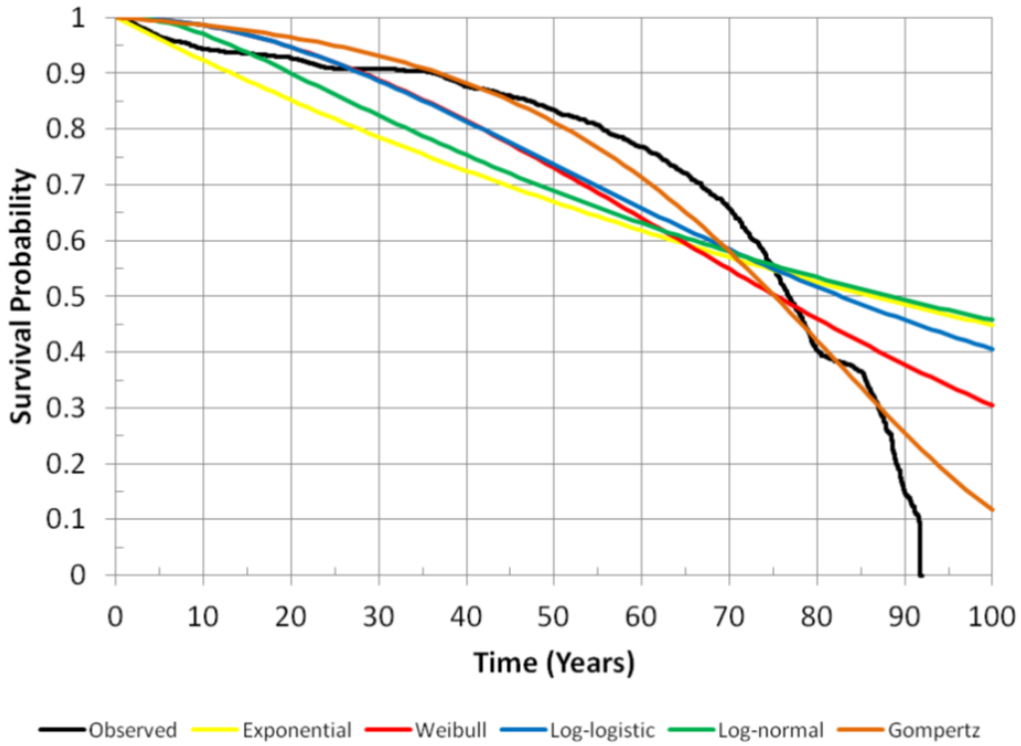


Figure 61: Long-term projections for parametric curve fits



Although the lowest AIC and BIC were for the generalised gamma curve fit, the Gompertz curve fit was determined to be the best-fitting, due to a better estimation of median survival and better visual match of the shape of the curve, despite some overestimation of survival in the long term. The coefficient estimates are presented in Table 115.

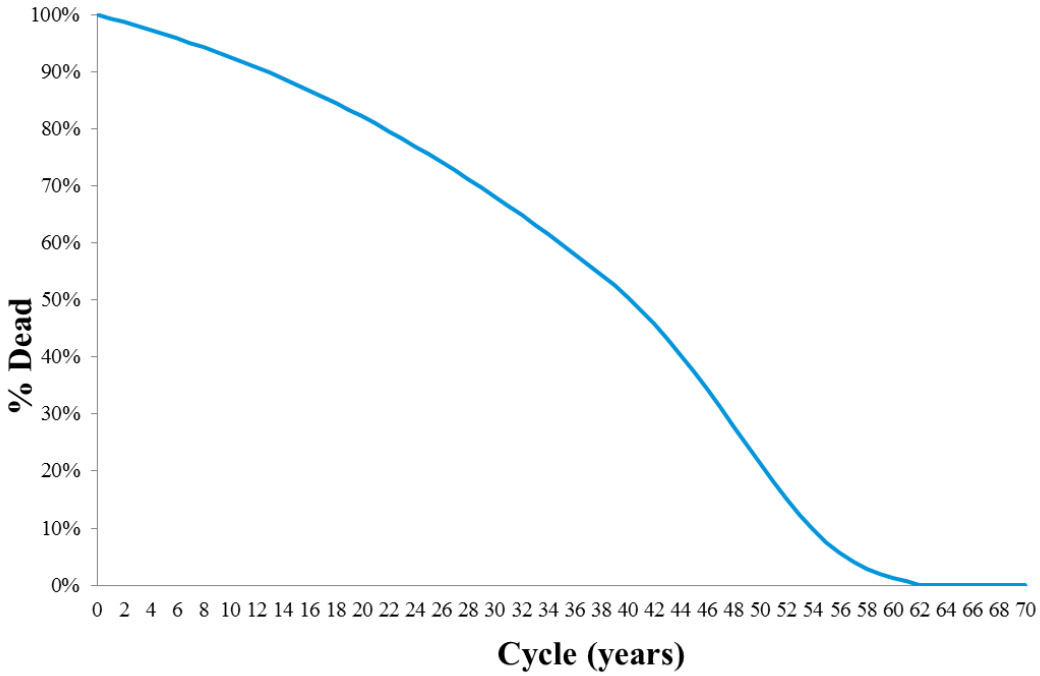
Table 115: Parameter estimates for the best-fitting curve (Gompertz)

Gompertz Distribution	Gaucher Disease Type 1
S(t) = EXP [(1-EXP(Gamma*time))*(Lambda/Gamma)]	
Lambda	0.001119
Gamma	0.0446

The fitted curve for Gaucher disease mortality overestimates patient survival in the long term. To address this, the curve was compared against general population mortality data from 2011 UK life tables.[143] As the Gaucher disease fitted curve overestimates survival compared with the general population survival, the model uses the greatest risk from either the Gaucher disease or general population mortality curves. Each cycle in the model, the higher of the two risks of death is used for the transitions to the death state. This ensures that the survival rate of the modelled cohort is always lower or equal to that of the UK general population. This should be considered in the context of reported life expectancy in

treated patients on the ICGG Registry of 68 years compared with 77 years in a US reference population. The resulting survival curve used in the model is shown in Figure 62.

Figure 62: Comparison of survival projections for Gaucher disease vs. general UK population



Discontinuation

The model allows patients to discontinue treatment during the first 3 years following treatment initiation, following which patients are assumed to be stable on treatment. In the treatment naïve population, discontinuation rates are applied to both eliglustat and the comparators. In patients stable on ERT at baseline, discontinuation rates are applied only to eliglustat, under the assumption that patients in the comparator arm have been on treatment for a mean of 10.8 years (based on ERT stable adult patients in Wyatt et al. [2012]) and discontinuation rates after so many years can be assumed to be zero.[42] The annual risk of discontinuing is 1.9%. This was the rate of discontinuation in the ENCORE trial in the respective arms outlined in Section 9.7.3. No such discontinuation occurred in either the eliglustat or placebo arms in ENGAGE.

The three year duration of discontinuation results in a cumulative discontinuation of approximately 6% for ERT patients, This is roughly equivalent to the proportion of ERT initiated adult patients who were not stable on ERT after a mean 11 year follow up in a study of GD1 patients in England as outlined in Section 2.5.[42] The equivalence of velaglucerase and imiglucerase with respect to discontinuation is based on Ben Turkia *et al.* in which discontinuation was zero for both arms.[63]

Treatment after discontinuation

In both treatment naïve and treatment stable patients, patients that discontinue the comparator are assumed to be treated with the alternative ERT comparator (i.e. when imiglucerase is the comparator, discontinuing patients will receive velaglucerase), with the same dosing and outcomes used for the comparator arm of the model. Patients that discontinue eliglustat are assumed to be treated with the main ERT comparator considered (i.e. when imiglucerase is the comparator, discontinuing patients from eliglustat are assumed to receive imiglucerase).

As stated above, discontinuation rates of zero are applied to all comparator treatments in the treatment stable population.

Scenario analysis is used to test the assumptions regarding discontinuation. An alternative scenario is tested which assumes that discontinuation does not occur.

17.6 Appendix 6: Resource identification, measurement and valuation

The following information should be provided.

17.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

The following databases were searched:

- Medline,
- Medline In-process,
- EMBASE,
- NHS Economic Evaluations Database (EED),
- Health Technology Assessment (HTA) database, and
- EconLit.

Medline and EMBASE were searched via OVID, and the HTA database and EED were searched via the Cochrane Library.

17.6.2 The date on which the search was conducted.

Initial searches were conducted between 30 May 2014 and 12 June 2014. These were updated with identical searches between 27 July 2015 and 14 August 2015.

17.6.3 The date span of the search.

The search was restricted to papers published after 1 January 1990. This is consistent with the clinical systematic review, and reflects the emergence of SRT and ERT in the late 1990s. No relevant studies would be expected prior to this date. The update searches were restricted to studies published in 2014 to present.

17.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The full search strategies are shown below for each database included in the electronic searches. In the updated searches performed in 2015, the only amendment was the restriction of studies to those published 2014 or later, to aid the identification of newly published material.

MEDLINE

1	exp Gaucher Disease/ (3743)
2	Gaucher$ disease.ti,ab. (3766)
3	1 or 2 (4544)
4	Gaucher$.ti,ab. (4132)
5	exp Lysosomes/ or exp lipidoses/ or exp glucosidases/ or exp glucosylceramidase/ (63903)
6	(lysosom$ or intralysosom$ or lipidosis or glucosidase or glucocerebrosidase).ti,ab. (60931)
7	4 and (5 or 6) (3743)
8	**3 or 7 (4643)**
9	Economics/ (26984)
10	"costs and cost analysis"/ (41736)
11	Cost allocation/ (1942)
12	Cost-benefit analysis/ (60025)
13	Cost control/ (20234)
14	Cost savings/ (8738)
15	Cost of illness/ (17618)
16	Cost sharing/ (1944)
17	"deductibles and coinsurance"/ (1430)
18	Medical savings accounts/ (483)
19	Health care costs/ (27098)
20	Direct service costs/ (1030)

21 Drug costs/ (12159)
22 Employer health costs/ (1067)
23 Hospital costs/ (7751)
24 Health expenditures/ (13672)
25 Capital expenditures/ (1943)
26 Value of life/ (5903)
27 exp economics, hospital/ (19490)
28 exp economics, medical/ (13563)
29 Economics, nursing/ (3907)
30 Economics, pharmaceutical/ (2536)
31 exp "fees and charges"/ (27031)
32 exp budgets/ (12074)
33 (low adj cost).mp. (25233)
34 (high adj cost).mp. (8169)
35 (health?care adj cost$).mp. (4559)
36 (fiscal or funding or financial or finance).tw. (83762)
37 (cost adj estimate$).mp. (1462)
38 (cost adj variable).mp. (33)
39 (unit adj cost$).mp. (1592)
40 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (178431)
41 resource allocation/ (7392)
42 health care rationing/ (10703)
43 (resource$ adj2 (allocat$ or utili$ or usage or use$)).tw. (24890)
44 or/9-43 (500386)
45 Letter/ (843138)
46 Review/ (1882208)
47 Comment/ (587410)
48 animal/ (5321809)
49 human/ (13475945)
50 48 not (48 and 49) (3855883)
51 or/45-47,50 (6637369)
52 8 and 44 (72)
53 52 not 51 (41)
54 Ireland/ (12942)
55 (Ireland or irish or eire or Dublin$).ti,ab,in,hw. (123474)
56 exp Great Britain/ (302481)
57 (Britain or british or wales or welsh or Scottish or scots or Scotland or England or English or Birmingham or leeds or London or Liverpool or Manchester or Glasgow or Edinburgh or Cardiff or Belfast or UK or GB or aberdeen).ti,ab,in,hw. (3159954)
58 or/54-57 (3257829)
59 53 and 58 (6)
60 limit 59 to yr="1990 -Current" (6)

Embase
1 exp Gaucher disease/ (5807)
2 Gaucher$ disease.ti,ab. (4545)
3 1 or 2 (6314)
4 Gaucher$.ti,ab. (5014)
5 exp lysosome/ or exp lipidosis/ or exp glucosidase/ or exp glucosylceramidase/ (68070)
6 (lysosom$ or intralysosom$ or lipidosis or glucosidase or glucocerebrosidase).ti,ab. (69683)
7 4 and (5 or 6) (4690)
8 3 or 7 (6437)
9 Socioeconomics/ (108903)
10 Cost benefit analysis/ (64400)
11 Cost effectiveness analysis/ (97692)
12 Cost of illness/ (14075)
13 Cost control/ (48432)
14 Economic aspect/ (103074)
15 Financial management/ (100334)
16 Health care cost/ (128935)
17 Health care financing/ (11424)
18 Health economics/ (33558)

19	Hospital cost/ (13782)
20	(fiscal or financial or finance or funding).tw. (104976)
21	Cost minimization analysis/ (2471)
22	(cost adj estimate$).mp. (1991)
23	(cost adj variable$).mp. (157)
24	(unit adj cost$).mp. (2436)
25	resource allocation/ (15259)
26	(resource$ adj2 (allocat$ or utili$ or usage or use$)).tw. (32912)
27	**or/9-26 (690239)**
28	letter.pt. (845582)
29	review.pt. (1953054)
30	animal/ (1567216)
31	human/ (14682282)
32	30 not (30 and 31) (1188947)
33	**or/28-29,32 (3920690)**
34	**8 and 27 (185)**
35	**34 not 33 (115)**
36	Ireland/ (19876)
37	(Ireland or irish or eire or Dublin$).ti,ab,in,hw. (241312)
38	United-Kingdom/ (327200)
39	(Britain or british or wales or welsh or Scottish or scots or Scotland or England or English or Birmingham or leeds or London or Liverpool or Manchester or Glasgow or Edinburgh or Cardiff or Belfast or UK or GB or aberdeen).ti,ab,in,hw. (1694500)
40	or/36-39 (2052293)
41	**35 and 40 (16)**
42	limit 41 to yr="1990 -Current" (16)

Cochrane
NB: studies pertaining to the UK and Ireland were selected by hand and imported separately with the $$Resources keyword

1	MeSH descriptor: [Gaucher Disease] explode all trees
2	(Gaucher* disease):ti,ab
3	**1 or 2**
4	Gaucher*:ti,ab
5	MeSH descriptor: [Lysosomes] explode all trees
6	MeSH descriptor: [Lipidoses] explode all trees
7	MeSH descriptor: [Glucosidases] explode all trees
8	MeSH descriptor: [Glucosylceramidase] explode all trees
9	**5 or 6 or 7 or 8**
10	(lysosom* or intralysosom* or lipidosis or glucosidase or glucocerebrosidase):ti,ab
11	**4 and (9 or 10)**
12	**3 or 11 Publication Date from 1990 to 2014**

17.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

The most recent proceedings from two conferences were hand searched for relevant abstracts. These were the EWGGD and the ASHG, as abstracts from these conferences are not published in an indexed journal, and would therefore not be expected to be identified in the electronic searches. The following meetings were identified as relevant, but were not searched, as abstracts are published in journals that are indexed in the electronic databases:

- Lysosomal Disease Network (LDN) WORLD Symposium
- Society for the Study of Inborn Errors of Metabolism (SSIEM)
- International Society for Pharmacoeconomics and Outcome Research (ISPOR) - November

The hand searches consisted of a simple search for Gaucher disease, followed by screening for abstracts containing HRQL information. No relevant abstracts were identified through these hand searches.

17.6.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria have been provided in the main submission document (Table 54).

17.6.7 The data abstraction strategy.

The data extracted from the eligible cost and resource use studies are presented in Table 116.

Table 116: Data extraction from cost and resource use studies

	Connock et al. (2006)[37]	Wyatt et al. (2012)[42]
Full author details	M Connock, A Burls, E Frew, A Fry-Smith, A Juarez-Garcia, C McCabe, A Wailoo, K Abrams, N Cooper, A Sutton, A O'Hagan and D Moore	K. Wyatt; W. Henley; L. Anderson; R. Anderson; V. Nikolaou; K. Stein; L. Klinger; D. Hughes; S. Waldek; R. Lachmann; A. Mehta; A. Vellodi; S. Logan
Title	The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher disease: a systematic review	The effectiveness and cost-effectiveness of enzyme and substrate replacement therapies: a longitudinal cohort study of people with lysosomal storage disorders
Setting	NHS provision of care in the UK	National Specialised Commissioning Group-designated lysosomal storage disorder treatment centres in England
Brief study description	A Markov decision model was constructed to compare treatment with ERT compared to standard supportive care, based on the results of a systematic literature review. The costs were taken from standard UK sources, and the frequency of resource use was based on assumptions made regarding the definition of the model health states. Monitoring costs were not included, as these were assumed to be the same between the treatment arms of the model, and it was assumed there was no difference in survival.	Cohort study including prospective and retrospective clinical- and patient-reported data. The prospective data collection for ERT-treated patients was performed using questionnaires for HRQL and resource use. The frequency and duration of service use required, as elicited from patients (or by proxy were necessary), was used to calculate mean annual costs per patient for each type of medical resource use required.
Interventions	ERT compared to standard treatment	ERT and SRT
Patient population analysed	Type 1 Gaucher disease	Type 1 or 3 Gaucher disease (other lysosomal storage disorders were included in the study)
Inclusion/exclusion criteria	N/A	Patients with a diagnosis of Type 1 or 3 Gaucher disease who attended one of seven treatment centres in England
Outcomes	The costs estimated for the model were those associated with mild SSI, moderate SSI, severe SSI, splenectomy and ERT.	Clinical outcomes, HRQL, service use, annual costs of illness and HRQL effects on carers
Cohort size	N/A	175 with Gaucher disease
Country of study	UK	England

<table>
<tr><td>Date of study/cost year</td><td>2003/04</td><td>2011 (medical treatment) / 2010 (unit costs)</td></tr>
<tr><td>Applicability to UK clinical practise</td><td>The model adopts a UK clinical practice perspective</td><td>All participants were receiving treatment from a treatment centre in England</td></tr>
<tr><td>Payer</td><td>UK NHS</td><td>UK NHS and publically funded social care services</td></tr>
<tr><td>Costing methodology used</td><td>N/A</td><td>Data collection used an adapted version of the Client Services Receipt Inventory questionnaire, commonly used in UK-based cost analyses. The total costs were calculated from the reported service use and the unit costs of each resource.</td></tr>
<tr><td>Costs (CIs)</td><td>
<table>
<tr><th colspan="2">Annual health state costs</th></tr>
<tr><td>Mild SSI</td><td>£912</td></tr>
<tr><td>Moderate SSI</td><td>£3,144</td></tr>
<tr><td>Severe SSI</td><td>£7,857</td></tr>
<tr><td colspan="2">Treatment costs</td></tr>
<tr><td>Cost per unit of ERT</td><td>£2.975</td></tr>
<tr><td>Annual cost of ERT</td><td>£85,501</td></tr>
<tr><td>Annual cost of bisphosphonates</td><td>£301</td></tr>
<tr><td colspan="2">Unit costs</td></tr>
<tr><td>Blood transfusion</td><td>£76</td></tr>
<tr><td>Splenectomy</td><td>£2,751</td></tr>
<tr><td>Hip replacement</td><td>£4,660</td></tr>
<tr><td>Nursing care per week</td><td>£496</td></tr>
</table>
</td><td>Mean annual resource use costs per patient (standard deviation)
<table>
<tr><th colspan="2">Hospital services</th></tr>
<tr><td>Inpatient stays</td><td>£830 (3,999)</td></tr>
<tr><td>Outpatient stays</td><td>£1,200 (1,953)</td></tr>
<tr><td>Day cases</td><td>£410 (2,424)</td></tr>
<tr><td>Accident and emergency</td><td>£12 (72)</td></tr>
<tr><td colspan="2">Social care services</td></tr>
<tr><td>GP visits</td><td>£84 (116)</td></tr>
<tr><td>GP nurse appointments</td><td>£5 (15)</td></tr>
<tr><td>District nurses</td><td>£120 (1,072)</td></tr>
<tr><td>Community mental health nurse</td><td>£0 (0)</td></tr>
<tr><td>Other nurse or health visitor</td><td>£420 (1,428)</td></tr>
<tr><td>Counsellor</td><td><£1 (3)</td></tr>
<tr><td>Other therapist</td><td>£3 (19)</td></tr>
<tr><td>Alternative medicine or therapy</td><td><£1 (6)</td></tr>
<tr><td>Psychologist</td><td>£1 (14)</td></tr>
<tr><td>Psychiatrist</td><td>£0 (0)</td></tr>
<tr><td>Other community-based doctor</td><td>£0 (0)</td></tr>
</table>
</td></tr>
</table>

		Occupational therapist: <£1 (3) Social worker: £5 (41) Home help: £110 (890) Care attendant: £0 (0) Community support worker: £0 (0) Housing worker: <£1 (7) Medical treatment Imiglucerase (ERT): £126,261 Velaglucerase (ERT): £144,868 Miglustat (SRT): £54,320
Resource use	**Resource use requirement** *Unit of ERT required per year* 2395 *Number of blood transfusions per year* Mild: 12 Moderate: 12 Severe: 12 *Number of weeks of nurse care required per year* Mild: 0 Moderate: 2 Severe: 4 *Percentage of patient requiring hip replacement and bisphosphonates per year* Mild: 0% Moderate: 25%	Proportion of adult patients requiring each medical resource: **Hospital services** Inpatient stays: 17% Outpatient stays: 77% Day cases: 8% Accident and emergency: 0% **Social care services** GP visits: 68% GP nurse appointments: 37% District nurses: 7% Community mental health nurse: 0% Other nurse or health visitor: 14% Counsellor: 1% Other therapist: 4% Alternative medicine or therapy: 1%

	Severe: 100%	Psychologist	1%
		Psychiatrist	0%
		Other community-based doctor	0%
		Occupational therapist	4%
		Social worker	2%
		Home help	3%
		Care attendant	0%
		Community support worker	0%
		Housing worker	1%

Key: CI, confidence interval; ERT, enzyme replacement therapy; HRQL, health-related quality of life; N/A, not applicable; NHS, National Health Service; SRT, substrate replacement therapies; SSI, severity scale index.

18 Related procedures for evidence submission

18.1 Cost-consequence models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGS. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted

- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.
- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

18.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or

impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests regarding the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

18.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

19 Additional Appendices

19.1 Additional statistical analysis and outcome information

Table 117: Summary of statistical analyses in ENCORE RCT

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT00943111 (ENCORE)	To assess the efficacy and safety of eliglustat compared with imiglucerase after 52 weeks of treatment in patients with GD1 who have reached therapeutic goals with ERT	All statistical analyses were conducted using SAS version 9 or higher. For the primary efficacy analysis the per protocol set was used. The percentage of patients remaining stable, as well as exact 95% CI for that percentage, was computed at 52 weeks for both the eliglustat and imiglucerase treatment groups. A difference in the percentage of patients remaining stable in the two treatment groups along with a 95% CI for the difference between the eliglustat and imiglucerase treatment groups was calculated. If the lower-bound of the 95% CI for the difference was within the pre-specified non-inferiority margin of 25%, then eliglustat treatment was declared non-inferior to imiglucerase treatment. The secondary efficacy endpoints were analysed using ANCOVA, natural logarithm differences were used for the parameters that were analysed using percentage changes. Statistical tests were conducted at the 5% level of significance.	A sample size of 132 patients (88 eliglustat: 44 imiglucerase) was needed for this study to yield at least 105 evaluable patients in the PPS for analysis. The sample size for this non-inferiority study was based on expected stability rates of 95% for the imiglucerase treatment group (active-comparator) and 85% for the eliglustat treatment group (test treatment), power of 85%, a one-sided significance level of 0.025, a non-inferiority margin of 25%, and a 20% non-evaluable/drop-out rate.	The FAS included all patients who signed informed consent and received at least 1 dose of study drug (eliglustat or imiglucerase), and is equivalent to the intention-to-treat population referenced in the protocol. The ITT population consisted of 106 eliglustat patients and 53 imiglucerase patients. The per-protocol population consisted of 99 eliglustat patients and 47 imiglucerase patients. Reasons for exclusion from the per-protocol population included dosing compliance <80%, randomised to incorrect prior ERT dose stratum, and missing baseline or 12-month platelet or haemoglobin count. Last observation carried forward for used for the primary efficacy analysis.

Key: ANCOVA, analysis of covariance; CI, confidence interval; ERT, enzyme replacement therapy; FAS, full analysis set; GD1, Gaucher Disease Type 1; ITT, intention-to-treat; PPS, per protocol set.

Source: Cox et al., 2015[10]; Genzyme, 2014[72]

Table 118: Summary of statistical analysis in ENGAGE RCT

Trial No. (Acronym)	Hypothesis Objective	Statistical Analysis	Sample size, power calculation	Data management, patient withdrawals
NCT00891202 (ENGAGE)	To confirm the efficacy and safety of eliglustat after 39 weeks of treatment in patients with GD1.	The primary efficacy endpoint was analysed using an ANCOVA model, normal distribution was confirmed using the Shapiro-Wilk test at a 5% level of significance. Secondary endpoints were analysed using a closed-testing procedure. For within-patient analyses, a paired t-test was used for analysis of endpoints with normally distributed data, and a Wilcoxon signed-ranks test was used for analysis of endpoints with normally distributed data.	The planned enrolment of approximately 36 patients was expected to yield at least 28 evaluable patients at the end of the primary analysis period, allowing for a dropout rate of 20%. Twenty-eight patients was estimated to provide 92% power to detect a treatment difference between eliglustat and placebo in the primary efficacy endpoint, based on a 2-sided, 2-sample t-test with a 5% level of significance, and assuming mean percentage decreases in spleen volume from baseline to Week 39 of 25% and 5% for eliglustat and placebo, respectively, and a standard deviation of 15%.	The FAS included all 40 patients who signed informed consent and received at least 1 dose of study drug (placebo or eliglustat), and is equivalent to the intent-to-treat population referenced in the protocol. All efficacy analyses were conducted at the 5% level of significance. For all efficacy endpoints, LOCF was used if a result was unavailable for Week 39.

Key: ANCOVA, analysis of covariance; FAS, full analysis set; GD1, Gaucher Disease Type 1; LOCF, last observation carried forward.
Source: Mistry et al., 2015[9]; Genzyme, 2013[52]

ENCORE Study

An overview of the primary and secondary outcomes of the ENCORE trial is presented in Table 119.

Table 119: Primary and secondary outcomes of ENCORE

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
ENCORE	Percentage of patients who remained stable for 52 weeks (as measured by a composite endpoint of a combination of haematological parameters and organ volumes)	Patients must be stable on all four parameters to be considered to have demonstrated a clinically meaningful response to treatment. The composite endpoint measures the accepted therapeutic goals in Gaucher which are clinically meaningful common disease manifestations and the individual components have been investigated in previous studies of ERT in patients with GD1	Total T- and Z-scores for BMD, haemoglobin level, platelet count, spleen and liver volume	Includes the individual components of the composite endpoint. Clinically relevant endpoints; directly referenced in the decision problem; consistent with other studies of therapeutic agents in this study population

Key: BMD, bone marrow burden; ERT, enzyme replacement therapy; GD1, Gaucher Disease type 1.
Source: Cox et al., 2015[10]

The primary outcome measure of efficacy for the ENCORE study is the percentage of patients who remained stable at 52 weeks in all of the following parameters:

- Haemoglobin levels (i.e. a decrease of ≤1.5g/dL from baseline)
- Platelet counts (i.e. a decrease of ≤25% from baseline)
- Spleen volume (i.e. a increase of ≤25% from baseline)
- Liver volume (i.e. a increase of ≤20% from baseline)

This was assessed for both treatment groups separately along with a difference between the two treatment groups. Secondary endpoints included:

- Total T- and Z-scores for BMD of femur and lumbar spine (dual energy X-ray absorptiometry; DXA)
- Haemoglobin level (normal values are >12g/dL for males, >11g/dL for females)

- Platelet count (normal values are >120 x 10^3/mm^3)
- Spleen volume (in multiples of normal [MN], assessed by magnetic resonance imaging [MRI]) (normal size is ≤2.5MN)
- Liver volume (in MN, assessed by MRI) (normal size is ≤5MN)

These efficacy endpoints were chosen to confirm the reduction in glucosylceramide synthesis with eliglustat and to characterise its effects on organomegaly, haematological parameters and bone disease. They also represent common manifestations of Gaucher disease and have been investigated in previous studies of ERT in patients with GD1.

As it is known that Gaucher cells in the bone marrow trigger a series of events that lead to skeletal pathology in Gaucher disease, bone marrow infiltration by conventional MRI was evaluated. In addition to this, BMD by DXA, the established standard for this measurement, was determined. Total BMD and T- and Z-scores for the spine and bilateral femur were obtained through DXA. The BMB score was calculated by summing six MRI based scores for both lumbar spine and femur. This scale was used as it is more sensitive and specific than BMD for Gaucher disease-related skeletal abnormalities. BMD averages the total mineral content of the area of bone under investigation which is a reasonable assessment for osteoporosis and osteopenia. However, in Gaucher disease, areas of sclerosis with high mineral content but brittle bone can be found in areas with otherwise osteoporotic/osteopenic bone leading to a falsely reassuring BMD result. Furthermore, since accumulation of Gaucher cells in the bone marrow is fundamental in skeletal pathogenesis and bone marrow infiltration is increasingly measured by MRI in current clinical practice[23], this was also assessed in this study. DXA results are expressed as BMD in g/cm2 and as T- and Z-scores. T-scores compare a patient's bone density to that of a normal healthy young adult of the same sex. The normal range for a T-score is ≥ -1; osteopenia is defined by T-scores < -1 to > -2.5 and osteoporosis ≤ -2.5. Z-scores compare a patient's bone density to that of a normal healthy person of the same age, sex, weight and ethnicity. The normal range for a Z-score is ≥ -2 and ≤ 2 and an abnormally low score is < -2.

Other bone abnormalities such as infarction and fractures were evaluated as tertiary end-points by MRI and X-ray as these are well known manifestations of Gaucher disease. In particular, X-rays can detect late and destructive complications such as remodelling, deformity, osteonecrosis, lytic lesions, pathological fractures and joint collapse.

The ENCORE study's recorded tertiary endpoints included:

- Biomarkers of Gaucher cell activity and macrophage activation which have been shown to correlate with disease severity and treatment response:
  - Chitotriosidase
  - CCL18
  - Glucosylceramide
  - GM3
  - Macrophage inflammatory protein 1β
  - Ceramide
  - Sphingomyelin

These biomarkers are substantially increased in Gaucher disease. A normal range of chitotriosidase level is <15 to 181 nmol/h/mL and for CCL18 levels a normal range is 17 to 246 ng/mL.[12] In Gaucher disease chitotriosidase levels can be increased 100 fold. A decrease of these biomarkers is seen in response to ERT and, importantly, this decrease is correlated with dose and other indicators of clinical response.[144, 145]

- Bone disease assessments:
  - X-ray
  - MRI
  - BMB score – calculated by summing six MRI-based scores for the lumbar spine and femur.
- Gaucher assessments
  - Mobility
  - Bone crises – the number since the previous visit was recorded, where a bone crisis was defined as bone pain with acute onset requiring immobilisation of the affected area, narcotics for pain relief, and possibly accompanied by periosteal elevation, an elevated white blood cell count, fever and/or debilitation of >3 days.
  - Bone pain - assessed through patients own rating to the question "How would you rate your bone pain during the last 4 weeks?".

- HRQL measured through:
  - The Brief Pain Inventory (BPI)
  - Fatigue Severity Score (FSS)
  - Short Form-36 Health Survey (SF-36)
  - Treatment preference (oral versus IV therapy). – measured through a patient completed questionnaire that evaluated treatment preference, reasons for this and overall satisfaction with treatment

Several scoring systems have been developed to provide a semi-quantitative assessment of bone marrow infiltration. However, for this study the BMB scoring system was used because it evaluates marrow infiltration of the lumbar spine as well as the femur.

Other exploratory endpoints were also evaluated and included the Gaucher disease severity scoring system (DS3) score and the percentage changes from baseline in investigational biomarkers. The DS3 is used in clinical practice to measure the burden of disease on patients and was compiled from medical history, blood chemistry, liver and spleen volumes, and bone evaluations. The study also included:

- Safety outcomes (adverse events including SAEs)
- Evaluations of clinical parameters
- Pharmacokinetic parameters
- Although only included within the ENCORE clinical trial report as an exploratory efficacy analysis, GD-DS3 scores at baseline and at 52 weeks follow up are also shown. This is because the GD-DS3 scores have been used as the basis of incorporating trial data into the HE model reported in Section 6, and consequently, these data will be of value to the evaluation.

ENGAGE Study

An overview of the primary and secondary outcomes of the ENGAGE study is presented in Table 120.

Table 120: Primary and secondary outcomes of ENGAGE

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
ENGAGE	Percentage change in spleen volume (in MN) from baseline to 39 weeks of treatment	The clinical measures represent the accepted therapeutic goals in Gaucher disease which are clinically meaningful common disease manifestations and have been investigated in previous studies of ERT in patients with GD1	Absolute change from baseline in haemoglobin level (in g/dL), percentage change from baseline in liver volume (MN) and platelet count (in/mm^3)	Clinically relevant endpoints; directly referenced in the decision problem; consistent with other studies of therapeutic agents in this study population

Key: GD1, Gaucher Disease 1; ERT, enzyme replacement therapy; MN, multiples of normal,
Source: Mistry et al., 2015[52]

In the ENGAGE study, the primary efficacy endpoint was the percentage change in spleen volume (MN) from baseline to Week 39 of treatment.

Secondary efficacy endpoints included:

- Absolute change from baseline in haemoglobin level (in g/dL)
- Percentage change from baseline in liver volume (MN)
- Percentage change from baseline in platelet count (in /mm^3)
- Within patient changes from baseline to 39 weeks of treatment for percentage changes in spleen volume, liver volume, platelet count and absolute change in haemoglobin level.

Tertiary efficacy endpoints included:

- Absolute changes from baseline to Week 39 in bone assessments including:
  - Spine and femur T- and Z-scores
  - Spine, femur and total BMB scores
  - Bone crises – determined as the number of bone crises since the previous visit
- Absolute changes from baseline to Week 39 in patient-related outcomes including:
  - Total DS3 score

  - BPI pain severity scores
  - Average interference score
  - FSS
  - Short-form 36 (SF-36) physical and mental component summary scores and scale scores
- Percentage changes from baseline to Week 39 in:
  - Biomarkers – CCL18, normalised chitotriosidase
  - Bone assessments – total BMD for spine and femur
  - Exploratory biomarkers – plasma glucosylceramide, dried blood spots (DBS), glucosylceramide, GM3, ceramide, sphingomyelin, MIP-1β
- Gaucher disease assessments:
  - Mobility
  - Bone pain – rated through the question "How would you rate your bone pain during the last 4 weeks?"
  - Bone crises - determined as the number of bone crises since the previous visit

The BPI measures a patient's perception of their pain and the degree to which this interferes with daily activities. For this questionnaire each item is scored on an 11-point scale where a higher number indicates greater pain or interference. The FSS includes nine statements that attempt to explore a patient's severity of fatigue symptoms as they relate to daily activities such as exercise, physical functioning and work, family and social life. The SF-36 is based on 36 questions which measure a patient's functional health and well-being. The DS3 score was calculated from routine assessments including medical history, blood chemistry, liver and spleen volume measurements, and bone evaluations by MRI and DXA.

These endpoints were chosen to confirm the reduction in glucosylceramide synthesis and to characterise its effects on organomegaly, haematological parameters and bone disease. These represent the more common manifestations of Gaucher disease as shown in the Gaucher therapeutic goals.[54] They have also been investigated in previous studies of ERT in patients with GD1.

EDGE study

In the EDGE study, efficacy was assessed by number of patients who sustained or achieved individual therapeutic goals specified in randomised criteria as well as number of patients meeting all 5 goals. The lead-in period therapeutic goals included:

- ≤1 bone crisis and no symptomatic bone disease during previous 6 months of the lead-in period
- Haemoglobin ≥11 g/dL for females and ≥12 g/dL for males
- Platelet count ≥100,000/mm^3
- Spleen volume ≤10 MN (if applicable)
- Liver volume ≤1.5 MN

This allowed demonstrable clinical stability on a twice-daily dose of eliglustat prior to randomisation in to the 12-month primary analysis period.

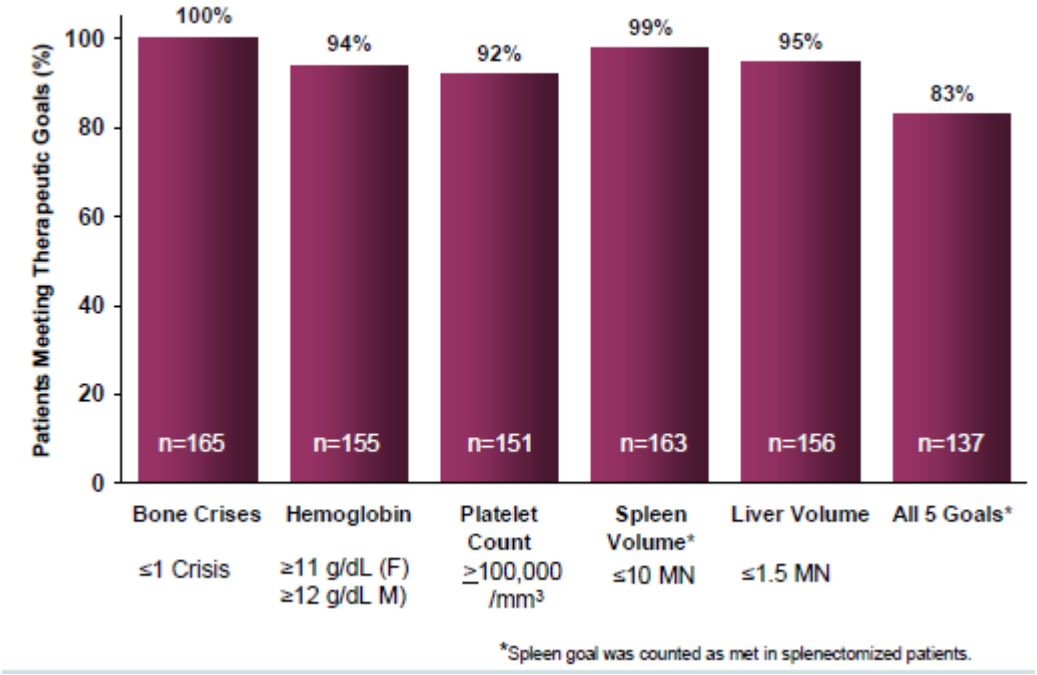
Safety was also assessed by adverse events and changes from baseline in vital signs, physical examinations, bone disease assessments, electrocardiography and routine laboratory tests. As the EDGE publication reports only interim analysis, results from the lead-in period are discussed in Section 19.2 .

19.2 Results from the lead-in period of the EDGE study

Primary outcome

The EDGE study interim analysis encompasses all data available as of 31 January 2013 and includes data from 27 patients still in the lead-in period as of that date who may or may not meet criteria for randomisation. The proportion of patients maintaining or achieving therapeutic goals at interim analysis during lead-in period is presented in Figure 63.

Figure 63: Patients maintaining or achieving therapeutic goals



Key: F, females; M, males; MN, multiples of normal.
Source: Charrow et al., 2014[13]

A total of 137 patients (83%) achieved all 5 therapeutic goals during the lead-in period.

Mean haemoglobin levels remained stable or showed minimal, transient changes around baseline levels. Mean platelet counts and spleen volume remained within ±20% of baseline levels, while mean liver volume remained within approximately ±5% of baseline values.

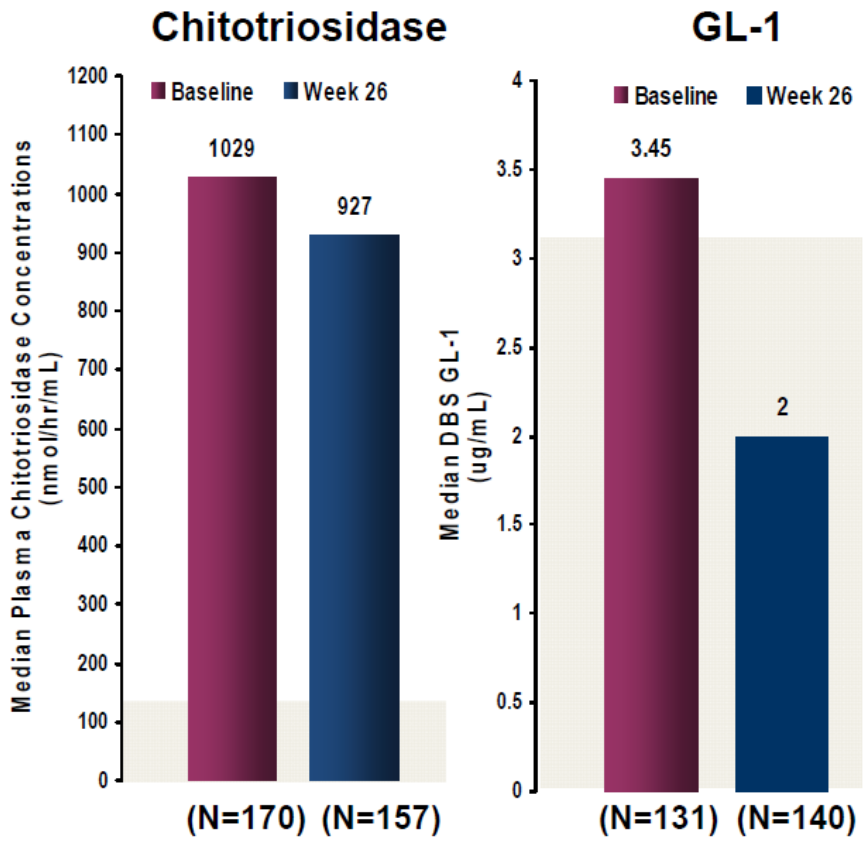
Biomarker changes

Due to the design of the EDGE study, the length of time in lead-in period varied, as patients were randomised as soon as they met all therapeutic goals. Therefore, the data show trends only.

Baseline chitotriosidase levels varied widely. Median values showed substantial reductions from baseline but stayed above the 120 nmol/hr/mL upper limit of normal throughout the lead-in period, as presented in Figure 64. For patients who remained in the lead-in period after Week 26, values continued to decrease.

GL-1 levels decreased markedly by Week 26 and remained below the 3.1 µg/mL upper limit of normal for the majority of patients, as presented in Figure 64. This is consistent with eliglustat's mechanism of action as an inhibitor of glucosylceramide synthase.

Figure 64: Biomarker changes from baseline to Week 26 in the lead-in period



Key: GL-1, glucosylceramide.
Source: Charrow et al., 2014[13]

Adverse events

In the EDGE lead-in phase AEs were reported for 141 patients (83%). A total of 94% of AEs were mild or moderate while 10% of patients had SAEs. A total of 76% of AEs were considered unrelated to treatment.

A summary of AEs in ≥5% of patients is presented in Table 121.

Table 121: Adverse events in ≥5% of patients in the lead-in period of the EDGE study, regardless of relationship

Adverse event	Patients, n (%)	Considered related, n (%)
Nasopharyngitis	24 (14)	0
Headache	21 (12)	8 (5)
Dizziness	20 (12)	11 (6)
Abdominal pain upper	12 (7)	5 (3)
Upper respiratory tract infection	11 (6)	0
Diarrhoea	11 (6)	5 (3)
Constipation	10 (6)	6 (4)
Back pain	9 (5)	0
Dyspepsia	9 (5)	6 (4)
Palpitations	9 (5)	3 (2)
Abdominal pain	8 (5)	5 (3)
Nausea	8 (5)	5 (3)
Arthralgia	8 (5)	0
Cough	8 (5)	0
Source: Charrow et al., 2014[13]		

Serious adverse events were reported for 12 patients (7%). The majority of SAEs were due to hospitalisations for intercurrent illness or events for which Gaucher patients are at increased risk, such as femur fracture and cholecystitis. There were no trends in the type of SAEs reported, and no SAE resulted in study discontinuation.

A total of two patients (1%) discontinued due to AEs, all of which were mild or moderate and included one patient with erectile dysfunction, which was considered unrelated, and one patient with nausea, asthenia (considered related to underlying disease), chills, headache and anaemia, which were considered possibly related.

Throughout the lead-in phase there were no deaths reported.

19.3 Critical appraisal

Table 122: Critical appraisal of randomised control trials: ENCORE (in line with table C7 in NICE HST template)

Study name	**ENCORE**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Stratified based on patients every 2 weeks equivalent ERT dose, randomised in a 2:1 ratio. Randomisation assignments were created centrally and were provided to the sites using a central online process. The sites logged onto the IVRS website, entered the relevant patient information (site and stratum) and an assignment from the central list was provided to them, to ensure balance across site and stratum.
Was the concealment of treatment allocation adequate?	N/A	This was an open-label study. However, selected efficacy and safety evaluations were performed by external central readers who were blinded to treatment assignment. A blinded Independent Adjudication Board (IAB) reviewed and confirmed instances of failure to meet the primary endpoint.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No	Overall baseline characteristics were well balanced between treatment arms in this study (Table 13), although there were some key differences. In particular, age at first symptom onset and age at Gaucher diagnosis was much later in the imiglucerase arm. In addition, rate of splenectomy in the imiglucerase arm is almost of half of the rate in the eliglustat arm, suggesting that patients receiving imiglucerase were of milder severity and that randomisation was unfavourable for eliglustat. This is a reflection of the small number of patients in the trial because of the rarity of the condition.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes, partially	Open-label study. However, selected efficacy and safety evaluations performed by external central readers who were blinded to treatment assignment. These blinded evaluations included organ volume and bone imaging data, ECG and Holter monitor data, and nerve conduction data. A blinded Independent Adjudication Board reviewed and confirmed instances of failure to meet the primary endpoint. No likely impact on risk of bias associated with primary outcomes. A potential risk of bias on patient reported outcomes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	Overall discontinuations comparable between groups

Study name	ENCORE	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Results for all outcomes presented in the CSRs
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The primary efficacy analysis in ENCORE was conducted using the per protocol population (PPP), which is common in non-inferiority studies. Efficacy analyses using ITT population were also conducted and the results were similar.

Key: CSR, clinical study report; ECG, electrocardiogram; ERT, enzyme replacement therapy; ITT, intention-to-treat; IVRS, interactive voice response system.

Notes: Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.

Source: Cox et al., 2015[10, 52, 71]

Table 123: Critical appraisal of randomised control trials: ENGAGE (in line with table C7 in NICE HST template)

Study name	ENGAGE	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Randomised through IVRS or IWRS, randomised in a 1:1 ratio stratified by spleen volume
Was the concealment of treatment allocation adequate?	Yes	Blinded study medication kits were supplied, all capsules were identical in appearance
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	All demographic and disease baseline characteristics were comparable across treatment arms, all patients had splenomegaly which was a requirement for study participation
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Patients, investigators and sponsor's investigational team were blinded to study treatment until completion of the initial double-blind primary analysis period
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	1 discontinuation in the eliglustat group which was voluntary for personal reasons, unlikely to have an effect on bias. No dropouts in the placebo arm
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Results for all outcomes presented in the CSRs
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	A full analysis set included all patients who received at least 1 study drug, this was equivalent to an intention-to-treat population and all efficacy analyses were carried out in this population

Key: CSR, clinical study report; IVRS, interactive voice response system; IWRS, interactive web response system.

Notes: Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.

Source: Mistry et al., 2015[9]

Table 124: Critical appraisal of randomised control trials: Ben Turkia et al. (2013)

Study name	Ben Turkia et al., 2013[63]	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Not clear	Details on randomisation method were not provided
Was the concealment of treatment allocation adequate?	Yes	The study was double blind, and patients were randomised 1:1 to receive imiglucerase or velaglucerase drug as a continuous 60-min intravenous infusion at a dose of 60 U/kg every other week
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Patient characteristics were well balanced between the two groups, although the imiglucerase paediatric population was skewed toward very young children (<5 years old). Overall, clinical characteristics were similar between the two groups at baseline, although there was a difference in median haemoglobin concentration between the imiglucerase and velaglucerase groups at baseline (10.6 g/dL vs. 11.4 g/dL; difference of 0.8 g/dL). However, this difference was not clinically relevant in terms of potential response to ERT.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	The study is reported as double blind although details on who was blinded for which assessments was not made clear.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No unexpected dropouts or imbalances. Yes, all were explained.	In the velaglucerase group, 1 patient was lost to follow-up after an SAE, while in the imiglucerase group, 1 patient discontinued treatment due to an AE. In addition, one patient randomised to receive imiglucerase was not included in the ITT population because they did not receive intervention due to incorrect randomisation.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Results for all outcomes mentioned as being assessed in the methods were provided in the results of the article.

Study name	Ben Turkia et al., 2013[63]	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Unless otherwise stated, all analyses were performed on an ITT basis, defined as all randomised patients who received at least one full or partial infusion. When values were missing for the primary or secondary efficacy endpoints, a pre-specified imputation strategy was applied. After applying last observation carried forward for post-baseline measurements, if data were still missing, the median value in the corresponding age group (2–17 years vs. ≥18 years) and treatment group was used. If a baseline value was missing, the median value in the corresponding age group for the pooled treatments was used. Sensitivity analyses were performed with multiple imputation and worst-case (no change from baseline) methods for the primary endpoint, and with exclusion of missing values for secondary endpoints.

Key: AE, adverse event; ERT, enzyme replacement therapy; ITT, intent-to-treat.

Notes: Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.

Source: Ben Turkia et al., 2013[63]

Table 125: Critical appraisal of non-randomised studies: Phase II study

Description of criteria	Response
Is the hypothesis/aim/objective of the study clearly described?	Yes
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes
Are the characteristics of the patients included in the study clearly described?	Yes (paper refers to these data being previously reported in another publication[11, 12, 98, 102])
Are the interventions of interest clearly described?	Yes (paper refers to these data being previously reported in another publication[11, 12, 98, 102])
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	No
Are the main findings of the study clearly described?	Yes
Does the study provide estimates of the random variability in the data for the main outcomes?	Yes
Have all important adverse events that may be a consequence of the intervention been reported?	Yes
Have the characteristics of patients lost to follow-up been described?	Yes
Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes (for most outcomes)
Were the subjects asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected.	No
Were those subjects who were prepared to participate representative of the entire population from which they were recruited? The proportion of those asked who agreed should be stated.	No
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	No
Was an attempt made to blind study subjects to the intervention they have received? For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.	No, single-arm study
Was an attempt made to blind those measuring the main outcomes of the intervention?	No
If any of the results of the study were based on “data dredging”, was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. Retrospective = NO. Prospective = YES	N/A
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the	Unclear

Description of criteria	Response
intervention and outcome the same for cases and controls?	
Were the statistical tests used to assess the main outcomes appropriate?	Yes
Was compliance with the intervention/s reliable?	Yes
Were the main outcome measures used accurate (valid and reliable)?	Yes
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? Patients for all comparison groups should be selected from the same hospital. The question should be answered UTD for cohort and case control studies where there is no information concerning the source of patients	UTD
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time?	Yes (data previously reported in another publication[11, 12, 98, 102])
Were study subjects randomised to intervention groups? Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation.	N/A
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N/A
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes
Were losses of patients to follow-up taken into account?	Yes
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance?	Yes (data previously reported in another publication[11, 12, 98, 102])
Key: UTD, unable to determine **Source:** Lukina et al. 2014[12]	

19.4 Indirect comparison

Sections 9.1 and 9.2 provide full details of the methodology of the systematic literature review which was carried out and identified one comparator head-to-head RCT, which compared imiglucerase to velaglucerase in ERT-naïve patients.[63] This trial has been used to inform a formal indirect comparison. The critical appraisal for this RCT is presented in Section 19.3, and a summary of patient characteristics for this trial is presented alongside ENGAGE and ENCORE in Table 126.

For the purposes of indirect comparative evidence described in this section, we have focused on the four outcomes of primary importance to the decision problem, i.e. change from baseline in haemoglobin levels, platelet counts, spleen volume and liver volume.

Table 126: Patient characteristics and treatments

Author, year	Treatment	Comparator	Total sample size, follow-up months	Patient characteristics: % adult, % splenectomised baseline spleen volume (multiples of normal)
ERT-naïve RCTs				
Ben Turkia, 2013[63] (HGT-GCB-039)	Velaglucerase (60 U/kg Q2W)	Imiglucerase (60 U/kg Q2W)	35, 9	73.5%, 58.8%, 8.25
ENGAGE, 2013[52]	Eliglustat [50mg, 100mg BID]	Placebo	40, 9	100%, 0%, 13.20
ERT-treated RCT				
ENCORE, 2013[72]	Eliglustat [50mg, 100mg, 150mg BID]	Imiglucerase [15-75 U/kg Q2W or 30-130 U/kg/ monthly]	160, 12	100%, 25%, 3.01 (1.2L)

Key: BID, twice daily; ERT, enzyme replacement therapy; Q2W, twice weekly; RCT, randomised controlled trial.
Source: Evidera lit review[146]

Patients with Gaucher disease are naturally heterogeneous and their possible treatment responses depend on severity of disease, treatment dose, and treatment duration. For example, response determined by haemoglobin levels is dependent on rate at which haemoglobin normalises, which in turn is dependent on treatment dose.[147] Consequently for indirect treatment comparisons to be appropriate and robust, we require trials to be well balanced with respect to all of these factors, as they can and do influence patient response/outcomes.

ENCORE, the RCT of eliglustat and imiglucerase, is by far the largest study in terms of patient numbers and has the longest follow-up period. While differences in sample size do not explicitly prohibit indirect treatment comparison, it is an important consideration when evaluating the weight and strength of evidence from each study. Unfortunately follow-up differs markedly across these three RCTs, and while there is 6-month data available for all

studies which might be considered as a basis for comparison, great caution is required as the half-life of response of the parameters are at least 6 months (or very much longer) and are highly dose dependent. Furthermore the ENCORE data show significant results at 9 months for all parameters but not at 6 months indicating a similar long half-life for response.

Patient disease severity

Spleen size and change in spleen size are important clinical indicators of severity of Gaucher disease and response to treatment, and a goal of treatment is to reduce spleen size to less than eight times normal.[35] Spleen size at presentation can be thirty to even sixty times normal. There will therefore be enormous variation in spleen size dependent on duration of prior treatment and dose. As shown in Table 126, there is a large degree of heterogeneity between the RCTs with respect to baseline spleen size. The proportion of patients entering the studies that have been splenectomised also differs greatly between the studies. The studies therefore are not comparable with respect to baseline severity of patients and therefore in terms of potential for treatment response after study entry.

Dose dependent response and half-life

The largest study of the effect of different doses of ERT was published by Grabowski et al. (2009).[147] This demonstrated time and dose dependent normalisation of the clinical parameters (haemoglobin, platelets, spleen volume and liver volume). The half-life of platelet recovery to normal levels was approximately 5 months at high doses in the range of 48 to 75 U/kg/Q2W and approximately 12 months at lower doses in the range of 29 U/kg to 48 U/kg and even slower (18 months) in the 5 U/kg to 28 U/kg group which are a common range of doses used in the UK. The half-life of spleen volume shrinkage was between 2 and 5 years; the maximum shrinkage was approximately 90% from baseline with high doses and 70% with low doses. These considerations and results indicate that comparison of different clinical trials with ERT used at different doses requires great care. In particular for indirect treatment comparisons to be possible with these three RCTs, it is necessary for imiglucerase to be considered the common comparator, which in turn would preferably require similarity of the imiglucerase groups across the studies. The imiglucerase groups cannot be considered similar across the studies since studies contain both pre-treated stable patients, as in ENCORE, and untreated patients as in ENGAGE and Ben-Turkia. Table 28 also shows that in the two studies including imiglucerase, the dose administered varies considerably. Therefore, given the effect of dosing on outcomes,

the studies cannot be deemed comparable with respect to treatment doses (for the common comparator).

Treatment experience

Patients with Gaucher disease are heterogeneous; at one end of the spectrum patients present in childhood with splenic enlargement up to 30 times normal size or more and with episodes of bleeding, infections, bone crises and aggressive destructive bone disease; at the other end, middle aged adults present with slight splenomegaly (five to ten multiples of normal) as a clinical finding associated with mild anaemia or thrombocytopenia. Prior to the introduction of ERT the former patients suffered from early death or joint destruction and immobility, while the latter patients may not have required any treatment at all.

ERT has since transformed Gaucher disease and enables all GD1 patients to live a symptom-free life regardless of severity within a few years of starting appropriate management. Therefore, a group of patients that are ERT-naïve cannot be considered homogeneous with a group that have previously received ERT, and treatment responses/outcomes would not be expected to be the same in the two groups. As two of the three included RCTs have been conducted in ERT-naïve patients and one in ERT-stable/treated patients, the studies cannot be deemed comparable with respect to treatment (ERT) experience.

Summary of indirect comparison feasibility

We have identified substantial differences between these three RCTs with respect to patient severity at baseline, treatment doses administered and ERT experience. Each of these factors influence measure of treatment response, as such these studies do not allow for robust indirect treatment comparisons.

In the following sections we present within trial results for each of the three studies for the clinical parameters of primary interest (change from baseline in haemoglobin, platelets, spleen volume and liver volume).

Treatment comparisons of interest and strategy

There are four treatment comparisons are of interest in this decision problem:

- In patients that are ERT-naïve:
  - eliglustat vs. imiglucerase
  - eliglustat vs. velaglucerase

- In patients that are ERT-stable/treated:
  - eliglustat vs. imiglucerase
  - eliglustat vs. velaglucerase

Table 127 details if, and how, the four treatment comparisons (direct or indirect) can be made.

Table 127: Possible treatment comparison strategy

Comparison	How to construct comparison	Limitations
1. (ERT-naïve): eliglustat vs imiglucerase	Direct comparison of eliglustat and imiglucerase from ENCORE	ENCORE is in patients that are ERT-stable rather than ERT-naive
2. (ERT-naïve): eliglustat vs velaglucerase	Adjusted indirect comparison using ENCORE and Ben-Turkia (2013) and imiglucerase as the common comparator	ENCORE includes patients that are ERT-stable rather than ERT-naïve. Different doses (ranges) for imiglucerase have been used in the studies, and baseline severity (spleen measures) differ between the studies.
3. (ERT-stable/treated): eliglustat vs imiglucerase	Direct comparison of eliglustat and imiglucerase from ENCORE	None
4. (ERT-stable/treated): eliglustat vs velaglucerase	Adjusted indirect comparison using ENCORE and Ben-Turkia (2013) and imiglucerase as the common comparator	Ben-Turkia (2013) includes patients that are ERT-naïve rather than ERT-stable. Different doses (ranges) for imiglucerase have been used in the studies, and baseline severity (spleen measures) differ between the studies.
Key: ERT, enzyme replacement therapy.		

There are major limitations for three of these four treatment comparisons, due to the heterogeneity between trials as described in the previous section. As noted above there are limitations in the eliglustat versus velaglucerase comparison in the ITC.

Summary of relevant data for indirect treatment comparisons

Table 128, Table 129 and Table 130 present data for the outcomes of interest for the three qualifying RCTs. For consistency across all trials, the outcomes at 6 months are presented. Outcomes at 9 months are also presented where these can be used in indirect comparisons, but not all trials report 9-month data for each endpoint. In addition, as the measurement units used were different between studies for spleen and liver volume, the

percentage change from baseline is presented. Data have been extracted from the trial publications (including digitisation of graphs), clinical trial study reports (for eliglustat), and supplemented with regulatory documents where necessary.

For context of these results, consider the results in light of 'normal' ranges defined in the DS3, which are:

- Haemoglobin
  - Normal (DS3 score of 0): >12g/dL (males), >11 (females)
  - First level away from normal (DS3 score of 2): 8-12g/dL (males), 8-11 (females)
- Platelets
  - Normal (DS3 score of 0): >120 $x10^3/mm^3$
  - First level away from normal (DS3 score of 2): 21-119 $x10^3/mm^3$
- Liver volume can vary greatly by age and gender, and as such is presented in terms of multiples of normal (MN):
  - Normal (DS3 score of 0): ≤2.5 MN
  - First level away from normal (DS3 score of 2): >2.5 MN
- Spleen volume can vary greatly by age and gender, and as such is presented in terms of multiples of normal (MN):
  - Normal (DS3 score of 0): ≤5 MN
  - First level away from normal (DS3 score of 2): 5-15 MN
  - Second level away from normal (DS3 score of 5): >15 MN or splenectomised

Table 128: Outcome data for ENCORE

	Eliglustat						Imiglucerase						Eliglustat - imiglucerase	
	Baseline			CFB at Month 6			Baseline			CFB at Month 6			Difference in CFB at Month 6	
	n	mean	SE	n	mean	SE	n	mean	SE	n	mean	SE	mean	SE
Haemoglobin (g/dL)	98	13.59	0.13	98	-0.28	0.07	47	13.80	0.18	46	0.07	0.11	-0.35	0.13
Platelet Count (x10^9/L)	98	206.75	5.62	98	3.19	3.97	47	192.30	8.36	45	3.67	3.08	-0.48	5.02
Spleen volume (MN)	70	3.23	0.16	70	-0.15	0.06	39	2.63	0.17	39	-0.12	0.05	-0.03	0.08
Liver volume (MN)	98	0.95	0.02	97	0.00	0.01	47	0.91	0.02	47	0.02	0.01	-0.02	0.02
	Baseline			CFB at Month 9			Baseline			CFB at Month 9			difference in CFB at Month 9	
	n	mean	SE	n	mean	SE	n	mean	SE	n	mean	SE	mean	SE
Haemoglobin (g/dL)	98	13.59	0.13	97	-0.36	0.08	47	13.80	0.18	46	0.14	0.10	-0.50	0.13
Platelet Count (x10^9/L)	98	206.75	5.62	96	0.38	3.18	47	192.30	8.36	46	8.64	3.67	-8.26	4.85

Key: CFB, change from baseline, SE, standard error.

Notes: CFB for spleen and liver volume presented as percentage change from baseline. Data presented are per-protocol. Spleen volume and liver volume were not measured at 9 months.

Source: FDA review[148]

Table 129: Outcome data for ENGAGE

	Eliglustat						Placebo						Eliglustat - placebo	
	Baseline			CFB at Month 6			Baseline			CFB at Month 6			Difference in CFB at Month 6	
	n	Mean	SE	n	mean	SE	n	mean	SE	n	mean	SE	mean	SE
Haemoglobin (g/dL)	20	12.05	0.41	19	0.72	0.21	20	12.75	0.36	20	-0.51	0.22	1.23	0.31
Platelet Count (x10^9/L)	20	75.05	3.15	19	11.24	3.93	20	78.48	5.06	19	-7.78	2.82	19.02	4.84
Spleen volume (MN)	20	13.89	1.33	19	-25.16	1.72	20	12.50	1.33	20	0.73	2.29	-25.89	2.86
Liver volume (MN)	20	1.44	0.08	19	-2.97	1.84	20	1.36	0.06	19	1.25	1.69	-4.22	2.50

Key: CFB, change from baseline; SE, standard error.

Notes: CFB for spleen and liver volume presented as percentage change from baseline.

Source: FDA review[148]

Table 130: Outcome data for Ben-Turkia, 2013

	velaglucerase						imiglucerase						velaglucerase - imiglucerase	
	Baseline			CFB at Month 6			Baseline			CFB at Month 6			difference in CFB at Month 6	
	n	mean	SE	n	mean	SE	n	mean	SE	n	mean	SE	mean	SE
Haemoglobin (g/dL)	17	11.50	NR	17	1.12	0.28	17	10.50	NR	17	1.35	0.29	-0.23	0.40
Platelet Count (x10^9/L)	17	161.00	NR	17	99.43	17.54	17	181.00	NR	17	135.23	17.25	-35.80	24.60
Spleen volume (MN)	17	2.53	NR	17	-1.71	0.26	17	4.20	NR	17	-1.54	0.21	-0.17	0.33
Liver volume (MN)	17	4.40	NR	17	-1.18	0.13	17	4.24	NR	17	-1.18	0.14	0.00	0.19
	Baseline			CFB at Month 9			Baseline			CFB at Month 9			difference in CFB at Month 9	
	n	mean	SE	n	mean	SE	n	mean	SE	n	mean	SE	mean	SE
Haemoglobin (g/dL)	17	11.50	NR	15	1.68	NR	17	10.50	NR	15	1.52	NR	0.16	0.39
Platelet Count (x10^9/L)	17	161.00	NR	17	108.00	NR	17	181.00	NR	17	146.70	NR	-38.70	25.36

Key: CFB, change from baseline; NR, not reported; SE, standard error.

Notes: CFB for spleen and liver volume presented as percentage change from baseline.

For Table 128, a mean difference between treatments would favour eliglustat when the value is positive for the haemoglobin and platelet counts data, and when the value is negative for the spleen and liver volume data. Therefore, for ENCORE, the change from baseline at Month 6 results (point estimates) favour imiglucerase for the haemoglobin and platelet count outcomes and the results favour eliglustat for the spleen and liver volume outcomes. The change from baseline at month 9 results (point estimates) favour imiglucerase for the haemoglobin and platelet count outcomes. The magnitude of all of these differences are small and not clinically relevant (by comparison with the DS3).

For Table 129, a mean difference between treatments would favour eliglustat when the value is positive for the haemoglobin and platelet counts data, and when the value is negative for the spleen and liver volume data. Therefore, for ENGAGE, the change from baseline at Month 6 results (point estimates) favour eliglustat for all outcomes (haemoglobin, platelet count, spleen volume, and liver volume). Note the sample size is small for this trial and results should be viewed with caution.

For Table 130, a mean difference between treatments would favour velaglucerase when the value is positive for the haemoglobin and platelet counts data, and when the value is negative for the spleen and liver volume data. Therefore, for Ben-Turkia (2013)[63] the change from baseline at Month 6 results (point estimates) favour imiglucerase for the haemoglobin and platelet count outcomes and the results favour velaglucerase for the spleen volume outcome. The change from baseline at Month 9 results (point estimates) favour velaglucerase for the haemoglobin outcome and the results favour imiglucerase for the platelet count outcome. With the exception of platelet count, the magnitude of each of these differences is small and not clinically meaningful (as determined by comparison with the DS3). The difference in platelet count is noteworthy, but of questionable clinical relevance. For example, it can also be argued that a reduction of 36 x10^9/L in platelet count from a baseline of 160-180 x10^9/L would not result in change of categorisation using the DS3. Again, note the sample size is small for this trial and results should be viewed with caution. None of the treatment comparisons for the four outcomes were considered statistically significant for this trial. Although the trial is small, and not powered to detect differences, from the data we have in Ben-Turkia (2013)[63], it is not unreasonable to assume equal efficacy between velaglucerase and imiglucerase.

Indirect comparisons methodology and results

For illustration purposes only, a simple adjusted indirect comparison has been performed to compare eliglustat with velaglucerase, using imiglucerase as the common comparator.

The adjusted indirect comparison point estimate is formed by taking the difference between the two differences to imiglucerase with respect to the change from baseline measures at Month 6. The associated standard error is estimated by taking the square root of the sum of the variances of the within trial Month 6 change from baseline difference between treatments.

Table 131 presents the inputs and results from the adjusted indirect treatment comparison of eliglustat versus velaglucerase at both 6 and 9 months, using ENCORE and Ben-Turkia (2013), and imiglucerase as a common comparator.

Table 131: Indirect treatment comparison of eliglustat versus velaglucerase

	ENCORE **Eliglustat – imiglucerase**	**Ben-Turkia, 2013** **Velaglucerase - imiglucerase**	**Adjusted indirect comparison** **Eliglustat - velaglucerase**
	Mean (SE)	**Mean (SE)**	**Mean (95% confidence interval)**
6 months data			
Haemoglobin (g/dL)	-0.35 (0.13)	-0.23 (0.40)	XX (XXXXXXX)
Platelet count (x10^9/L)	-0.48 (5.02)	-35.80 (24.60)	XX (XXXXXX)
Spleen volume	-0.03 (0.08)	-0.17 (0.33)	XX (XXXXXX)
Liver volume	-0.02 (0.02)	0.00 (0.19)	XX (XXXXXX)
9 months data			
Haemoglobin (g/dL)	-0.50 (0.13)	0.16 (0.39)	XX (XXXXXX)
Platelet count (x10^9/L)	-8.26 (4.85)	-38.70 (25.36)	XX (XXXXXX)
Key: SE, standard error.			

Differences between eliglustat and velaglucerase are XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX. Acknowledging the limitations of the indirect comparison, there is no evidence to suggest a difference between eliglustat and velaglucerase. Although not a direct, randomised comparison, there is further evidence to support similarity of eliglustat and velaglucerase in Section 6.5.3, where the subgroup of patients switching from velaglucerase to eliglustat maintain their treatment effects.

Heterogeneity

The heterogeneity in this limited evidence base is fundamental with respect to the differing treatment experience and severity of patients at baseline, as determined by trial design, and differing treatment regimens for imiglucerase between the trials. As we do not recommend the indirect comparisons to be used as the base-case, we have not explored heterogeneity further.

As described, the evidence base is limited as is usual in ultra-rare diseases in terms of both similarity of trial designs, and patient numbers in two of the three included trials, which makes indirect treatment comparisons unsuitable. In light of this and considering each of the within trial results, the four treatment comparisons of interest are handled as described in Table 132.

Table 132: Treatment comparison strategy

Comparison	How to construct comparison	Assumptions
1. (ERT-naïve): eliglustat vs imiglucerase	Use eliglustat arm from ENGAGE in both the eliglustat and imiglucerase arms	This assumes parity between eliglustat and imiglucerase in ERT-naïve setting patients
2. (ERT-naïve): eliglustat vs velaglucerase	Use eliglustat arm from ENGAGE in both the eliglustat and velaglucerase arms	This is based on an assumption of parity between velaglucerase and eliglustat in ERT-naïve patients
3. (ERT-stable/treated): eliglustat vs imiglucerase	Use eliglustat versus imiglucerase results from ENCORE	None
4. (ERT-stable/treated): eliglustat vs velaglucerase	Use eliglustat versus imiglucerase results from ENCORE	This is based on an assumption of parity between velaglucerase and imiglucerase in ERT-treated patients
Key: ERT, enzyme replacement therapy.		

Clearly, the key evidence of relative efficacy is derived from the results of the ENCORE study. Although, assumptions regarding transferability of effects are necessary as detailed in Table 132, it is encouraging that the trial results that are used (ENCORE), come from the largest (by far) RCT conducted in Gaucher disease in terms of patient numbers and an adequate duration to observe effects on the accepted goals of treatment. Outside of this trial, comparative clinical trial evidence is limited.

19.5 Adverse event data extracted from trial publications

The tables below (Table 133 and Table 134) present the pooled numbers of adverse events across the published studies available presenting safety data for each of the comparators, which are split by population; ERT stable and treatment naive.

Table 133: Pooled incidence rates of adverse events – treatment-naïve population

Treatment	Eliglustat	Imiglucerase		Velaglucerase
Fatigue	2/46 (4.35%)			
Nausea	4/46 (8.70%)	0/17 (0 %)		1/17 (5.88%)
Diarrhoea	6/46 (13.04%)			4/25 (16 %)
Headache	11/46 (23.91%)	2/17 (11.76%)		19/54 (35.19%)
Back pain	1/46 (2.17%)			7/37 (18.92%)
Upper extremity pain	3 /46 (6.52%)	0/17 (0 %)		4 /29 (13.79%)
Abdominal pain	3/46 (6.52%)			8/37 (21.62%)
Joint pain	12/46 (26.09%)	0/17 (0 %)		10/42 (23.81%)
Fever	4/46 (8.70%)	1/17 (5.88%)		7/42 (16.67%)
Weakness	0/19 (0 %)			6/37 (16.22%)
Tremor	1/39 (2.56%)			
Weight loss				
Oropharyngeal pain	4/46 (8.70%)			
Infusion reaction		4/17 (23.53%)		28/54 (51.85%)
Flatulence	2/20 (10 %)			
URTI	5/46 (10.87%)			9/25 (36 %)
Dizziness	2/46 (4.35%)			11/37 (29.73%)
SAEs	3/46 (6.52%)	0/66 (0 %)		3/54 (5.56%)
Peripheral neuropathy	1/26 (3.85%)			

Key: SAEs, serious adverse events; URTI, upper respiratory tract infection.

Table 134: Pooled incidence rates of adverse events – ERT population

Treatment	Eliglustat	Imiglucerase	Velaglucerase
Fatigue	12/106 (11.32%)	1/65 (1.54%)	5/40 (12.50%)
Nausea	13/106 (12.26%)	1/65 (1.54%)	4/40 (10 %)
Diarrhoea	13/106 (12.26%)	5/65 (7.69%)	4/40 (10 %)
Headache	14/106 (13.21%)	1/65 (1.54%)	12/40 (30 %)
Back pain	13/106 (12.26%)	3/65 (4.62%)	8/40 (20 %)
Upper extremity pain	12 /106 (11.32%)	1 /53 (1.89%)	4 /40 (10 %)
Abdominal pain	11/106 (10.38%)	1/65 (1.54%)	6/40 (15 %)
Joint pain	16/106 (15.09%)	10/65 (15.38%)	
Fever	2/106 (1.89%)	1/65 (1.54%)	5/40 (12.50%)
Weakness		0/12 (0 %)	
Tremor	3/106 (2.83%)	0/65 (0 %)	
Weight loss	2/106 (1.89%)	2/65 (3.08%)	
Oropharyngeal pain			
Infusion reaction	0/106 (0 %)	1/53 (1.89%)	9/40 (22.50%)
Flatulence	3/106 (2.83%)	0/65 (0 %)	
URTI	11/106 (10.38%)	3/53 (5.66%)	13/40 (32.50%)
Dizziness	9/106 (8.49%)	0/65 (0 %)	
SAEs	11/106 (10.38%)	11/165 (6.67%)	5/76 (6.58%)
Peripheral neuropathy	4/106 (3.77%)	1/53 (1.89%)	

Key: ERT, enzyme replacement therapy; SAE, serious adverse event; URTI upper respiratory tract infection.

19.6 Parameters for adverse events and trial transitions

Table 135 shows the point estimates and upper and lower bounds of 1 year transitions used in sensitivity analysis. Where there was no information a transition (e.g. if there were no patients in a DS3 state at baseline), patients are assumed to stay in the same state, with transitions fixed at 1 (as shown). This does not affect the base case model, as the DS3 distributions from the trials are used in the model, so no patients are in these states in the first cycle of the model. Transitions not presented are fixed at 0 (i.e. there no patients made a particular transition in the trial).

The table also presents the parameter values for the adverse event incidence rates for each drug in each population. Where the incidence rate was 0%, the parameters is omitted from the table for brevity.

Table 135: Parameters mean values and upper and lower bounds: first year state transitions and adverse event incidence rates

Parameter	Point estimate	Lower bound	Upper bound
ERT stable (ENCORE trial; eliglustat arm for eliglustat, imiglucerase arm for comparators)			
Year 1 transition: Eliglustat - state 1 to 1	0.8545	0.8742	0.8742
Year 1 transition: Eliglustat - state 1 to 2	0.0182	0.0129	0.0129
Year 1 transition: Eliglustat - state 1 to 3	0.0545	0.0500	0.0500
Year 1 transition: Eliglustat - state 1 to 4	0.0182	0.0129	0.0129
Year 1 transition: Eliglustat - state 1 to 5	0.0545	0.0500	0.0500
Year 1 transition: Eliglustat - state 2 to 1	0.6667	0.6975	0.6975
Year 1 transition: Eliglustat - state 2 to 2	0.2500	0.2415	0.2415
Year 1 transition: Eliglustat - state 2 to 5	0.0833	0.0610	0.0610
Year 1 transition: Eliglustat - state 3 to 3	1.0000	1.0000	1.0000
Year 1 transition: Eliglustat - state 4 to 1	0.1429	0.1096	0.1096
Year 1 transition: Eliglustat - state 4 to 4	0.7143	0.7809	0.7809
Year 1 transition: Eliglustat - state 4 to 5	0.1429	0.1096	0.1096
Year 1 transition: Eliglustat - state 5 to 5	1.0000	1.0000	1.0000
Year 1 transition: Eliglustat - state 6 to 6	1.0000	1.0000	1.0000
Year 1 transition: Eliglustat - state 7 to 7	1.0000	1.0000	1.0000
Year 1 transition: Eliglustat - state 8 to 8	1.0000	1.0000	1.0000
Year 1 transition: Eliglustat - state 9 to 9	1.0000	1.0000	1.0000
Year 1 transition: Comparators - state 1 to 1	0.8611	0.8840	0.8840
Year 1 transition: Comparators - state 1 to 2	0.0556	0.0481	0.0481

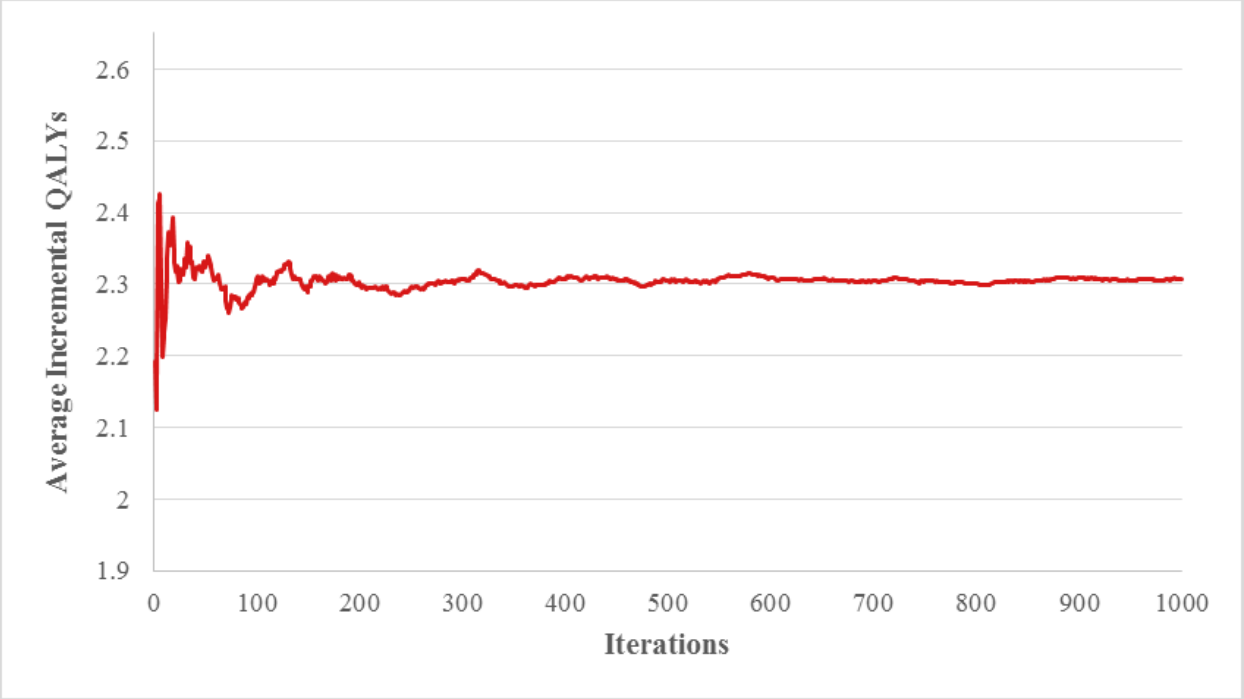
Parameter	Point estimate	Lower bound	Upper bound
Year 1 transition: Comparators - state 1 to 3	0.0278	0.0198	0.0198
Year 1 transition: Comparators - state 1 to 5	0.0556	0.0481	0.0481
Year 1 transition: Comparators - state 2 to 1	0.6667	0.7286	0.7286
Year 1 transition: Comparators - state 2 to 2	0.3333	0.2714	0.2714
Year 1 transition: Comparators - state 3 to 3	1.0000	1.0000	1.0000
Year 1 transition: Comparators - state 4 to 1	0.2000	0.1627	0.1627
Year 1 transition: Comparators - state 4 to 2	0.2000	0.1627	0.1627
Year 1 transition: Comparators - state 4 to 4	0.6000	0.6746	0.6746
Year 1 transition: Comparators - state 5 to 5	1.0000	1.0000	1.0000
Year 1 transition: Comparators - state 6 to 6	1.0000	1.0000	1.0000
Year 1 transition: Comparators - state 7 to 7	1.0000	1.0000	1.0000
Year 1 transition: Comparators - state 8 to 8	1.0000	1.0000	1.0000
Year 1 transition: Comparators - state 9 to 9	1.0000	1.0000	1.0000
Treatment naïve (eliglustat arm of ENGAGE trial for eliglustat and comparators)			
Year 1 transition: All drugs - state 1 to 1	1.0000	1.0000	1.0000
Year 1 transition: All drugs - state 2 to 2	1.0000	1.0000	1.0000
Year 1 transition: All drugs - state 3 to 3	1.0000	1.0000	1.0000
Year 1 transition: All drugs - state 4 to 1	0.1765	0.1628	0.1628
Year 1 transition: All drugs - state 4 to 4	0.8235	0.8372	0.8372
Year 1 transition: All drugs - state 5 to 5	1.0000	1.0000	1.0000
Year 1 transition: All drugs - state 6 to 4	1.0000	1.0000	1.0000
Year 1 transition: All drugs - state 7 to 7	1.0000	1.0000	1.0000
Year 1 transition: All drugs - state 8 to 8	1.0000	1.0000	1.0000
Year 1 transition: All drugs - state 9 to 9	1.0000	1.0000	1.0000
AE incidence rates			
AE: Back pain - Eliglustat	9.21%	5.93%	13.12%
AE: Joint pain - Eliglustat	18.42%	11.77%	26.16%
AE: Abdominal - Eliglustat	9.21%	5.93%	13.12%
AE: Fever – Eliglustat	8.70%	5.60%	12.39%
AE: Weakness -Eliglustat	0.00%	0.00%	0.00%
AE: Infusion reaction - Eliglustat	0.00%	0.00%	0.00%
AE: URTI - Eliglustat	10.87%	6.99%	15.48%
AE: Dizziness - Eliglustat	4.35%	2.81%	6.20%
AE: Headache - Eliglustat	16.45%	10.53%	23.38%
AE: Back pain - Imiglucerase	4.62%	2.98%	6.58%
AE: Joint pain - Imiglucerase	12.20%	7.83%	17.36%

Parameter	Point estimate	Lower bound	Upper bound
AE: Abdominal pain - Imiglucerase	1.54%	0.99%	2.20%
AE: Fever – Imiglucerase	5.88%	3.79%	8.39%
AE: Weakness - Imiglucerase	0.00%	0.00%	0.00%
AE: Infusion reaction - Imiglucerase	23.53%	14.97%	33.34%
AE: URTI - Imiglucerase	0.00%	0.00%	0.00%
AE: Dizziness - Imiglucerase	0.00%	0.00%	0.00%
AE: Headache - Imiglucerase	3.66%	2.36%	5.22%
AE: Back pain - Velaglucerase	19.48%	12.44%	27.65%
AE: Joint pain - Velaglucerase	23.81%	15.14%	33.73%
AE: Abdominal pain - Velaglucerase	18.18%	11.62%	25.82%
AE: Fever - Velaglucerase	16.67%	10.67%	23.68%
AE: Weakness - Velaglucerase	16.22%	10.38%	23.05%
AE: Infusion reaction - Velaglucerase	51.85%	31.58%	71.81%
AE: URTI - Velaglucerase	36.00%	22.58%	50.64%
AE: Dizziness - Velaglucerase	29.73%	18.79%	41.99%
AE: Headache - Velaglucerase	32.98%	20.77%	46.49%
Key: AE, adverse event; ERT enzyme replacement therapy; URTI, upper respiratory tract infection.			

19.7 Justification of PSA iterations

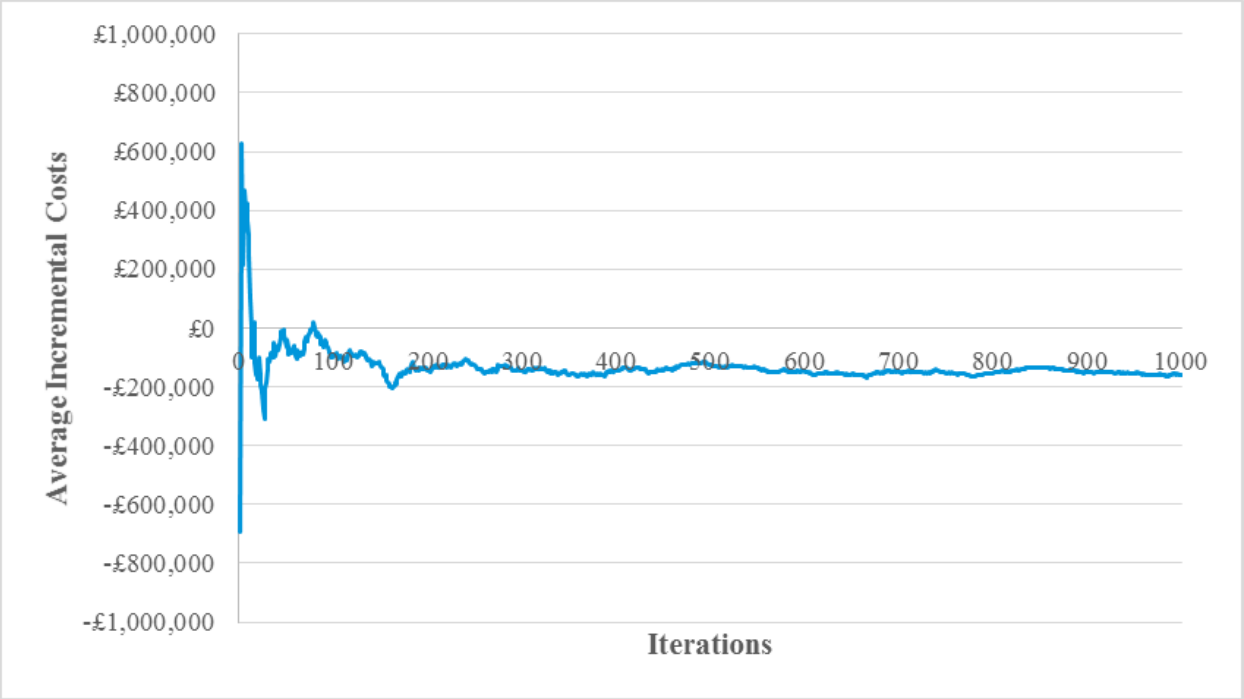
Figure 65 and Figure 66 show the stabilisation of the average incremental costs and QALYs over 1,000 PSA iterations for the ERT population for imiglucerase. As shown both graphs show stabilised results from around 150-200 iterations. 1,000 iterations were performed throughout all probabilistic sensitivity analyses in line with prior submissions to NICE.

Figure 65: Plot of average incremental QALYs from PSA output: ERT stable population – IM/EM patients switching from imiglucerase



Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Figure 66: Plot of average incremental costs from PSA output: ERT stable population – IM/EM patients switching from imiglucerase



Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; PSA, probabilistic sensitivity analysis.

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Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease [ID709]

10/10/2016

Dear Leanne,

Please find below the redacted version of the response to clarification questions initially submitted on the 24th May 2016.

The additional documents provided in May should remain confidential:

- The Statistical Analysis Plan for the ENCORE trial
- The revised cost-effectiveness and budget impact model (combined)
- ENCORE and ENGAGE CSR Demographics Individual Patient Data

When I have more clarity on the expected publication dates I will share them with you.

Best wishes

Claire Grant
Head of UK Health Outcomes
Sanofi

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Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease [ID709]

24/05/2016

Dear Leanne,

Please find enclosed Sanofi Genzyme's response to the clarification questions from the Evidence Review Group received on the 10th May 2016.

Alongside this response we have also provided:

- The Statistical Analysis Plan for the ENCORE trial
- The revised cost-effectiveness and budget impact model (combined)
- ENCORE and ENGAGE CSR Demographics Individual Patient Data

Please let me know if you have any additional questions.

Yours sincerely

Roben Das Gupta, HTA and Market Access Manager

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Section A: Clarification on clinical effectiveness data

A1. **Priority Question:** Please provide a copy of the clinical study report (CSR) for the EDGE study. If the CSR is not yet finalised, please provide baseline characteristics of patients by treatment arms (i.e. once daily dosing regimen vs. twice daily dosing regimen of eliglustat) and, if completed, results for the randomised 12-month primary analysis period.

The CSR for the EDGE study is not yet finalised therefore results for the randomised 12-months primary analysis period cannot be provided. A summary of baseline characteristics is provided for the per protocol population (Table 1) and the intent-to-treat population (Table 2).

Table 1: Summary of EDGE baseline patient demographics: Per Protocol Population

Treatment	**Per Protocol population (n=115)**		
Variable, n (%)	**QD (n=56)**	**BID (n=59)**	**Overall (n=115)**
Sex			
Male	30 (54)	36 (61)	66 (57)
Female	26 (46)	23 (39)	49 (43)
Race			
White	42 (75)	42 (71)	84 (73)
Black or African American	2 (4)	2 (3)	4 (3)
Asian	12 (21)	15 (25)	27 (23)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	0 (0)
White/American Indian	0 (0)	0 (0)	0 (0)
Ethnicity			
Hispanic or Latino	20 (36)	21 (36)	41 (36)
Not Hispanic or Latino	36 (64)	38 (64)	74 (64)
Jewish Descent			
Yes	9 (16)	10 (17)	19 (17)
Ashkenazi	9 (16)	10 (17)	19 (17)
Sephardic	0 (0)	1 (2)	1 (1)
No	47 (84)	49 (83)	96 (83)
Japanese Descent			
Yes	4 (7)	3 (5)	7 (6)
No	52 (93)	56 (95)	108 (94)
Chinese Descent			

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Treatment	**Per Protocol population (n=115)**		
Yes	6 (11)	11 (19)	17 (15)
No	50 (89)	48 (81)	98 (85)
Age at Study Entry (years)			
Mean (SD)	39.6 (15.83)	36.5 (14.49)	38.1 (15.17)
Median (min, max)	37.8 (18.1, 75.0)	33.2 (18.1, 68.5)	34.3 (18.1, 75.0)
Age Group at Study Entry (years)			
<18	0 (0)	0 (0)	0 (0)
18 - <65	52 (93)	57 (97)	109 (95)
>65	4 (7)	2 (3)	6 (5)
Weight at Lead-In Period Baseline (kg)			
Mean (SD)	68.9 (17.55)	67.1 (14.17)	68.0 (15.86)
Median (min, max)	66.3 (40.7, 118.2)	65.3 (40.0, 117.0)	66.0 (40.0, 118.2)
BMI at Lead-In Period: Baseline (kg/m^2)			
Mean (SD)	24.3 (4.93)	23.2 (3.71)	23.7 (4.36)
Median (min, max)	23.7 (15.1, 43.4)	22.8 (15.8, 33.5)	22.9 (15.1, 43.4)
Smoking Status			
None	35 (63)	46 (78)	81 (70)
Current Smoker	6 (11)	7 (12)	13 (11)
Past Smoker	15 (27)	6 (10)	21 (18)
CYP2D6 Metabolizer status			
Poor	0 (0)	0 (0)	0 (0)
Pending	0 (0)	0 (0)	0 (0)
Intermediate	5 (9)	11 (19)	16 (14)
Extensive	50 (89)	46 (78)	96 (83)
Ultrarapid	1 (2)	1 (2)	2 (2)
Indeterminate	0 (0)	1 (2)	1 (1)

Key: BID, twice daily; BMI, body mass index; CYP2D6, cytochrome P450 family 2 subfamily D member 6; Kg, kilogram; QD, once a day; SD, standard deviation.

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Table 2: Summary of EDGE baseline patient demographics: Intent-to-treat Population

Treatment	**Intent-to-treat Population (n=131)**		
Variable, n (%)	**QD (n=65)**	**BID (n=66)**	**Overall (n=131)**
Sex			
Male	37 (57)	37 (56)	74 (56)
Female	28 (43)	29 (44)	57 (44)
Race			
White	49 (75)	48 (73)	97 (74)
Black or African American	3 (5)	3 (5)	6 (5)
Asian	13 (20)	15 (23)	28 (21)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	0 (0)
White/American Indian	0 (0)	0 (0)	0 (0)
Ethnicity			
Hispanic or Latino	22 (34)	22 (33)	44 (34)
Not Hispanic or Latino	43 (66)	44 (67)	87 (66)
Jewish Descent			
Yes	10 (15)	10 (15)	20 (15)
Ashkenazi	10 (15)	10 (15)	20 (15)
Sephardic	0 (0)	1 (2)	1 (1)
No	55 (85)	56 (85)	111 (85)
Japanese Descent			
Yes	5 (8)	3 (5)	8 (6)
No	60 (92)	63 (95)	123 (94)
Chinese Descent			
Yes	6 (9)	11 (17)	17 (13)
No	59 (91)	55 (83)	114 (87)
Age at Study Entry (years)			
Mean (SD)	39.6 (15.26)	36.5 (13.88)	38.0 (14.60)
Median (min, max)	38.1 (18.1, 75.0)	33.2 (18.1, 68.5)	35.7 (18.1, 75.0)
Age Group at Study Entry (years)			
<18	0 (0)	0 (0)	0 (0)
18 - <65	61 (94)	64 (97)	125 (95)
>65	4 (6)	2 (3)	6 (5)

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Treatment	Intent-to-treat Population (n=131)		
Weight at Lead-In Period Baseline (kg)			
Mean (SD)	69.5 (18.33)	67.2 (14.40)	68.3 (16.45)
Median (min, max)	66.0 (40.7, 128.7)	65.2 (40.0, 117.0)	65.9 (40.0, 128.7)
BMI at Lead-In Period: Baseline (kg/m^2)			
Mean (SD)	24.4 (5.26)	23.4 (3.93)	23.9 (4.65)
Median (min, max)	23.8 (15.1, 43.4)	23.0 (15.8, 35.7)	23.1 (15.1, 43.4)
Smoking Status			
None	41 (63)	51 (77)	92 (70)
Current Smoker	8 (12)	7 (11)	15 (11)
Past Smoker	16 (25)	8 (12)	24 (18)
CYP2D6 Metabolizer status			
Poor	0 (0)	1 (2)	1 (1)
Pending	0 (0)	0 (0)	0 (0)
Intermediate	6 (9)	12 (18)	18 (14)
Extensive	57 (88)	51 (77)	108 (82)
Ultrarapid	2 (3)	1 (2)	3 (2)
Indeterminate	0 (0)	1 (2)	1 (1)

Key: BID, twice daily; BMI, body mass index; CYP2D6, cytochrome P450 family 2 subfamily D member 6; Kg, kilogram; QD, once a day; SD, standard deviation.
Source: EDGE Interim report[1]

A2. **Priority Question:** The company submission (pg. 141) states that eliglustat is expected to be used in enzyme replacement therapy (ERT)-unsuitable patients instead of miglustat. Please provide a comparison of eliglustat with miglustat in this specific population. If this cannot be provided, please provide further clarification as to why such a comparison is not relevant, or should not have been presented.

The sentence on page 141 contains a typographical error and it should read “In the very small number of patients for whom ERT is unsuitable, miglustat is used at present and eliglustat would not be expected to be used in place of it”.

As indicated on page 53, eliglustat would be expected to be used in place of ERT treatment, either in treatment naïve patients or patients whose disease is stable on ERT and who will be switched to eliglustat. It would not be expected to be used in place of miglustat.

A3. Please provide detailed information on inclusion/exclusion criteria relating to outcomes in the systematic review (Table 6). Please give detailed information on eligible primary outcomes and secondary outcomes for clinical efficacy and for the safety evaluation.

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As reported in Table 6, articles were included if they reported any efficacy, safety or PRO outcomes, but were excluded if they reported any of the following types of outcomes: in vitro, animal, foetal, molecular, genetic, PD/PK, biopsy findings, plasma or serum levels of antibodies, lipids and proteins only.

Regarding data extraction, the following outcomes were extracted:

- Clinical efficacy outcomes:
    - Spleen volume or size, mean changes or percent increase or reduction
    - Liver volume or size, mean changes or percent increase or reduction
    - Haemoglobin level and platelet counts, mean changes or percent increase or reduction
    - Biomarker results (chemokine CC motif ligand 18 [CCL18], chitotriosidase)
- Skeletal pathology
    - Assessment methods such as radiographs (X-ray), MRI, or bone densitometry (dual-energy X-ray absorptiometry [DXA]), including the spine and bilateral femur
    - Total density measurements as well as T- and Z-scores of bone mineral density (BMD) score (change from baseline)
    - Bone marrow burden (BMB) score (change from baseline)
    - Bone crises
- Patient reported outcomes:
    - Bone pain (Brief Pain Inventory [BPI])
    - Fatigue (Fatigue Severity Score [FSS])
    - General quality of life (Short Form-36 Health Survey [SF-36] – total, physical and mental score)
    - Other PROs
- Clinical safety outcomes:
    - Any adverse events (AEs) reported (including but not limited to neurologic, gastrointestinal [GI], cardiovascular, especially cardiac arrhythmias and syncopal episodes)
    - Treatment discontinuations (total, due to AEs, due to lack of efficacy)

A4. Please confirm how the risk of bias assessment was carried out and whether two independent assessors were used with a third member to confirm any disagreements (pg. 298).

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Two levels of study screening were performed using the exclusion and inclusion criteria below. Abstracts identified during the literature searches were screened by one reviewer. Articles accepted at the abstract level were retrieved in full text and screened for inclusion by two reviewers working independently. Any discrepancies with regard to inclusion or exclusion of an article were resolved by a third reviewer

A5. Figure 10 and Figure 12 (CONSORT diagram of participant flow) show that many patients were screened but not randomised or recruited. Please provide reasons why these patients were not randomised or recruited (for example, refusal to participate in the study or not recruited due to specific exclusion criteria).

Reasons for screen failure in the ENCORE and ENGAGE studies are provided in **Table *3***.

Table 3: Reasons for screen failure

Reason for screen failure	**ENCORE, no. of patients**	**ENGAGE, no. of patients**
Total	**46**	**32**
Additional disease characteristics	10	2
Did not meet inclusion criteria	10	0
Screen failure due to use of drug	7	0
Patient wish to withdraw	5	1
Met exclusion criteria	4	4
Abnormal test results	4	0
Low haemoglobin level	2	1
Low platelet count	1	7
Planned surgery	1	0
HIV positive	1	0
HCV positive	1	0
Spleen volume not at least 6 times MN	0	6
Thrombocytopenia	0	3
High platelet count	0	2
Information around patient characteristic missing	0	2
Splenomegaly	0	2
Patient count not complete MRI	0	1
Patient did not wish to be randomised	0	1

Key: HCV, hepatitis C; HIV, human immunodeficiency virus; MN, multiples of normal; MRI, magnetic resonance imagery

Source: Genzyme 2013[2]; Genzyme 2014[3]

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A6. **Priority Question:** The company submission states that the last observation carried forward method (LOCF) was used for the primary efficacy analysis of ENCORE (Table 117) and for ENGAGE at week 39 (Table 118).

- For ENCORE, please confirm that this approach was used for the primary efficacy outcome of proportion of patients stable in the composite endpoint at week 52.
- Please provide the number of missing values imputed using this method for both trials on the outcomes of haemoglobin, platelet count, spleen and liver volume.
- Please provide evidence on the validity of using this LOCF method to impute missing data in these trials. For example, please provide evidence that patients with missing data did not get worse in their symptoms over the trial period.
- Did other trials (Phase II and EDGE) use the LOCF imputation method for missing values? If so please provide the number of missing values imputed using this method on the outcomes of haemoglobin, platelet count, spleen and liver volume.

The ENCORE primary efficacy analysis was performed using the Per-Protocol Set. One of the criteria for inclusion in the Per-Protocol Set was that a patient must have observed baseline and Week 52 measurements for the variables composing the stability endpoint. The below table summarizes the number of patients who were excluded from the Per-Protocol Set along with the reason for exclusion.

Genzyme Corporation - GZGD02607 Page 1 of 1

TABLE 14.1.2.5
Summary of Analysis Sets
All Randomized Patients

	Eliglustat (N=106)	Cerezyme (N=54)	Total (N=160)
Randomized, n (%)	106 (100)	54 (100)	160 (100)
Safety/Full Analysis Set, n (%)	106 (100)	53 (98)	159 (99)
Patients Excluded, n (%)	0	1 (2)	1 (1)
Patient not treated, n (%)	0	1 (2)	1 (1)
Per Protocol Set, n (%)	99 (93)	47 (87)	146 (91)
Patients Excluded, n (%)	7 (7)	7 (13)	14 (9)
Did not reach Week 52	2 (2)	1 (2)	3 (2)
Dosing Compliance < 80%	2 (2)	3 (6)	5 (3)
Mismatch between randomized dose stratum and actual Cerezyme dosing	2 (2)	2 (4)	4 (3)
Missing Baseline and/or Week 52 Platelet; Missing Baseline and/or Week 52 Hemoglobin	1 (1)	0	1 (1)
Randomized but not dosed	0	1 (2)	1 (1)

Additional analyses were conducted using the Full Analysis Set, comprised of patients who were randomized and who received at least 1 dose of eliglustat or 1 Cerezyme infusion post

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randomization. An analysis that classified patients with missing composite variables as failures and an analysis restricting to patients who completed 52 weeks of follow-up and who had all composite variables observed were conducted and the results are shown in the table below:

Analysis Set	Description of Analysis	Lower 97.5% confidence limit
Per-Protocol	Primary efficacy analysis	-0.176
Full Analysis	Restricted to study completers with all composite variables observed	-0.158
	Treat patients with incomplete data as failures	-0.171

In summary, missing values for the primary efficacy endpoint were treated as described above and the conclusion of non-inferiority remains the same if we conduct the analysis using the per-protocol population or if we treat patients with missing values as failures.

In the ENGAGE study, 1 patient treated with eliglustat withdrew from the study. This patient's Week 39 measurements were the only values imputed using LOCF for the primary and secondary efficacy endpoint analysis. In the Phase 2 study, 2 patients withdrew immediately after the first dose of eliglustat and were not included in the efficacy summaries. Two additional patients withdrew from the study prior to the Year 1 study visit due to pregnancy. Therefore, the 1-year summaries are based on the values from 22 of the 26 treated patients. Likewise, for the 4-year summaries, 7 of the original 26 treated patients had withdrawn and were not included in the analysis. There was no additional imputation performed. The EDGE analysis was based on an interim cut of the data and only focused on the lead-in period. Patients had to have complete observed information to qualify for the subsequent randomization so missing data was minimal.

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A7. **Priority Question:** The European Public Assessment Report (EPAR) states that the EMA recommended that the non-inferiority margin for the ENCORE study should be 20%. Please provide justification for why a non-inferiority margin of 25% was selected.

- Does the company consider the -25% margin used in the non-inferiority trial to be clinically acceptable?
- Please specify how the clinical meaningful difference between the two treatments was calculated?
- What would 25% difference in the primary outcome mean for the prognosis of Gaucher disease patients?
- Please perform a re-analysis using the non-inferiority margins of 20% and 15%. Please include evidence of whether the trial is still efficiently powered at these alternative margins, and whether the conclusion of non-inferiority is met.

The EMA approved a licence for eliglustat based upon acceptance of non-inferiority of eliglustat and imglucerase within the ENCORE study. As stated in the Section 5.2. of the SPC for eliglustat based on the aggregate data from all doses tested in the ENCORE study, Eliglustat met the criteria set in this study to be declared non-inferior to imiglucerase)in maintaining patient stability." .The company supports this conclusion from the EMA, reporting a positive benefit-risk for eliglustat.

Based on the primary efficacy analysis, the lower 97.5% confidence bound of the difference between the proportions of patients remaining stable on eliglustat compared to patients on imiglucerase is -17.56%. Therefore, the ENCORE study demonstrated non-inferiority between eliglustat and imiglucerase if a -25% or a -20% margin were used. Non-inferiority was not demonstrated if a 15% margin is used.

The power to demonstrate non-inferiority using the assumptions used at the ENCORE study design stage regarding the stability rates of imiglucerase (95%) and eliglustat (85%) but the observed number of per-protocol population patients for imiglucerase (n = 47) and eliglustat (n = 99) is shown in Table 4 for different non-inferiority margins. As seen in Table 4, the power to demonstrate non-inferiority using a 15% margin is low (21%).

Table 4: Power to demonstrate non-inferiority in the ENCORE study per-protocol population for different margins

Non-inferiority margin	Power (%)*
-25%	91
-20%	61
-15%	21

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Notes: *, power using the non-stratified Agresti-Caffo method. Similar results are obtained with the Newcombe test.
Source: Agresti and Caffo, 2000[4]; Newcombe 1998[5]

A8. **Priority Question:** In the ENCORE trial, the 95% confidence intervals for the non-inferiority difference were calculated using the method of Agresti and Caffo's adjusted Wald. Was an alternative approach considered, such as Newcombe's hybrid score interval to analyse the two independent samples? Please present a re-analysis of the trial using the Newcombe approach

There are numerous methods available to compute the 95% confidence interval of the difference between two binomial proportions, including the Newcombe method.[5] Table 5 contains the confidence intervals for the ENCORE study primary efficacy endpoint computed using the per-protocol population and the full analysis set with the methods evaluated in Newcombe (1998)[5], Santner et al. (2007)[6], Dann and Koch (2008)[7], Reiczigel et al. (2008)[8], Wang (2010)[9] and Fagerland et al. (2011)[10]. As shown in Table 5, all methods tested exclude the -20% non-inferiority margin with the exception of the Santner and Snell method (PP and FA sets) and continuity corrected Wald test (PP set).[11] The Santner and Snell and the continuity corrected Wald test have exact type I error rates of 0.0006 and 0.0093, respectively, when a 95% imiglucerase response rate is assumed so are extremely conservative and would not have been considered for the primary analysis when the non-inferiority analysis method was selected.

Table 5: Lower 97.5% confidence limits of the difference between the proportions of patients remaining stable on eliglustat compared to patients on imiglucerase for the Per-Protocol and Full Analysis Sets using various statistical methods

Analysis Type	Method	Per-Protocol	Full Analysis Set
Exact (non-stratified)	1. Santner and Snell (1980)[6]	-0.2594	-0.2420
	2. Chan and Zhang (1999)[12]	-0.1875	-0.1794
	3. Agresti and Min (2001)[13]	-0.1880	-0.1795
	4. Reiczigel et al. (2008)[8]	-0.1830	-0.1769
	5. Shan and Wang (2013)[14]	-0.1945	-0.1805
Asymptotic (stratified)	6. Agresti-Caffo (MH)+	-0.1756	-0.1706
	7. Wald (MH)	-0.1870	-0.1820
	8. Newcombe-Wilson (MH)	-0.1810	-0.1750
Asymptotic (non-stratified)	9. Agresti-Caffo (2000) [4]	-0.1814	-0.1761
	10. Wald (1940) [11]	-0.1870	-0.1818
	11. Wald (cc)	-0.2027	-0.1959
	12. Newcombe-Wilson (1998) [5]	-0.1811	-0.1739

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	13. Newcombe-Wilson (cc)	-0.1795	-0.1724
	14. Hauck-Anderson (1986)[15]	-0.1985	-0.1920
	15. Farrington-Manning (1990)[16]	-0.1854	-0.1774
	16. Miettinen-Nurminen (1985)[17]	-0.1852	-0.1775
Key: cc, continuity-correction; MH, Mantel-Haenszel weights **Notes:** +, primary efficacy analysis method			

While there was a randomisation stratification based on prior ERT therapy exposure in ENCORE, the results in Table 5 include several non-stratified methods which have been included because of the very similar response rates across strata.

Additional reasons why the Santner and Snell method and the continuity corrected Wald test would not have been used for the primary method to determine non-inferiority include the following:

- The Santner and Snell method is based on an unstandardized test statistic[6] and has an exact type I error rate of 0.06%, which is far short of the nominal 2.5%. This extreme conservativeness is known in the statistical literature and the use of this method is not recommended (Cytel, 2007).[18] The results from other unconditional exact methods that are based on standardized test statistics and that have improved statistical properties[12, 13] pass the -20% non-inferiority margin (Table 5) and the p-value associated with testing non-inferiority with a -20% margin based on the Chan and Zhang (1999) method is 0.024.[12] These methods have exact type I error rates that are below, but closer than the Santner-based method to, 2.5%, indicating that they are more efficient.

- The Wald method with continuity correction is not recommended in the literature due to its conservativeness.[4, 5, 10] If the imiglucerase is between 0.90 and 0.99, the exact type I error rate varies between 0.0093 and 0.0124. Such conservativeness results in an inefficient method that would not be used as a primary efficacy method. For example, the power of the Wald method with continuity correction is 0.81 with a -25% non-inferiority which is less than the power noted in Table 4.

In summary, exact and asymptotic methods that have the necessary statistical properties robustly demonstrate non-inferiority between eliglustat and imiglucerase using a -25% or -20% non-inferiority margin.

A9. The secondary endpoints in the ENGAGE trial were analysed using a closed-testing procedure to control the type I error rate (Table 118). Please explain what procedure was used, and provide details on whether this was applied when analysing both the efficacy and safety outcomes. Please also explain why a similar control procedure for type I error was not included in the ENCORE and EDGE studies.

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The closed-testing procedure used in the ENGAGE study for the secondary endpoints was the following:

- First, the absolute change in haemoglobin levels (in g/dL) from Baseline to Week 39 was analysed at the 5% level of significance.
- If there was a statistically significant eliglustat treatment effect for the change in haemoglobin levels, then the percentage change in liver volumes (in MN) from Baseline to Week 39 was analysed at the 5% level of significance.
- If there was a statistically significant eliglustat treatment effect for the percentage change in liver volumes (in MN), then the percentage change in platelet counts (in /mm3) from Baseline to Week 39 was analysed at the 5% level of significance.

Due to the order being pre-specified, no further p-value adjustments were needed for multiple comparisons.

Similar testing procedures were not implemented for the ENCORE and EDGE studies. These studies were designed to demonstrate non-inferiority for the primary endpoint and not to demonstrate statistically significant across multiple secondary efficacy endpoints.

A10. **Priority Question:** Please provide a justification for the pooling of health state utility estimates from ENCORE and ENAGE trials. Was it assumed that as patients had been on treatment long enough in both trials, that they will have gained the full treatment effect from eliglustat, and thus be similar enough?

Health states in the economic model are based on GD-DS3 categories. There are nine health states defined by disease severity plus a consideration of bone pain and skeletal complications, as outlined in Figure 23 of the submission. It was possible to extract utility values from the trials that also matched each of these nine health states. It is assumed that the utility for each health state is consistent regardless of clinical trial, patient characteristics, time on treatment or level of treatment effect. For example, a patient in health state three (mild disease with severe skeletal complications) from the ENCORE trial will have the same utility value in that health state as a patient also in health state three from the ENGAGE trial. As such pooling the utility values from the trials was justified.

Health state utilities were estimated separately by each source of data as noted on Page 149 (“Utility data were analysed separately by source (Phase II, ENGAGE, ENCORE, and the DS3 Score Study) to avoid confounding study design and participant characteristics with the health state-utility relationships. Figure 18 displays the health state-utility results using a combination of variables capturing the DS3 category (mild, moderate, marked, severe) and the absence or presence of bone pain or SSC (severe skeletal complications) to measure

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health state"). The submission further notes on Page 150 that "we recommend using the predicted health state utilities.

The pooling of data from the two trials included aggregating patients on different treatments (and placebo) and (prior to trial entry) treatment naïve and experienced patients. This is outlined on pages 147-153 of the submission. This was considered justifiable because this pooling was carried out to obtain estimates of the utility associated with the different health states (based on disease symptomology) in the health economic model. This is based on the assumption that these utility valuations are driven by disease symptomology although it is accepted that such valuations will also include components associated with the disutility associated with treatment administration and the adverse event profile of the drugs.

A11. **Priority Question:** Please provide additional subgroup analyses based on patients' CYP2D6 metaboliser status (extensive, intermediate and poor; EM, IM and PM) for ENCORE and ENGAGE trials.

Currently we have not presented any subgroup analysis for metaboliser status in the clinical sections of the submission and we do not define these in the decision problem. However, analysis based on metaboliser status is referred to in the economic sections. Table 6 and Table 7 provide a summary of key efficacy outcomes by metaboliser status in patients receiving eliglustat, within ENCORE and ENGAGE, respectively.

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Table 6:Summary of the proportion of patients who maintained stability at week 52 and for patients on Eliglustat, a summary of the haemoglobin, platelet count, liver volume and spleen volume over time, ENCORE study, per protocol population

	CYP2D6 Phenotype					
Study variable, n (%)	**Poor (n=4)**	**Intermediate (n=10)**	**Extensive (n=79)**	**Ultrarapid (n=4)**	**Indeterminate (n=2)**	**Overall (n=99)**
Primary Composite Endpoint	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemoglobin (g/dL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet Count (10^9/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liver Volume (MN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spleen (MN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemoglobin (g/dL) Change BL to Week 52						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet Count (10^9/L) % Change BL to Week 52						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liver Volume (MN) % Change BL to Week 52						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	CYP2D6 Phenotype					
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spleen (MN) % Change BL to Week 52						
N	3	8	55	3	2	71
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BL, baseline; CI, confidence interval; CYP2D6, cytochrome P450 family 2 subfamily D member 6; g/dL, grams per decilitre; Kg, kilogram; L, litre; max, maximum; min, minimum; MN, multiples of normal; NR, not reported; SD, standard deviation.

Source: Genzyme 2013[19]

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***Table 7**: Summary of haemoglobin, platelet count, liver volume and spleen volume over time for patients on Eliglustat (by dose and CYP2D6 phenotype), ENGAGE study, full analysis set*

	CYP2D6 Phenotype			
Study variable, n (%)	**Intermediate (n=1)**	**Extensive (n=18)**	**Ultrarapid (n=1)**	**Overall (n=20)**
Haemoglobin (g/dL) Change BL to Week 39				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
Platelet Count (10^9/L) % Change BL to Week 39				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
Liver Volume (MN) % Change BL to Week 39				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
Spleen (MN) % Change BL to Week 39				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]

Key: BL, baseline; CI, confidence interval; CYP2D6, cytochrome P450 family 2 subfamily D member 6; g/dL, grams per decilitre; Kg, kilogram; L, litre; max, maximum; min, minimum; MN, multiples of normal; NR, not reported; SD, standard deviation.

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	CYP2D6 Phenotype
Source: Genzyme 2013[19]	

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Table 8 and Table 9 present safety results for patients receiving eliglustat, by metaboliser status in ENCORE, and ENGAGE, respectively.

Table 8: Patients with TEAEs by CYP2D6 metabolizer status, ENCORE study

System organ class	Eliglustat (n=106), n (%)			
	Poor (n=4)	Intermediate (n=12)	Extensive (n=84)	Ultra-rapid (n=4)
Patients with events	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]	[redacted]

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Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Social circumstances	[redacted]	[redacted]	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Source: Genzyme 2014[3]				

Table 9: Patients with TEAEs by CYP2D6 metabolizer status, ENGAGE study

System organ class	Eliglustat (n=106), n (%)			
	Poor (n=0)	Intermediate (n=2)	Extensive (n=18)	Ultra-rapid (n=0)
Patients with events	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]

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Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Source: Genzyme 2013[2]				

A12. Post-hoc analyses were performed in ENCORE trial for the subgroup of patients pre-treated on velaglucerase (pg. 103). Please provide the results of these analyses.

Subgroup data for patients pre-treated with imiglucerase and velaglucerase is presented below.

Within the ENCORE clinical trial patients may have been pre treated with either velaglucerase or imiglucerase. A post hoc subgroup analysis is presented for patients in ENCORE pre-treated on velaglucerase and switching to either eliglustat or imiglucerase in the trial. It is thought that evidence of patients remaining well controlled on eliglustat after switching from velaglucerase is useful supporting evidence with regard to the use of eliglustat in velaglucerase stable patients. Similarly, a post hoc subgroup analysis is presented for patients in ENCORE pre-treated imiglucerase and switching to either eliglustat or imiglucerase in the trial.[20,3] This also may provide some additional supporting evidence in imiglucerase stable patients switched to eliglustat remaining well-controlled. To summarise:

- Eliglustat has similar efficacy both post-imiglucerase and post-velaglucerase treatment
- Haemoglobin levels showed a similar change from baseline to Week 52 in the eliglustat arms both post-imiglucerase and post-velaglucerase treatment (mean change of [redacted]g/dL and [redacted]g/dL, respectively)
- This was also seen for spleen and liver volume outcomes. Mean change to Week 52 in spleen volume was [redacted] MN compared with [redacted] MN in eliglustat patients pre-treated with imiglucerase and velaglucerase, respectively. Liver volume showed a mean change of [redacted] MN and [redacted] MN, respectively.
- A difference in pre-treated groups was seen in platelet count outcomes with a greater increase seen in patients pre-treated with imiglucerase then those with velaglucerase ([redacted] x 10^9/L vs. [redacted] x 10^9/L)

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Table 10: Summary of changes in haemoglobin levels and platelet count in patients pre-treated with imiglucerase or velaglucerase in ENCORE

Time Point / Change	Haemoglobin Levels (g/dL)				Platelet Count (10^9/L)			
	Pre-treated with imiglucerase		Pre-treated with velaglucerase		Pre-treated with imiglucerase		Pre-treated with velaglucerase	
Treatment arm	Eliglustat [redacted]	Imiglucerase [redacted]	Eliglustat [redacted]	Imiglucerase [redacted]	Eliglustat [redacted]	Imiglucerase [redacted]	Eliglustat [redacted]	Imiglucerase [redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to Week 52, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: SD, standard deviation.
Source: Genzyme, 2014[3]

Table 11: Summary of changes in spleen and liver volume in patients pre-treated with imiglucerase or velaglucerase in ENCORE

Time point/change	Spleen Volume (MN)				Liver Volume (MN)			
	Pre-treated with imiglucerase		Pre-treated with velaglucerase		Pre-treated with imiglucerase		Pre-treated with velaglucerase	
Treatment arm	Eliglustat [redacted]	Imiglucerase [redacted]	Eliglustat [redacted]	Imiglucerase [redacted]	Eliglustat [redacted]	Imiglucerase [redacted]	Eliglustat [redacted]	Imiglucerase [redacted]
Baseline, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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(SD)	[redacted]							
Week 52, mean (SD)	[redacted]							
Change from baseline to Week 52, mean (SD)	[redacted]							

Key: MN, multiples of normal; SD, standard deviation.
Source: Genzyme, 2014[3]

Table 12: Summary of changes in BMD, T- and Z- scores of spine and femur in patients pre-treated with imiglucerase or velaglucerase in ENCORE

	Pre-treated with imiglucerase		Pre-treated with velaglucerase	
	Eliglustat (n=99)	**Imiglucerase (n=47)**	**Eliglustat (n=99)**	**Imiglucerase (n=47)**
Total Spine BMD (g/cm^2)				
Baseline, mean (SD)	[redacted]			
% change from baseline to Week 52, mean (SD)	[redacted]			
Total Spine T-score				
Baseline, mean (SD)	[redacted]			
% change from baseline to Week 52, mean (SD)	[redacted]			
Total Spine Z-score				
Baseline	[redacted]			

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	Pre-treated with imiglucerase		Pre-treated with velaglucerase	
	Eliglustat (n=99)	**Imiglucerase (n=47)**	**Eliglustat (n=99)**	**Imiglucerase (n=47)**
	[redacted]	[redacted]	[redacted]	[redacted]
% change from baseline to Week 52, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Worst Total Femur BMD				
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
% change from baseline to Week 52, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Total Femur T-score				
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
% change from baseline to Week 52, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Total Femur Z-score				
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
% change from baseline to Week 52, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Key: BMD, bone mineral density; SD, standard deviation.
Source: Genzyme, 2014[3]

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A13. The submission reports (pg. 280) that patient preference for oral therapy was clearly demonstrated in the ENCORE trial, and patients completed questionnaires indicating their preferred route of administration. Please provide the results from these questionnaires, and explain how the data were analysed.

Patients completed a questionnaire that evaluated treatment preference (oral vs. IV), reasons for treatment preference, and overall satisfaction with treatment. The questionnaire was administered at screening at Week 52 (if randomised to eliglustat) A summary of the results of this questionnaire is presented in Table 13. Analysis of this questionnaire was conducted on the per protocol set. Frequencies and percentages of patients were summarised for each visit by treatment. The changes from baseline were summarised by treatment group, as appropriate.

Table 13: Summary of treatment preference (oral vs. infusion), per protocol set

Parameter	**Eliglustat (n=99)**		**Imiglucerase (n=47)**	
	Screening	**Week 52**	**Screening**	**Week 52**
Preferred treatment				
Oral	93 (94)	93 (94)	44 (94)	0 (0)
IV	3 (3)	0 (0)	2 (40)	0 (0)
Reason for preference				
More convenient	80 (81)	80 (81)	41 (87)	0 (0)
Taken at home	63 (64)	68 (69)	30 (64)	0 (0)
Given in hospital	1 (1)	0 (0)	0 (0)	0 (0)
Given by injection	0 (0)	0 (0)	0 (0)	0 (0)
Given by tablets	48 (48)	58 (59)	22 (47)	0 (0)
May be more effective	32 (32)	0 (0)	8 (17)	0 (0)
May cause fewer side effects	13 (13)	0 (0)	1 (2)	0 (0)
Felt better after treatment	0 (0)	22 (22)	0 (0)	0 (0)
Causes fewer side effects	0 (0)	11 (11)	0 (0)	0 (0)
Other reasons	0 (0)	9 (9)	0 (0)	0 (0)

Key: IV, intravenous
Source: Genzyme, 2014[3]

A14. The submission provides results from the Phase II trial for years 1, 2 and 4; please explain why the results for year 3 were not reported, and provide the results.

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Please find below the results for Year 3 for the Phase II trial. Please note that the Year 3 results were not presented because the sponsor chose only to present the published data for these results.

Table 14: 3 year results from Phase II study, full analysis set

	Baseline, median (range)	**Change from baseline, median (range)**	**% change from baseline, median (range)**
Haemoglobin, g/dL (n=18)	11.60 (8.80, 14.60)	2.50 (-0.25, 5.40)	24.7 (-2.0, 55.7)
p-value	<0.0001		
Platelets, 10^9/L (n=18)	66.75 (39.0, 105.5)	41.0 (11.0, 155.0)	63.3 (18.0, 221.4)
p-value	<0.0001		
Spleen volume, cc (n=19)	1659.0 (1244.0, 5565.0)	-853.0 (-3326.0, -301.0)	-59.6 (-84.2, -21.0)
p-value	<0.0001		
Liver volume, cc (n=19)	2413.0 (1638.0, 3469.0)	-504.0 (-1085.0, -66.0)	-21.0 (-34.6, -3.2)
p-value	<0.0001		
CCL18, ng/mL (n=18)	3560.2 (1280.0, 6563.0)	-2606.9 (-5023.1, -238.0)	-73.1 (-92.8, -14.3)
p-value	<0.0001		
Chitotriosidase, nmol/hr/mL (n=17)	8084.0 (3924.0, 23759.0)	-5350.0 (-20130.0, -4394.0)	-79.6 (-94.8, -50.2)
p-value	<0.0001		
Lumbar spine BMD, g/cm^2 (n=16)	0.98 (0.74, 1.29)	0.05 (-0.06, 0.44)	4.7 (-6.9, 49.3)
p-value	0.0301		
Lumbar spine T-score (n=16)	-1.9 (-3.1, 0.6)	0.4 (-0.4, 3.6)	-31.2 (-128.6, 14.8)
p-value	0.0285		
Lumbar spine Z-score (n=16)	-1.6 (-2.7, 0.7)	0.6 (-0.3, 2.5)	-35.3 (-125.0, 500.0)
p-value	0.0038		
Femur BMD, g/cm^2 (n=14)	1.0 (0.7, 1.3)	0.01 (-0.1, 0.3)	0.6 (-7.2, 29.0)
p-value	0.2209		
Femur T-score (n=14)	-0.1 (-2.0, 1.5)	0.1 (-0.7, 2.3)	-10.5 (-400.0, 100.0)
p-value	0.3437		
Femur Z-score (n=14)	0.2 (-1.3, 1.4)	0.2 (-0.7, 1.6)	-22.2 (-200.0, 400.0)
p-value	0.1357		

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SF-36 (n=17)			
Physical functioning	85.0 (50.0, 100.0)	5.0 (-5.0, 50.0)	NR
Role – physical	87.5 (31.3, 100.0)	6.25 (-25.0, 62.5)	NR
Bodily pain	84.0 (22.0, 100.0)	0.0 (-28.0, 40.0)	NR
General health	62.0 (15.0, 92.0)	10.0 (-23.0, 70.0)	NR
Vitality	62.5 (25.0, 81.3)	6.3 (-12.5, 68.8)	NR
Social functioning	87.5 (25.0, 100.0)	12.5 (-25.0, 37.5)	NR
Role – emotional	100.0 (33.3, 100.0)	0.0 (-25.0, 41.7)	NR
Mental health	80.0 (25.0, 90.0)	5.0 (-20.0, 50.0)	NR
Physical component scale	51.1 (36.0, 56.4)	5.8 (-4.8, 17.9)	NR
Mental component scale	51.4 (20.0, 60.0)	2.7 (-11.6, 19.9)	NR
FSS score	4.3 (1.4, 7.0)	-1.55 (-4.4, 4.0)	-32.9 (-73.3, 142.9)
Total DS3 score	5.0 (1.4, 8.6)	-1.5 (-5.0, 2.0)	-34.1 (-77.8, 37.0)

Key: BMB, bone marrow burden; BMD, bone mineral density; CCL18, chemokine ligand 18; NR, not reported; SF-36, short form 36;
Source: Genzyme 2012[21]

A15. **Priority Question:** Please clarify if the SAEs reported in table 20 are all SAEs or only those reported by at least 10% of the population. If the latter, please provide the full set of data on all SAEs. Please provide details of all 18 SAEs in eliglustat treatment groups, with a breakdown of their severity grading based on treatment dosing regimens.

SAEs were reported in 21 patients overall with 18 in the eliglustat group and 3 in patients who switched for imiglucerase to eliglustat after Week 52 to Week 104. Table 20 of the submission presents SAEs reported by the whole population. Details of all 21 SAEs in the eliglustat treatment group is presented in Table 15.

Table 15: Summary of patients with treatment-emergent SAEs

Patient number	Patient ID#	System Organ Class (S) Preferred term (P)	Severity	Relation to study drug/G. disease	Eliglustat dose
1	2101	S: Cardiac disorder P: Myocardial infarction	Severe	Not related/No	50mg BID
2	2703	S: Nervous system disorder P: Syncope	Severe	Remote/Unlikely/ No	150mg BID
3	2818	S: Hepatobiliary disorder P: Cholecystitis	Severe	Not related/No	150mg BID
4	5806	S: Nervous systems	Severe	Remote/Unlikely/	150mg BID

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		disorder P: Syncope		No	
5	5812	S: Gastrointestinal disorder P: Colitis ischemic	Moderate	Remote/Unlikely/ No	100mg BID
6	5954	S: Injury, poisoning and procedural complications P: Joint dislocation	Moderate	Not related/No	100mg BID
7	5957	S: Neoplasm benign, malignant and unspecified (incl cysts and polyps) P: Uterine leiomyoma	Moderate	Not related/No	100mg BID
8	6203	S: Infections and infestations P: Diverticulitis	Moderate	Not related/No	50mg BID
9	7001	S: Neoplasm benign, malignant and unspecified (incl cysts and polyps) P: Hepatic neoplasm malignant	Severe	Possible	50mg BID
10	7302	S: Surgical and medical procedures P: Mammoplasty	Mild	Not related/No	50mg BID
11	9202	S: Infections and infestations P: Appendicitis	Severe	Not related/No	100mg BID
12	2203	S: Cardiac disorders P: Myocardial infarction	Moderate	Remote/Unlikely/ No	Imiglucerase => eliglustat - 50mg BID
13	3302	S: Injury, poisoning and procedural complications P: Injury	Severe	Not related/No	Imiglucerase => eliglustat – 50mg BID
14	6702	S: Cardiac disorders P: Acute myocardial infarction	Severe	Remote/Unlikely	Imiglucerase => eliglustat – 50mg BID
15	0108	S: General disorders and administration site conditions P: Device malfunction	Moderate	Not related/Yes	150mg BID
16	2209	Nervous system disorders P: Syncope	Severe	Remote/Unlikely/ No	150mg BID
17	2211	S: Nervous system disorders P: Neuropathy peripheral	Moderate	Possible	150mg BID
18	2602	S: Gastrointestinal disorders	Severe	Possible	150mg BID

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		P: Intestinal obstruction			
19	2702	S: Respiratory, thoracic and mediastinal disorders P: Nasal septum deviation	Moderate	Not related/No	150mg BID
20	2820	S: Hepatobiliary disorders P: Biliary colic	Severe	Not related/Yes	150mg BID
21	8303	S: General disorders and administration site conditions P: Pain	Severe	Remote/Unlikely/ No	150mg BID
	8303	S: General disorders and administration site conditions P: Pyrexia	Severe	Remote/Unlikely/ No	150mg BID
Source: Genzyme 2014[22]					

A16. **Priority Question:** For the indirect treatment comparison, please provide the comparative tabulated baseline characteristics of patients in the included trials.

Details of the indirect treatment comparison was detailed in Appendix 19.5 of the company submission and baseline characteristics tabulated in Table 129. This is reproduced below.

Table 16: Patient characteristics and treatments

Author, year	**Treatment**	**Comparator**	**Total sample size, follow-up months**	**Patient characteristics: % adult, % splenectomised baseline spleen volume (multiples of normal)**
ERT-naïve RCTs				
Ben Turkia, 2013[23] (HGT-GCB-039)	Velaglucerase (60 U/kg Q2W)	Imiglucerase (60 U/kg Q2W)	35, 9	73.5%, 58.8%, 8.25
ENGAGE, 2013[2]	Eliglustat [50mg, 100mg BID]	Placebo	40, 9	100%, 0%, 13.20
ERT-treated RCT				
ENCORE, 2013[3]	Eliglustat [50mg, 100mg, 150mg BID]	Imiglucerase [15-75 U/kg Q2W or 30-130 U/kg/ monthly]	160, 12	100%, 25%, 3.01 (1.2L)
Key: BID, twice daily; ERT, enzyme replacement therapy; Q2W, twice weekly; RCT, randomised controlled trial. **Source:** Evidera lit review[24]				

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A17. The company submission states on pg. 46 that 'it is assumed that there will be a 0.4% growth in the diagnosis of GD1 between 2015 and 2017, and 0.4% growth each year between 2017 and 2021.' What is the figure of 0.4% based on? Please provide more information on this.

This estimation was based on the mean annual increase in symptomatic prevalent patients assumed internally by Genzyme: 451 (2012), 453 (2013), 454 (2014), 456 (2015). It may have been more appropriate to have applied the annual mean increase in diagnosed Gaucher Disease patients in the UK of 3%: 272 (2012), 276 (2013), 283 (2014), 293 (2015).

The number of patients anticipated to receive eliglustat included in the submission is an accurate statement about Genzyme's internal forecasts of uptake.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question:** Please provide further information on the models fitted to the ICCG mortality data, including providing the IPD data used to fit the models. In addition, please further justify the choice of model with respect to predicted median and mean survival. Please confirm that Gaucher disease mortality is used in the base-case analysis.

As explained in Section 17.5.6 of the submission, we only had access to the life table from the Weinreb article (reproduced in Table 113 in the submission). We generated simulated patient level (SPL) data from Table 113. The parametric mortality curves were fit to the SPL. We did not have access to any actual individual patient data with mortality information. The mortality risk for any given age in the model was defined as max(G,O), where G is the mortality risk taken from the fitted Gaucher curve and O is the overall population risk (taken from a fitted curve or the actual UK life table [which is a user-selected option in the model]). The reason we used the max(G,O) is because at older ages, the predicted Gaucher mortality risks were actually smaller than those of the overall population.

B2. **Priority Question:** Please provide further justification of why the generalised gamma curve was not selected for the analysis of Gaucher disease mortality. Please provide diagnostic plots for this function.

In selecting which parameterisations best described the mortality trajectory of the Gaucher Type 1 patient consideration was given to AIC/BIC statistics but also 'the face validity' of the parameterisation. From the AIC/BIC fit statistics the generalized Gamma is the best fit. However, comparing the shape of the parameterised curves with the observed mortality data, the

Gamma (purple) is far off from the observed curve (black) compared to Gompertz (orange), which is a much better fit.

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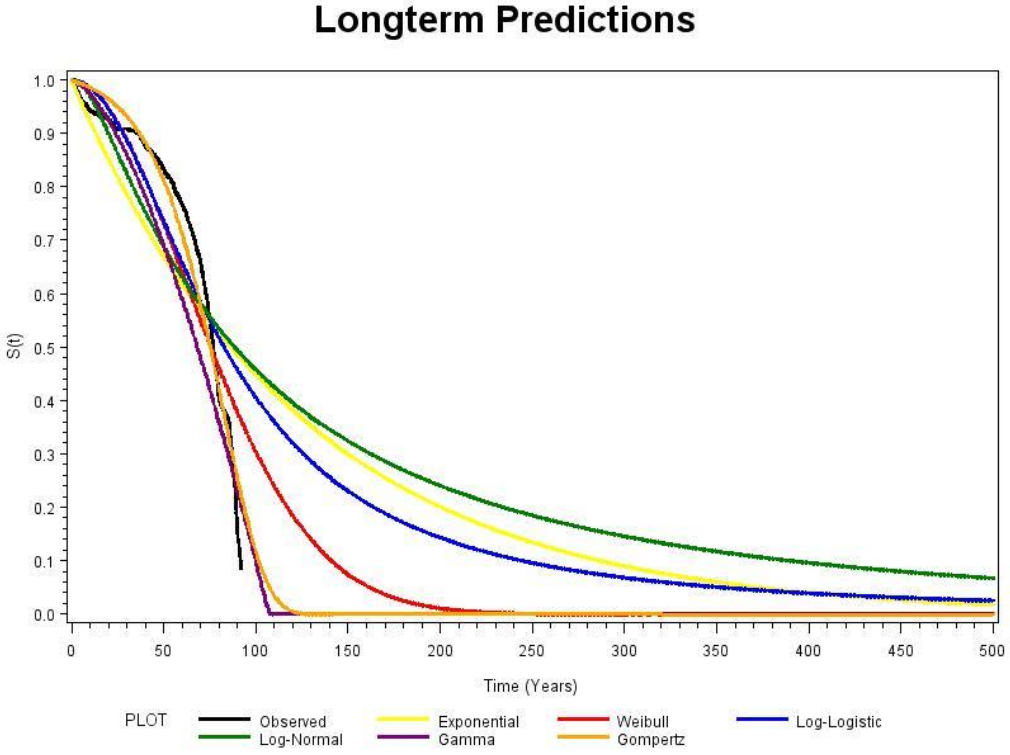

B3. **Priority Question:** Please justify why a parametric curve was fitted to the mortality data, rather than using the mortality rates directly from the lifetables. Please consider presenting an additional analysis to incorporate this simplification.

The intention in using a parametric curve to model mortality data within the model, was to describe as accurately as possible mortality within the Gaucher Type 1 patient. The model has the ability to run mortality based on both parametric curve fitting and lifetables.

For the general mortality, there is an option to use a mortality function or life table that can be selected in the <Settings> worksheet.

The simplest approach to projecting outcomes would be based on the observed rate of the event (expressed in terms of events per person-time); however, this requires an assumption of constant hazard, which is usually too restrictive. A more general approach uses methods for parametric time-to-event analyses. Here, various parametric survival distributions are tested for fit against the data; these include the exponential, Weibull, Gompertz, log-logistic, log-normal, and the generalized Gamma distributions. These distributions cover a broad range of hazard shapes.

B4. **Priority Question:** Please provide further information on the quality of life (QoL) gains associated with oral therapy. Are the QoL gains from oral therapy are likely to be as the result of improved health-related quality of life (HRQoL) or as a result of more general improvements in QoL? If these improvements reflect improvements in HRQoL, please provide evidence on the health gains resulting from oral therapy.

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It is not possible based on the TTO study which estimated the QoL gains associated with oral treatment compared to ERT infusion therapy to determine to what extent this relates to HRQoL although it is noted such infusions may be associated with anxiety and stress which may impact upon health related quality of life. This quality of life impact is sufficiently high to be captured in a TTO study where participants were willing to trade off a period of their remaining life years in order to forego the QoL decrement associated with infusions. In this study the utility valuation of oral therapy compared to ERT infusion was estimated to be 0.12 (n=100).

B5. **Priority Question:** Can you provide a comparative analysis of the EQ-5D data from the ENCORE study, comparing the EQ-5D scores between the treatment arms?

EQ-5D data were not collected in ENCORE.

SF-36 patient level responses at baseline and 52 weeks are used to derive SF-6D according to the methodology described by Brazier, Roberts, and Devrill (2002) Table 1, p.274.

SF-6D patient level scores are used to to derive utilities using weights given by Brazier and Roberts (2004) Table 4, p.856.

Patient level data is aggregated to give trial arm means and standard deviations at baseline and 52 weeks. (Table 17)

Interpretation of SF6D and utility results is consistent with other results from the ENCORE trial with only small differences at baseline and 52 weeks for both imiglucerase and eliglustat treatments.

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Table 17: ENCORE mean SF-6D and utility data for eliglustat and imiglucerase

SF-6D Results and Estimated Utility Using Patients from the Encore Trial (GZGD02607)														
Variable	Imiglucerase							Eliglustat						
	Baseline			52 Week			Mean Difference (%)	Baseline			52 Week			Mean Difference (%)
	Number of Patients	Mean	Std	Number of Patients	Mean	Std		Number of Patients	Mean	Std	Number of Patients	Mean	Std	
sfphys	52	[redacted]	[redacted]	52	[redacted]	[redacted]	[redacted]	105	[redacted]	[redacted]	101	[redacted]	[redacted]	[redacted]
sfrole	52	[redacted]	[redacted]	52	[redacted]	[redacted]	[redacted]	105	[redacted]	[redacted]	101	[redacted]	[redacted]	[redacted]
sfsocial	51	[redacted]	[redacted]	52	[redacted]	[redacted]	[redacted]	104	[redacted]	[redacted]	101	[redacted]	[redacted]	[redacted]
sfpain	52	[redacted]	[redacted]	52	[redacted]	[redacted]	[redacted]	104	[redacted]	[redacted]	101	[redacted]	[redacted]	[redacted]
sfmental	52	[redacted]	[redacted]	51	[redacted]	[redacted]	[redacted]	103	[redacted]	[redacted]	101	[redacted]	[redacted]	[redacted]
sfvital	52	[redacted]	[redacted]	52	[redacted]	[redacted]	[redacted]	103	[redacted]	[redacted]	101	[redacted]	[redacted]	[redacted]
Utility	51	[redacted]	[redacted]	51	[redacted]	[redacted]	[redacted]	103	[redacted]	[redacted]	101	[redacted]	[redacted]	[redacted]

Note: The first six dimensions in the table for SF-6D are derived from SF-36 using the method described by Brazier, Roberts and Deverill (2002). Utilities are derived from SF-6D values using the method described by Brazier and Roberts (2004) .

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B6. **Priority Question:** Please provide the following additional data on the dosing of enzyme replacement therapy (ERT):

- Mean dose of ERT by metaboliser status from the ENCORE trial
- IPD data of weight of patients in the ENCORE and ENGAGE trials

Mean dose of ERT by metaboliser status not provided. There is no rationale for there to be a relationship for ERT and metaboliser status and any observed differences will be incidental. ERTs are not metabolised using the CYP2D6 pathway.

The requested IPD of weight is included in the attached CSR Tables 16.2.4. for ENGAGE and 16.2.4.1. for ENCORE

B7. **Priority Question:** Please comment on whether the dose of ERT therapies is likely to differ according to metabolism status and, if so, why this might be.

There is no reason why ERT dosing should be effected by metaboliser status. ERTs are not metabolised using the CYP2D6 pathway.

B8. **Priority Question:** Please comment on the likelihood of vial sharing of ERT therapies and the shelf life of a vial once it has been opened?

Vial sharing is limited in England because the product is administered and stored in over 90% of cases in the patients home.

The SPC states that from a microbiological safety point of view, the product should be used immediately. If not used immediately, in-use storage and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C - 8°C under protection from light.

B9. **Priority Question:** The submission highlights that dosing in the ENCORE study for ERT is significantly higher than the average dose used in the UK (pg. 141). Please comment on how this may impact on the external validity of the ENCORE trial.

There are two important contextual points to consider when considering the difference in dosing between the ENCORE study and clinical practice in the UK:

- ERT dosing in ENCORE is based on international real life clinical dosing. The ERT dosing in ENCORE was the same as that at which patients had been stabilised on ERT treatment prior to the trial commencement based on the decision taken by clinicians in real life clinical practice. 39 centres in Latin America, US, Canada, Australia, Middle East and Europe participated in this study.
- As outlined on pages 48 and 49 of the submission, recommended dosing for ERTs in the UK Gaucher Disease SOP is related to symptomology with higher dosing recommended for higher risk patients.

The difference between the dosing seen in the ENCORE trial and in UK practice may be for two potential reasons.

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- Firstly, risk / severity of disease may differ between the trial and UK practice. However the evidence provided on pages 142-144 of the submission suggests that the risk / severity of ERT-stable patients in the UK is similar to those in the ENCORE study.
- Secondly ERT dosing may not be as well aligned to risk / severity in UK practice as in the trial. This could mean that the lower doses of ERT seen in clinical practice in the UK compared to the dosing seen in the ENCORE trial may be associated with lower efficacy. It is noted that at least one UK study as outlined on page 42 suggests that there was a substantial number of high risk patients who should need high dose ERT treatment (this study was in a centre which treats approximately 40% of patients in England). If some patients in the UK are receiving lower doses of ERT than recommended for their level of risk / severity it is difficult to estimate the impact of this in reducing the efficacy of their treatments. A similar challenge generally exists in estimating the impact of high non-compliance rates in clinical practice upon drug efficacy relative to that which would be produced if used as recommended.

B10. Please provide further details of the testing regime necessary to determine metaboliser status, including:

- Capacity of UK laboratories to carry out such tests and availability of necessary expertise

- Whether tests have been validated

- Confirmation of how the cost of testing will be borne by the company

Currently, Sanofi Genzyme Europe has contracted a laboratory in Belgium to carry out all the CYP2D6 testing that is likely to be generated in Europe by the introduction of eliglustat to the various markets. LabCorp Clinical Trials Laboratory, Mechelen, Belgium is an ISO and College of American Pathologists accredited laboratory. They use the Luminex xTAG v3 kit which is the only CE-marked CYP2D6 kit currently available.

Should the UK clinicians require a UK service, we have explored using The Doctors Laboratory (TDL) in London as an alternative centralised UK service and have received a quote for their services. TDL hold Clinical Pathology Accreditation (CPA) but are moving over to UK Accreditation Service (UKAS) ISO 15189 in the near future. They, too, would be using the Luminex xTAG v3 kit and easily have the capacity to deal with the likely number of UK requests. TDL has provided satisfactory CYP2D6 testing to Sanofi Genzyme in the past as part of the eliglustat clinical trial programme.

The cost of testing will be borne by Sanofi Genzyme through a package deal, where the service will be provided as part of the purchase price of the product, as outlined in Clause 18.1 of the ABPI Code of Practice.

B11. The economic model includes costs associated with homecare services for delivering eliglustat. Please comment on how eliglustat will be delivered to patients' homes, and how this will work with regard to obtaining prescriptions and patient monitoring.

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Healthcare professional (HCP) writes prescription for patient for eliglustat and sends to Homecare Company that the patient is already receiving current therapy under. Homecare Company (HCC) arranges delivery to patient at either home address or nominated patient address. This delivery could be 1, 2 or 3 months' worth of eliglustat but this would be determined by the HCP/ treating centre/ prescription.

HCC would invoice treating centre as they would have for the patient on imiglucerase and replenish their eliglustat stocks via the normal means with Sanofi Genzyme.

If the above case was for a new Gaucher patient who was not already receiving therapy then the patient would probably receive eliglustat from his/her relevant treating centre whilst the administration of setting the patient up with a nominated homecare company progresses as per the current process for ERT therapies. Once all the administration has been completed (approx. 2-4 weeks) the patient would receive eliglustat as above.

Monitoring – this would be done in hospital and not via HCC.

B12. **Priority Question:** The current estimates of the prevalence of Type 1 Gaucher disease appear to assume that there are no Ashkenazi Europeans in the UK population. Please comment on the likely size of the Ashkenazi Jewish population in England and how this may impact on the estimated size of the Gaucher Type 1 population?

The prevalence of disease and numbers of ERT stable patients and treatment naïve patients who require drug treatment presented in the submission all include Ashkenazi Jewish GD Type 1 patients.

B13. Please comment on the likely impact of excluding mortality from the budget impact model.

The impact of excluding mortality is likely to be small. The average age of treatment naïve patients (adult and children) is estimated to be 21 years old and of ERT stable patients 46 years in England based on the studies presented on page 143 of the submission. The mortality data for GD 1 patients at these ages is low as presented on page 331-332, 0.4% and 0.6% per year.

Similarly, in the HE model presented in the submission indicates that treatment naïve patients receiving eliglustat are 32 and ERT stable are 38, (showing 0.1 and 0.65 deaths per 100 person years based on evidence from page 331 and 332.

B14. Please provide IPD data on the age of participants in the ENCORE and ENGAGE studies?

The requested IPD of age is included in the attached CSR Tables 16.2.4. for ENGAGE and 16.2.4.1. for ENCORE

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B15. On pg. 48 and 49 the company presents evidence on a potential dose response relationship for imiglucerase. Please provide further information on the nature of any dose response relationship.

There is evidence of a dose response relationship for imiglucerase, as such the SmPC refers to imiglucarase dosing as follows:

> "A range of dosage regimens has proven effective towards some or all of the non-neurological manifestations of the disease. Initial doses of 60 U/kg of body weight once every 2 weeks have shown improvement in haematological and visceral parameters within 6 months of therapy and continued use has either stopped progression of or improved bone disease. Administration of doses as low as 15 U/kg of body weight once every 2 weeks has been shown to improve haematological parameters and organomegaly, but not bone parameters."

The UK Gaucher Disease SOP explicitly recommends varying dosing according to a combination of both disease severity (according to platelet count) and to symptomology

The main dosing relationship outlined on pages 48 and 49 of the submission were that in the UK Gaucher Disease SOP it states that:

- Lower starting doses may be considered for mild disease (e.g. platelet count 100-150 X109/L, or mild splenomegaly), while higher doses of up to 60 U/kg every two weeks should be considered for patients at higher risk, including patients with: severe or symptomatic thrombocytopenia, previous osteonecrosis (especially in the context of prior splenectomy), or Gaucher–related liver or pulmonary disease.
- After 12 months of treatment, dose should be reduced, once the patient is stabilised, with ongoing monitoring. A maintenance dose of 15-30 U/kg every 2 weeks is expected to be adequate in most cases although this may be increased incrementally to 60 U/kg every 2 weeks if therapeutic goals are not met within the expected timeframe.

The evidence for such a dosing response with the need for higher dosing for high risk patients or those not reaching therapeutic goals is described within the SPC for imiglucerase and is as follows:

- Under section 4.2. of the SPC describing posology it is stated that "A range of dosage regimens has proven effective towards some or all of the non-neurological manifestations of the disease. Initial doses of 60 U/kg of body weight once every 2 weeks have shown improvement in haematological and visceral parameters within 6 months of therapy and continued use has either stopped progression of or improved bone disease. Administration of doses as low as 15 U/kg of body weight once every 2 weeks has been shown to improve haematological parameters and organomegaly, but not bone parameters. The usual frequency of infusion is once every 2 weeks; this is the frequency of infusion for which the most data are available".
- Under Section 5.2. describing Pharmacokinetics statements are made:
    - The rate and extent of response to imiglucerase treatment is dose-dependent. Generally, improvements in organ systems with a faster turnover rate, such

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as the haematological, can be noted far more rapidly than in those with a slower turnover, such as the bone.

- In an ICGG Gaucher Registry analysis of a large cohort of patients (n=528) with Gaucher disease type 1, a time- and dose-dependent effect for imiglucerase was observed for haematological and visceral parameters (platelet count, haemoglobin concentration, spleen and liver volume) within the dose range of 15, 30 and 60 U/kg body weight once every 2 weeks. Patients treated with 60 U/kg body weight every 2 weeks showed a faster improvement and a greater maximum treatment effect as compared to patients receiving the lower doses.
- Similarly, in an ICGG Gaucher Registry analysis of bone mineral density using dual-energy X-ray absorptiometry (DXA) in 342 patients, after 8 years of treatment normal bone mineral density was achieved with a imiglucerase dose of 60 U/kg body weight once every 2 weeks, but not with lower doses of 15 and 30 U/kg body weight once every 2 weeks (Wenstrup et al, 2007).
- In a study investigating 2 cohorts of patients treated with a median dose of 80 U/kg body weight every 4 weeks and a median dose of 30 U/kg body weight every 4 weeks, among the patients with bone marrow burden score ≥ 6, more patients in the higher dose cohort (33%; n=22) achieved a decrease in the score of 2 points after 24 months of imiglucerase treatment compared with patients in the lower dose cohort (10%; n=13) (de Fost et al, 2006).
- Treatment with imiglucerase at a dose of 60 U/kg body weight once every 2 weeks, showed improvement in bone pain as early as 3 months, decrease in bone crises within 12 months, and improvement in bone mineral density after 24 months of treatment (Sims et al, 2008).

The usual frequency of infusion is once every 2 weeks (see section 4.2). Maintenance therapy every 4 weeks (Q4) (unlicensed dosing, not consistent with licence) at the same cumulative dose as the bi-weekly (Q2) dose has been studied in adult patients with stable residual Gaucher disease type 1. Changes from baseline in haemoglobin, platelets, liver and spleen volumes, bone crisis, and bone disease comprised a predefined composite endpoint; achievement or maintenance of established Gaucher disease therapeutic goals for the hematologic and visceral parameters comprised an additional endpoint. Sixty-three percent of Q4- and 81% of Q2-treated patients met the composite endpoint at Month 24; the difference was not statistically significant based on the 95% CI (-0.357, 0.058). Eighty-nine percent of Q4- and 100% of Q2-treated patients met the therapeutic goals-based endpoint; the difference was not statistically significant based on the 95% CI (-0.231, 0.060). A Q4 infusion regimen may be a therapeutic option for some adult patients with stable residual Gaucher disease type 1, but clinical data are limited.

B16. **Priority Question:** The ERG has noticed some errors in the executable model. Please fix these errors and provide an updated model:

- The AE rate calculations appear incorrect; please check the calculations and amend as necessary

The AE rate calculations have been fixed, this error was based on the VBA code overwriting the inputs. This has been amended by writing VBA code in the worksheet that updates when the AE selection on sheets “Settings” cell “aes.pooled” is selected.

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- There are minor calculation errors on “Results” sheet Cells E125 and E127 (calculation of undiscounted administration and management costs)

The minor errors seen in cells E125 and E127 on the “Results” sheet were a result of values within the patient flow sheet titled “Stable Comp2 Engine” cells CM2 and CO2 referring to the wrong cells, such that the management cost of ERT therapy was being added to the administration cost as opposed to the delivery cost of the ERT therapy being added to the administration cost.

CM2 read:
=SUMPRODUCT($D$5:$D$105,CM5:CM105)+SUMPRODUCT($D$5:$D$105,CO5:CO105)

However CM2 should read:

=SUMPRODUCT($D$5:$D$105,CM5:CM105)+SUMPRODUCT($D$5:$D$105,CP5:CP105)

CO2 read:

=SUMPRODUCT($D$5:$D$105,CP5:CP105)

However CO2 should read:

=SUMPRODUCT($D$5:$D$105,CO5:CO105)

- The patient access scheme (PAS) for ERT does not work properly due to failure to apply the PAS to the costs of ERT for discontinued eliglustat patients

The calculations for the discontinued eliglustat patients located on sheet “Cost Inputs” cells H110 and H112 have been amended to incorporate the PAS discount included. Within the Basecase analysis there was no PAS incorporated to either ERT, and therefore this had no effect on the Basecase results of the health economic model.

All errors acknowledged within health economic model have been amended. These do not affect any of the overall outcomes of the base case cost-effectiveness analysis.

- The budget impact model does not appear to work correctly, possibly due to missing input in cells H84:H85 on the “Budget impact” sheet.

The budget impact model has been updated to include relevant input cells in H82:H83 which represent Genzyme market share data relating to the number of ERT stable patients receiving imiglucerase and velaglucerase.

B17. **Priority Question:** Please present a scenario analysis in which the transition probabilities for the first year are based on extrapolations of the ENCORE data – that is, assuming a constant rate of transition in the first year and extrapolating the 9 month data accordingly.

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The updated transition probabilities which extrapolate the 9 month ENGAGE trial results to 12 months are reported in

Table *18*. The original transition probabilities are reported in Table 19. The results of the health economic analysis are reported in the tables below (Table 19 to Table 25).

Table 18: ENGAGE transition probabilities 12 month transitions (extrapolated from 9 months)

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	12-MONTH TRANSITION PROBABILITY MATRIX									
		ENDING								
		Mild	Mild + Bone Pain	Mild + SSC	Moderate	Moderate + SSC	Marked	Marked + SSC	Severe	Severe + SSC
STARTING	Mild	1.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000
	Mild + Bone Pain	0.000000	1.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000
	Mild + SSC	0.000000	0.000000	1.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000
	Moderate	0.228117	0.000000	0.000000	0.771883	0.000000	0.000000	0.000000	0.000000	0.000000
	Moderate + SSC	0.000000	0.000000	0.000000	0.000000	1.000000	0.000000	0.000000	0.000000	0.000000
	Marked	0.063198	0.000000	0.000000	0.934385	0.000000	0.002417	0.000000	0.000000	0.000000
	Marked + SSC	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	1.000000	0.000000	0.000000
	Severe	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	1.000000	0.000000
	Severe + SSC	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	1.000000

Table 19: ENGAGE transition probabilities 9 month transitions

	NINE-MONTH TRANSITION PROBABILITY MATRIX									
		ENDING								
		Mild	Mild + Bone Pain	Mild + SSC	Moderate	Moderate + SSC	Marked	Marked + SSC	Severe	Severe + SSC
STARTING	Mild	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mild + Bone Pain	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mild + SSC	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Moderate	0.1765	0.0000	0.0000	0.8235	0.0000	0.0000	0.0000	0.0000	0.0000
	Moderate + SSC	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000
	Marked	0.0000	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Marked + SSC	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000	0.0000

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	Severe	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000
	Severe + SSC	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000

Health Outcomes

Table 20: Disaggregated life years

Health state LYs	Versus imiglucerase		Versus velaglucerase	
	Eliglustat	**Imiglucerase**	**Eliglustat**	**Velaglucerase**
DS3: 1	28.82	28.82	28.82	28.82
DS3: 2	5.15	5.15	5.15	5.15
DS3: 3	0.30	0.30	0.30	0.30
DS3: 4	7.55	7.55	7.55	7.55
DS3: 5	0.24	0.24	0.24	0.24
DS3: 6	0.11	0.11	0.11	0.11
DS3: 7	0.09	0.09	0.09	0.09
DS3: 8	0.00	0.00	0.00	0.00
DS3: 9	0.01	0.01	0.01	0.01
Total	**42.28**	**42.28**	**42.28**	**42.28**
Key: DS3, disease severity scoring system; LY, life years.				

Table 21: Disaggregated QALYs

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Health state Lys	Versus imiglucerase		Versus velaglucerase	
	Eliglustat	**Imiglucerase**	**Eliglustat**	**Velaglucerase**
DS3: 1	10.77	10.77	10.77	10.77
DS3: 2	1.70	1.70	1.70	1.70
DS3: 3	0.10	0.10	0.10	0.10
DS3: 4	2.94	2.94	2.94	2.94
DS3: 5	0.07	0.07	0.07	0.07
DS3: 6	0.04	0.04	0.04	0.04
DS3: 7	0.03	0.03	0.03	0.03
DS3: 8	0.00	0.00	0.00	0.00
DS3: 9	0.00	0.00	0.00	0.00
IV disutility	2.43	0.00	2.43	0.00
Adverse events	0.00	-0.01	0.00	-0.02
Total	**18.07**	**15.64**	**18.07**	**15.62**
Key: DS3, disease severity scoring system; IV, intravenous; Lys, life years; QALYs, quality-adjusted life years.				

IM and EM Costs

Table 22: Disaggregated health state costs: IM and EM population

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Health state	Versus imiglucerase			Versus velaglucerase		
	Eliglustat	**Imiglucerase**	**Absolute increment versus imiglucerase**	**Eliglustat**	**Velaglucerase**	**Absolute increment versus velaglucerase**
DS3: 1	£ 2,946,299	£ 3,087,778	-£ 141,479	£ 2,993,238	£ 3,885,005	-£ 891,767
DS3: 2	£ 532,694	£ 558,375	-£ 25,681	£ 541,307	£ 702,171	-£ 160,864
DS3: 3	£ 31,294	£ 32,781	-£ 1,487	£ 31,791	£ 41,122	-£ 9,331
DS3: 4	£ 897,358	£ 938,659	-£ 41,301	£ 909,662	£ 1,185,273	-£ 275,611
DS3: 5	£ 26,082	£ 27,319	-£ 1,237	£ 26,494	£ 34,277	-£ 7,782
DS3: 6	£ 12,057	£ 12,631	-£ 574	£ 12,248	£ 15,860	-£ 3,613
DS3: 7	£ 10,191	£ 10,672	-£ 481	£ 10,351	£ 13,378	-£ 3,027
DS3: 8	£ 282	£ 296	-£ 13	£ 287	£ 371	-£ 85
DS3: 9	£ 969	£ 1,015	-£ 46	£ 984	£ 1,272	-£ 288
Total	**£ 4,457,227**	**£ 4,669,526**	**-£ 212,299**	**£ 4,526,362**	**£ 5,878,729**	**-£ 1,352,367**

Key: DS3; disease severity scoring system; EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser.

Table 23: Disaggregated cost components: IM and EM population

Health state	Versus imiglucerase			Versus velaglucerase		
	Eliglustat	**Imiglucerase**	**Absolute increment versus imiglucerase**	**Eliglustat**	**Velaglucerase**	**Absolute increment versus velaglucerase**
Treatment costs	£ 4,388,685	£ 4,330,992	£ 57,693	£ 4,457,820	£ 5,540,195	-£ 1,082,375
Testing costs	£ 0	£ 0	£ 0	£ 0	£ 0	£ 0
Admin costs	£ 11,619	£ 281,611	-£ 269,992	£ 11,619	£ 281,611	-£ 269,992
Adverse event costs	£ 0	£ 0	£ 0	£ 0	£ 0	£ 0
Direct medical resource use costs	£ 56,881	£ 56,881	£ 0	£ 56,881	£ 56,881	£ 0

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Social services resource use costs	£ 41	£ 41	£ 0	£ 41	£ 41	£ 0
Total	**£ 4,457,227**	**£ 4,669,526**	**-£ 212,299**	**£ 4,526,362**	**£ 5,878,729**	**-£ 1,352,367**
Key: EM, extensive metaboliser; IM, intermediate metaboliser.						

PM Costs

Table 24: Disaggregated health state costs: PM population

Health state	Versus imiglucerase			Versus velaglucerase		
	Eliglustat	**Imiglucerase**	**Absolute increment versus imiglucerase**	**Eliglustat**	**Velaglucerase**	**Absolute increment versus velaglucerase**
DS3: 1	£ 1,569,437	£ 3,087,778	-£ 1,518,342	£ 1,616,375	£ 3,885,005	-£ 2,268,630
DS3: 2	£ 284,112	£ 558,375	-£ 274,263	£ 292,724	£ 702,171	-£ 409,446
DS3: 3	£ 16,878	£ 32,781	-£ 15,903	£ 17,376	£ 41,122	-£ 23,746
DS3: 4	£ 475,055	£ 938,659	-£ 463,604	£ 487,359	£ 1,185,273	-£ 697,914
DS3: 5	£ 14,064	£ 27,319	-£ 13,256	£ 14,475	£ 34,277	-£ 19,801
DS3: 6	£ 6,478	£ 12,631	-£ 6,152	£ 6,669	£ 15,860	-£ 9,191
DS3: 7	£ 5,515	£ 10,672	-£ 5,157	£ 5,676	£ 13,378	-£ 7,703
DS3: 8	£ 152	£ 296	-£ 144	£ 156	£ 371	-£ 215
DS3: 9	£ 524	£ 1,015	-£ 490	£ 540	£ 1,272	-£ 732
Total	**£ 2,372,216**	**£ 4,669,526**	**-£ 2,297,310**	**£ 2,441,350**	**£ 5,878,729**	**-£ 3,437,379**
Key: DS3; disease severity scoring system; EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser.						

Table 25: Disaggregated cost components: PM population

Health state	Versus imiglucerase			Versus velaglucerase		
	Eliglustat	**Imiglucerase**	**Absolute increment versus imiglucerase**	**Eliglustat**	**Velaglucerase**	**Absolute increment versus velaglucerase**
Treatment costs	£ 2,303,674	£ 4,330,992	-£ 2,027,318	£ 2,372,809	£ 5,540,195	-£ 3,167,387

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Testing costs	£ 0	£ 0	£ 0	£ 0	£ 0	£ 0
Admin costs	£ 11,619	£ 281,611	-£ 269,992	£ 11,619	£ 281,611	-£ 269,992
Adverse event costs	£ 0	£ 0	£ 0	£ 0	£ 0	£ 0
Direct medical resource use costs	£ 56,881	£ 56,881	£ 0	£ 56,881	£ 56,881	£ 0
Social services resource use costs	£ 41	£ 41	£ 0	£ 41	£ 41	£ 0
Total	**£ 2,372,216**	**£ 4,669,526**	**-£ 2,297,310**	**£ 2,441,350**	**£ 5,878,729**	**-£ 3,437,379**
Key: EM, extensive metaboliser; IM, intermediate metaboliser.						

B18. Please provide details of how the executable model updates the 1st year transition probabilities in the deterministic sensitivity analysis.

The programming used to normalize the dropped in values is in column H in the Parameters worksheet (see image below). Each set of transitions has its own array that references the entire possibility of transitions (9 states). The array takes the single overridden value and normalizes the rest of the possible transitions.

For example, modifying the transition from state 1 to state 1 from being 80% to 60%, patients in state 1 can only transition to state 4 at a probability of 20%. When we modify that transition from state 1 to state 1, the transition from state 1 to state 4 is normalized to 40%. If a transition previously equaled 0% (state 1 to state 5) before the modification, it will remain 0% regardless of how low the probability of the transition from state 1 to state 1 is. The purpose of the DSA is to test single parameter changes, if one wishes to modify the transition from state 1 to state 1 and move the 20% elsewhere,that is handled through the scenario runner.

Although not applicable given the current values of the trial duration state transitions, the calculation cannot handle a modification of a transition array where 100% of patients transition to a single state.

```
{=IF(COUNTBLANK(F445:F453)=9,G445,IF(NOT(ISBLANK(F445)),F445,IF(SUM(IF(ISBLANK(F445:F453),G445:G453))=0
 SUM(IF(ISBLANK(F445:F453),G445:G453))))))}
```

Section C: Textual clarifications and additional points

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C1. Page 63 states that, for the updated systematic review searches, CDSR and DARE were searched. Please provide the search strategies for these databases.

For the original reviews, a separate search in CDSR and DARE, as described on page 62 of the submission document was conducted outside of the formal review, using the terms:

"gaucher's disease" OR "gaucher disease") OR (gaucher* AND (lysosom* OR intralysosom* OR lipidosis OR glucosidase OR glucocerebrosidase)))

In the updated searches conducted on 14 August 2015, formal searches were conducted in all relevant databases including DARE and CSDR, as described and listed on page 63. The search strategy used for DARE and CDSR in the updates was exactly the same as that used for CENTRAL as described on page 290 of section 17.1.4 (Appendix), although note that this is currently referred to under the broader heading for CENTRAL only.

C2. Please confirm if the searches also looked for trials of imiglucerase vs placebo (or no treatment) and velaglucerase vs placebo (or no treatment), and confirm there no such trials were found.

As described in the search strategies in section 17.1.4 of the company submission, we did not restrict searches by intervention. Also, as detailed in section 9.2.1 of the submission and listed in Table 6, imiglucerase and velaglucerase were two of several relevant interventions. As such, any studies with imiglucerase or velaglucerase (or one of the other relevant comparators) in at least one of the arms were included; as specified in section 17.1.6 (Table 104), relevant comparators were “Placebo or best supportive care or any of the interventions or no treatment.”

No relevant comparator trials were found that compared imiglucerase or velaglucerase with placebo.

C3. **Priority Question:** Please confirm the actual number of patients in the eliglustat group in the ENCORE trial; there appears to be a discrepancy between Table 17 and Table 117.

The per protocol population in the ENCORE trial consisted of 99 eliglustat patients and 47 imiglucerase patients.

C4. Table 23 shows that 5 patients received eliglustat for over 5 years; however, pg. 121 states that 14 patients received eliglustat for over five years. Please confirm which is correct.

There appears to be a typographical error in the table which should read 14 patients received eliglustat over 5 years. However, in checking this response we referred back to the original source of the data and discovered it was actually 19 patients who have received eliglustat for at least 60 months.

Therefore, please note the correct number of 19 patients should be used in the text and the table. The right hand column in Table 117 (Data management, patient withdrawls) consistently reports the n=99 eliglustat patients in line with the value reported in Table 17.

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C5. **Priority Question:** Please provide the Statistical Analysis Plan for the ENCORE trial (missing from the CSR appendix).

The Statistical Analysis Plan for the ENCORE trial has been supplied separately with this response.

C6. Please provide the journal publication for the Pooled safety analysis; the ERG only has the poster presentation and conference abstract (http://dx.doi.org/10.1016/j.ymgme.2013.12.218)

No published journal article exists for this data. A manuscript for the pooled safety analysis is in development and is planned to be submitted for publication by the end of 2016.

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Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: Addenbrooke's hospital Cambridge UK
Are you (tick all that apply):

√ A specialist in the treatment of people with the condition for which NICE is considering this technology

√ A specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None whatsoever: no shares, no family member working in that industry and no prior involvement ever.

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

There are about 300 known patients with Gaucher disease in England (this is substantially less than the prevalence from expected survival and incidence at birth predicted from estimates using different methods published from Portugal, Australia, The Netherlands, The Czech Republic and Austria).

Of these, approximately 30 patients (10%) have type 3 (chronic neuronopathic) Gaucher disease, for whom the drug is not yet licenced and of whom many but by no means all are children, for whom the drug is not yet known to be safe.

I would predict that at least 70% of the adult patients would eventually wish to receive and be eligible to receive eliglustat. About 5% of persons would not be suitable for eliglustat on the basis of the frequency of CYP2D6 genotypes (ultrarapid or indeterminate); young adults who wish to start a family are pregnant or who are breast feeding should not take the drug; and those who need to take, or are taking a range of co-medication which substantially change the bioavailability of eliglustat should not take it.

How is the condition currently treated in the NHS?

In the UK, Gaucher disease is treated at centrally designated Specialist Centres based in England; four were established for Gaucher disease in 1997. There are now eight such centres commissioned by NHS England since 2007, including three in which children are treated and monitored; formal arrangements for transitioning patients from Paediatric to Adult care are long-established. The activities of these expert centres set out in the section below ensure that there is consensus in practice. For this ultra-orphan disease, all specialist centres seek to provide continuity of care with active shared-care arrangements with referring Consultant staff and other practitioners local to and familiar with the patient.

Most patients receive enzyme therapy and a majority receive this biweekly at home, either self-administered or with the help of a visiting healthcare nurse, a relative, partner or spouse. Some travel to their local GP surgery/Health Centre or local hospital for infusions under the care of a local physician with a shared-care arrangement, especially those with disability. Overall the infusion process and set up takes about 2 hours to initiate and conclude. Some patients, particularly when there have been infusion reactions or when they are initiating treatment with a given preparation attend their specialist centre, at least for a period while they acclimate to the infusions and are shown not to develop reactions. Monitoring of the disease is carried out at least every six months in a majority of patients with agreed protocols for radiological review, blood testing and other investigations as well as specialist assessments from associated clinical services, eg orthopaedic surgical consultants who frequently provide key elements of multidisciplinary care.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

Comprehensive treatment of Gaucher disease involves:-

(1) Coordinated interdisciplinary care and monitoring – often employing specialised imaging techniques with genetic and biochemical testing.

This is a multisystem genetic disease accompanied by numerous comorbidities (haematological failure due to cytopenias and coagulopathy; visceral disease; complex and episodic skeletal manifestations, Parkinsonism – and a greatly increased risk of autoimmunity and B-cell proliferative disease with cancers, such as multiple myeloma and B-cell lymphoma.

Specialised interdisciplinary expertise in contemporary radiology, orthopaedic surgery, haematology, biochemistry and genetics, neurology, oncology services as well as organ transplantation may be required.

(2) Specific molecular therapies (orphan medicinal products) – macrophage-targeted enzyme therapy (ERT) and substrate-reduction therapy (SRT).

(a) Enzyme augmentation (often termed enzyme replacement therapy, or ERT) was first introduced for Gaucher disease in 1992 – alglucerase (Ceredase) was a tissue-derived purified human protein. Since then, two EMA-approved recombinant enzyme preparations are licenced for type 1, ('non-neuronopathic') Gaucher disease in Europe and reimbursed by the NHS: the first, available from the early-mid 1990's, was imiglucerase, (Cerezyme – manufactured by Genzyme, now Sanofi Genzyme). Since about 2010-11, velaglucerase alfa (VPRIV – formerly developed by Transkaryotic Therapies, TKT, and now incorporated by Shire) has become available. In the last 4-5 years, the drive for efficiency gains and price competition has promoted the market position of velaglucerase alfa and currently this has become the enzyme therapy of majority use in England.

(b) In 2003, the first orally active agent, miglustat (Zavesca - Actelion), was approved for adults with type 1 Gaucher disease. Although it is a second-line agent for those patients with mild-to-moderate disease unable or unwilling to be treated with enzyme infusions, miglustat was first-in-class with a novel mode of action as a substrate-reduction agent. The drug was designed to rebalance glucosylceramide biosynthesis with the impaired turnover of this glycosphingolipid induced by the primary enzyme defect in Gaucher disease. Miglustat occupies a minor therapeutic position for Gaucher disease and probably less than 10 adult patients with Gaucher disease are currently taking the drug in the UK (to avoid miscounting of sale figures, miglustat is efficacious in Niemann-Pick disease type C and the only drug approved in the EU for this indication). However, in primary and non-inferiority trials versus enzyme therapy, miglustat has modest efficacy in Gaucher disease but its unwanted effects (flatulence, diarrhoea, tremor and peripheral neuropathy) have prevented widespread acceptance.

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Evidence obtained from clinical trials indicates that eliglustat, with greater specificity and potency directed towards the molecular target for SRT (uridine diphosphate-glucose: N-acylsphingosine transferase), meets criteria for safety, tolerability and efficacy, meriting approval as a first-line drug for adults with type 1 Gaucher disease.

Is there significant geographical variation in current practice?

Geographical variation in practice is not significant in the England (or the UK). Please see below for more information, explanation and perspective.

National Guidelines are in place for the diagnosis, treatment and monitoring of all patients with Gaucher disease; these are regularly reviewed and discussed at meetings of the Lysosomal diseases group with designated experts. While there is a strong commitment to individualized therapy based on clinical dialogue and patient choice as well as response measures, agreed protocols for therapy ensure that clinical practice is built on a strong consensus and there is little material variation across England and the UK in principle. Consensus development for the best principles of international clinical practice is also furthered at biennial meetings of the independent European Working Group for the study of Gaucher disease (EWGGD). Active involvement of the UK Gauchers Association (as well as the European Gaucher Alliance) ensures that individual practices are maintained in a mode of responsiveness to patients' needs and expectations. Advanced development of these activities ensures that within England, the UK and Europe, there is generally little geographical variation. This principle relates to the two approved enzyme therapies in Europe (administered parenterally) and, including eliglustat, two approved substrate-reduction therapies (given orally).

Are there differences of opinion between professionals as to what current practice should be?

Not appreciably in relation to enzyme therapy. It is possible that one or other institution may have a bias towards drugs manufactured by Shire and in the current climate where an appreciable cost-incentive exists, all centres are encouraged to transfer patients to velaglucerase alfa this might serve as a temporary brake on uptake of an oral drug from a competing manufacturer. Apart from cost considerations, there is no definitive evidence that one or other of the two EMA-approved enzyme therapies has any intrinsic advantage.

As to eliglustat, if NICE were to provide a positive recommendation, I suggest that the will of patients – their expressed desire for a safe and tolerable first-line orally active drug will rapidly drive adoption of the agent in the UK - indicates that there will be a steady and quite rapid transfer to eliglustat for those patients in whom the agent is indicated.

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What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Eliglustat is an orally active drug approved as a first-line therapy for adults with type 1 Gaucher disease: the only comparable alternative is miglustat, which is a second line agent for those unwilling or unable to receive enzyme therapy (Cox TM, Aerts JMFG, Andria G et al (2003) The role of the iminosugar N-butyldeoxynojirimycin (miglustat) in management of type 1 (non-neuronopathic) Gaucher disease: a position statement. J Inherit Met Dis 26: 513-526).

Advantages of an oral therapy:

These will be attested from the viewpoint of patient choice and preference. Intravenous enzyme therapy is an undoubted burden and a financial cost whether delivered at home or in hospital. Infusions and venepuncture are painful as well as inconvenient (irrespective of whether this is addressed in part by provision of home therapy by NHS providers in specialist centres). Intravenous therapy carries with it a risk of developing needle-phobia, poor venous access through damaged veins and impaired compliance; there is a small risk of septic infection.

As to miglustat, very few patients are genuinely unable or unwilling to receive enzyme therapy with either of the available recombinant enzyme products when rapid control of the disease (debulking) is required after diagnosis. Later, however, after years of effective therapy, the inconvenience, minor pain and low self-esteem (and sometimes troublesome venous access or lifestyle factors usually linked to accommodation, travelling and occupation) associated with biweekly infusions becomes an increasing burden. Here miglustat proved often a disappointment or not well tolerated, even in the pivotal clinical trial situation (Cox T, Lachmann R, Hollak C, et al. Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. Lancet 2000; 355: 1481–85., and as the non-inferiority study showed in relation to short-term switching of patients stabilised on imiglucerase (Cox TM, Amato D, Hollak CE, et al. Evaluation of miglustat as maintenance therapy after enzyme therapy in adults with stable type 1 Gaucher disease: a prospective, open-label non-inferiority study. Orphanet J Rare Dis 2012; 7: 102). Miglustat occupies a minor therapeutic position for Gaucher disease and probably less than 10 adult patients with Gaucher disease are currently taking the drug in the UK (to avoid errors related to sales figures, miglustat is approved for Niemann-Pick disease type C).

Enzyme therapies are effective treatments but the burden of fortnightly infusions is unpleasant and inconvenient for patients. In addition to the physical pain and risk of bruising, tissue infiltration, infection and hypersensitivity, there are accompanying psychological complications from long term intravenous therapy. Patients report a feeling of "medicalization" that makes them feel "different" from their peers. They experience a reduction in their self-esteem and describe changes in the family dynamics as a result of the stress/responsibility of regularly obtaining venous access. Treatment necessitates regular visits to hospital or a nurse visiting at home as well as the need to wait in for cold chain medication deliveries - all of this results in time away from work on a regular basis. Difficulties with cannulation can lead to needle-

phobia and this fear has to be faced every two weeks with many patients describing the dread they feel in the days before their infusion is due.

Currently both intravenous and oral therapies are dispensed to patients using a homecare service. This service is provided under a national framework agreement negotiated by the commercial medicines unit, along with other enzyme therapies for related disorders. Whilst different levels of service provision are available to meet patients' individual needs, on average the price for a patient receiving enzyme replacement therapy is £500 per 4 weeks where as the price for delivery of the oral agent is approximately £35 per 4 weeks (details can be provided upon request).

Where the therapy can be delivered at home, as in the UK with NHS support, the patient experience and quality of life is improved. Oral miglustat was prescribed to patients in whom cannulation was difficult or impractical and in those with infusion reactions. In the event, however, despite initial enthusiasm the drug was often rejected by patients or failed because of tolerability and safety concerns – it also has poor efficacy, which in a retrospective study was not comparable to enzyme therapy (Kuter DJ, Mehta A, Hollak CE, et al. Miglustat therapy in type 1 Gaucher disease: clinical and safety outcomes in a multicenter retrospective cohort study. Blood Cells Mol Dis 2013; 51: 116–24).

In relation to eliglustat rather than miglustat, evidence has been obtained in clinical trials conducted with several hundred patients with Gaucher disease in nearly 20 countries over 8 years. This agent, has much greater specificity and potency directed towards the molecular target for SRT than miglustat (uridine diphosphate-glucose: *N*-acylsphingosine transferase) the first committed step in glycosphingolipid biosynthesis. In phase 2 and pivotal phase 3 studies, eligustat meets the criteria of safety, tolerability and efficacy that justified its approval by the FDA and EMA as a first-line drug for adults with type 1 Gaucher disease (Lukina E, Watman N, Dragosky M, et al. Eliglustat, an investigational oral therapy for Gaucher disease type 1: phase 2 trial results after 4 years of treatment. Blood Cells Mol Dis 2014; 53: 274–76; Mistry PK, Lukina E, Ben Turkia H, et al. Effect of oral eliglustat on splenomegaly in patients with Gaucher disease type 1: the ENGAGE randomized clinical trial. JAMA 2015; 313: 695–706; Cox TM, Drelichman G, Cravo R et al. Efficacy and safety of eliglustat compared with imiglucerase in Gaucher Disease type 1 stabilised on enzyme therapy. Lancet 2015; 385(9985): 2355-62).

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

Gaucher disease is notoriously diverse and GBA1 mutation analysis only provides a guide to clinical behaviour. At least three sets of twins, two proven monozygotic twin-pairs, have been reported with discordant manifestations and which so far have defied facile explanation. It is well known that patients with early-onset of clinical manifestations; those with established bone disease, and those whose disease has been treated by splenectomy to improve health and rescue them from the consequences of hypersplenism and cytopenias, have a greatly increased frequency of osteonecrosis. This latter painful and disabling complication is temporarily related

to the splenectomy procedure (Deegan, PB, Pavlova EV, Tindall, J et al. Osseous Manifestations of Adult Gaucher Disease in the Era of Enzyme Replacement Therapy. Medicine (Baltimore) 2011; 90: 52-60).

Other specific subgroups: (i) Those with poor or absent venous access and needle phobia who attend infrequently may need intensification of their care but have been put off by the need for enzyme therapy. (ii) Those (fortunately rare) who develop strong and persistently high antibody titres and/or infusion reactions to enzyme preparations. (iii) Some patients, about 30% with type 1 Gaucher disease, develop monoclonal gammopathy which is a risk-factor for the eventual development of multiple myeloma. This cancer can develop in patients who are receiving enzyme therapy (iv) Patients with cardiovascular and pulmonary manifestations of Gaucher disease. Macrophage-targeted enzyme therapy is not taken up by the expanded populations of pathological alveolar macrophages and a systemically active small molecular inhibitor of glucosylceramide biosynthesis is likely to have critical salutary effects in this life-threatening complication (v) Patients with type 1 Gaucher disease and Parkinsonism: their disability renders home care and independence from hospital services for infusions is particularly difficult and may lead to premature cessation of Gaucher-specific therapy.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

All of the above sub-groups of patients should enjoy the potential at least of enhanced benefit from the availability of this technology (eliglustat). In subgroup (iii) there may be important salutary effects not hitherto predicted on the development of cancers – now a leading cause of death in patients with non-neuronopathic Gaucher disease. This may prove to have a strong therapeutic advantage beyond the availability of a convenient oral treatment.

Prevention of the malignant complications of Gaucher disease, would provide more than niche value for the new technology (Hughes DA, Pastores GM. Eliglustat for Gaucher's disease: trippingly on the tongue. Lancet online March 26, 2015 http://dx.doi.org/10.1016/S0140-6736(15)60206-9). These findings are supported by evidence from studies in experimental mice in which of eliglustat prevents development of monoclonal gammopathy, lymphoma, and myeloma in mice with this model of type 1 Gaucher disease (Pavlova EV, Archer J, Wang S, Dekker N, Aerts JMFG, Karlsson S, Cox TM. Inhibition of UDP-glucosylceramide synthase in mice prevents Gaucher disease-associated B cell malignancy. J Path 2015; 235:113-24). While the effect was convincing with early administration of the drug to older affected mice still reduced lymphoid proliferation. The data have been confirmed and extended recently by studies in patients with myeloma and monoclonal gammopathy related to Gaucher disease: here the M-bands were shown to represent antibodies directed towards Gaucher-related glycosphingolipids which were also partially suppressed by eliglustat in a closely similar murine model of Gaucher disease (Nair S, Branagan AR, Liu J, Boddupalli CS, Mistry PK, Dhodapkar MV. Clonal immunoglobulin against lysolipids in the origin of myeloma. N Engl J Med 2016; 374: 555-61).

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What is the likely impact of the technology on the delivery of the specialised service?
The predicted widespread acceptance of the agent in the adult population of patients with Gaucher disease in the UK who attend the specialist Centres in England will reduce much of the exceptionally demanding administrative work and some minor costs associated with intravenous infusions at every location.

It will provide a more incentivized service offering greater patient choice with authentic clinical advantages and improved life-quality for Gaucher patients of all adult ages. Eliglustat is generally safe and well tolerated: its appeal for patients is very clear. In a switch trial, after stabilizing their disease for an average of 10 years on enzyme therapy at screening >160 patients, 94% in both treatment groups indicated a preference for oral treatment.

Eliglustat is a potent agent with an innovative and specific mode of action: there are indications of greater selectivity and preferential effects on some systemic features of the disease, especially the near-intractable and disabling effects on the skeleton. These make a large call on the service for premature joint replacement surgery, the accompanying expert haematological support and risky, as well as taxing revision procedures in young persons.

If NICE delivers the predicted recommendation this will restore the leading position of the service at the forefront of clinical research into a disease which provides a unique window on other conditions of more general clinical burden, including multiple myeloma - the second most frequent haematological cancer.

Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?

These are likely substantially to be reduced: an EMA approved reference centre for the CYP 2D6 predictive genotyping has already been established by the company for approved use. At present Sanofi Genzyme intend to provide this service, however arrangements in the long-term need to be established.

If the technology is already available, is there variation in how it is being used in the NHS?

After approval by EMA, continuing access to eligustat has been available to the few NHS patients attending National centres for the management of Gaucher disease treatment and who have participated in clinical trial programmes. The drug is also being made available to a few patients as part of an extended use or compassionate access programme where investigators have been able to make a convincing request successful against innumerable competitive requests for the drug without charge, worldwide (see response in next section, below).

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Is it always used within its licensed indications? If not, under what circumstances does this occur?

Eliglustat, approved by the FDA and EMA, is not currently available through the NHS.

Patients with saposin C deficiency (an exceptionally rare deficiency of a key cofactor required for lysosomal β-glucosylceramidase activity in situ) are eligible, and a young mother with this condition and massive visceromegaly that is not expected to respond to enzyme therapy has this indication.

Two further patients at our centre who represent long-term failures of miglustat maintenance therapy (one with peripheral neuropathy and no venous access due to thrombosed central cannulae, and another international traveller with deteriorating disease parameters and blood counts) are also candidates. The former, already receiving the drug on compassionate grounds is making excellent clinical progress from an otherwise disabling and intractable position.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used

1. As stated, National Clinical Guidelines are available for the management of Gaucher disease including the use of miglustat; these have been developed iteratively by experienced specialists in the Gaucher centres (UK National Guidelines for Adult Gaucher Disease: P Deegan, D Hughes, A Mehta, TM Cox). They are reviewed at intervals by the Specialised Services team (formerly National (Specialist) Commissioning Group) in committee at National Meetings and the Expert Advisory Group of the Lysosomal Diseases Consortium chaired by Dr EG Jessop.

2. A paper entitled 'Management goals for type 1 Gaucher disease: a consensus document from the European Working Group on Gaucher Disease' by M. Biegstraaten and numerous international investigators, including the author of this report, has been developed for current submission from the European Working Group on Gaucher disease (EWGGD). This publication represents the use of a more formal method based on the modified Delphi procedure among experts to reach consensus on management goals. All members of the EWGGD were invited to participate. Based on a literature review and with input from patients with Gaucher disease, 65 potential management goals were rated on a 5-point Likert-scale as to whether a specific statement merited inclusion. Consensus was taken when 75% of the participants agreed and none disagreed. Three survey rounds were needed consensus. The experts reached consensus on 42 short-term and long-term management goals. In addition to the traditional goals concerning haematological, visceral and bone manifestations, improvement in quality of life, fatigue and participation in social activities, and early detection of long-term complications or associated diseases are now included.

3. In relation specifically to the new methodology, ie. eliglustat, clinical guidelines are internationally based but with strong representation from the UK. 'Management and Monitoring Recommendations for the Use of Eliglustat in Adults with Type 1 Gaucher Disease in Europe' have been developed over a period of 15 months by the senior author (chair) and 14 other clinical experts in face-to-face and other discussions with physicians from 8 countries. This manuscript has been submitted for publication to the European Journal of Clinical Pharmacology. All those involved have had extensive experience of the drug and are aware of its characteristics through experience with clinical trials and subsequently. Before undertaking the role as Senior Principal Investigator of the Phase 3 clinical trial ENCORE, I was a member for about 5 years of the independent international safety monitoring committee for Genz 112638 (eliglustat). While the deliberations of this committee were supported by Sanofi Genzyme, the company played no material part in directing the content, offering instead a facilitating role.

These guidelines were developed over a longer time than those now recently published for USA practice by Balwani et al with a few material differences related to prescribing practices and healthcare and lack of specialist provision in the North American setting (Balwani M, Burrow TA, Charrow J, Goker-Alpan O, Kaplan P, Kishnani PS et al. Recommendations for the use of eliglustat in the treatment of adults with Gaucher disease type 1 in the United States. Mol Genet Metab. 2015. doi:10.1016/j.ymgme.2015.09.002). As to the appropriateness of such guidelines, their mandate and values follow the precepts set out in the Journal of the American Medical Association (May 11, 2011, Vol. 305, No. 18), The article addresses some of the eight recommendations in an Institute of Medicine paper where providing "trustworthy guidelines" is considered important to society related to the Institute of Medicine's two reports creating standards for guideline development.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the

trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The outcomes of the clinical trials contain key information of clear relevance to the UK population of patients in the NHS. Tolerability and other aspects of patient-reported outcomes were also collected as well as essential disease-related parameters including bone mineralization density, bone marrow radiology visceral volumes and haematological indices. Widely accepted biomarkers were also included and the rapid changes in their expression are highly supportive of specific biological effects but are not essential solely to the clinical efficacy outcomes.

Patient preference and convenience is personally familiar after 20 years of experience of introducing oral substrate reduction therapy into the clinic. As an example, at screening for the pivotal non-inferiority trial, ENCORE, 94% of the >160 patients expressed a preference for oral therapy. At 12 months, this preference was confirmed in all eliglustat patients who responded to the survey and the most frequent reasons cited for preferring oral treatment were: convenience, capsule formulation, availability at home, feeling better. After treatment after 24 months, 91% of the enrolled patients continued on eliglustat. These figures reflect the real-world of practice of Gaucher disease in the NHS.

What is the relative significance of any side effects or adverse reactions?

Continuous adverse-event reporting (severity, seriousness, treatment-relatedness) and physical examination together with scheduled laboratory and detailed electrocardiographic evaluations were collected. Cardiac effects, including arrhythmia were monitored because of modest cardiac conduction effects seen in early animal studies at high dose.

Attention was also paid to the development of peripheral neuropathy (a severe painful and intractable axonal neuropathy is associated with miglustat) and it was necessary to determine whether any class effect would be observed with agents (technologies) that have effects on glycosphingolipid biosynthesis. This did not occur with eliglustat but was clinically outspoken in 2 or 3 of the original 22 patients in the pivotal trial with miglustat. One patient with subclinical peripheral neuropathy took eligustat with no adverse clinical effect.

In the large multinational ENCORE phase 3 study, data from 507 patient years of exposure to the drug are now available. Adverse event withdrawals (three during 12-month primary analysis, nine during the prolonged extension. 11/12 withdrawals occurred during the first 18 months of eliglustat treatment; 8/12 during the first 12 months. Only 4/12 withdrawals were due to adverse events considered possibly or probably related to eliglustat, including a serious event of a malignant hepatic neoplasm, later shown to have been present in the liver before exposure to the drug.

In what ways do these affect the management of the condition and the patient's quality of life?

No consistent serious unwanted effects were identified that materially affect management beyond the potential interactions and cardiac toxicity that would result from prescribing inappropriate co-medication sharing metabolism by CYP 2D6 or in patients predicted by genotyping to be indeterminate or ultra-rapid metabolizers.

Thus management relates principally to communication and advice with appropriate monitoring and patient engagement and the conduct of predictive CYP 2D6 genotyping at an approved genetic testing facility in advance of prescription.

Since the drug is well tolerated, quality of life will in most cases not be materially reduced except in unwell patients who require numerous co-medications and whose medical advisers are not suitably informed or cognizant.

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

None so far to my intimate knowledge at the time of writing (10 April 2016).

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence?
Apart from published work in long-term phase 2 studies, tolerability safety and efficacy data are now available from the four-year follow-up of the ENCORE switch trial trial: oral eliglustat in patients with Gaucher disease type 1 stabilized on enzyme therapy. A manuscript is in early preparation but the findings have been the subject of a recent presentation (WORLD meeting March 2016). In long-term analysis evaluated from: Phase 2 trial in treatment-naïve patients (NCT00358150, N=26); ENGAGE, a randomized, placebo-controlled Phase 3 trial in treatment-naïve patients (NCT00891202, N=40); and ENCORE, a Phase 3 imiglucerase-controlled trial in patients previously stabilized on ≥3 years of enzyme replacement therapy (NCT00943111, N=159). Primary endpoints were met in all 3 trials (Lukina Blood 2010; Mistry JAMA 2015; Cox Lancet 2015). Eliglustat was generally well-tolerated and no new long-term safety concerns were identified. Clinical stability by both composite and individual measures was maintained in Gaucher patients who remained in ENCORE for up to 4 years.

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Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Given the established set-up and National Highly Specialised Centres for the management and treatment of Gaucher disease and cognate lysosomal diseases, if NICE recommended adoption of this technology (ie. the drug, eliglustat), the overarching principle of long-term disease management and clinical monitoring for this disease with prescribing by physicians with experience of the disease should not change. Beyond what will be needed transiently at any national launch of eliglustat, patients will need to be informed of the importance of these aspects and in accepting co-medication from non-expert physicians treating them for other conditions. Thus the role of the specialist centres will be of paramount importance.

Only modest training reinforcement will be needed during the time of a putative drug launch: given the general level of engagement by NHS experts and clinical staff in the community which provides highly specialised care for Gaucher disease, safe uptake and facile introduction of the drug is highly likely.

Introduction of eliglustat would involve minor reinforcement and instruction to specialist nursing staff of the mode of action, pharmacological properties and pharmacokinetics. The two main adult centres in England have been involved in clinical trials of the drug and thus most relevant specialist nursing staff and physicians are fully apprised of the prescribing requirements. Clear practical advice for prescribing eliglustat is available and carefully reviewed European guidelines have been submitted for publication. Sanofi Genzyme provides centralized advice on the possible adverse interactions of the agent with other co-prescribed drugs and over-the-counter medicines (due to interactions with common cytochrome P450 pathways).

However, compared with the prior technology enzyme infusions, compliance with eliglustat therapy is likely to be increased. Beyond the greatly enhanced convenience and liberation of the patients' lives as a result of an oral treatment, there would be a major clarification and modest *reduction* of some costs and workload to the NHS and at the centres. The anticipated reduction in administration of homecare would allow existing nursing and clinical staff to focus on managing the co-medication

requirements and improve the psychological care and transition management for patients with this chronic disease.

This shift would apply to the organization of both hospital-centred and home therapy – including nursing and transportation services for fortnightly infusions, as well as the delivery of infusion apparatus, saline, needles and related appurtenances. Patients receiving eliglustat would no longer need to have specific deliveries in place for refrigerated storage of enzyme vials (in practice, mostly in their homes) and other costly arrangements hypothecated to them before reconstitution and intravenous administration of their life-long treatment.

As cited above, patients expressed a strong preference for this orally active drug. It may be relevant to add that the long-term phase 2 trial patients and 4-year safety and efficacy data now available from the principal phase 3 clinical trial (ENCORE), continuing use, as well as emerging 'real world' safety experience in the USA and European countries, in which the drug is already reimbursed, has been favourable.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which eliglustat is/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

A minority of adults (~5%) will not be suitable to receive eliglustat on grounds of efficacy or safety on account of their predicted metabolizer status (ultra-rapid or indeterminate metabolisers).

The drug has not so far been tested in children. Some adults with long-standing medical conditions and those who will be taking medication incompatible with eliglustat or who are not compliant with monitoring will be unsuitable for the agent. The matter of exclusion of children from access to eliglustat is appropriate and prudent: as a systemically active drug affecting an essential biochemical pathway, its safety in immature and growing humans must be demonstrated before approval. Any temporary inequality will ultimately be addressed by the mandatory paediatric clinical trial programme promulgated by the EU and to which the manufacturer will have been required to commit.

A minority of otherwise eligible patients, who are either predicted to be ultra-rapid or indeterminate metabolisers of eliglustat by CYP 2D6 genotyping, or compulsorily receiving or likely to need interacting drugs long-term that would be unsafe in combination with eliglustat, may be denied the drug on proper medical grounds. This

cannot be regarded as discrimination and any disadvantage may be met either by enzyme therapy or prescription – or, technically if appropriate, miglustat.

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Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: [redacted]

Name of your organisation: Gauchers Association Ltd

Brief description of the organisation:

The Gauchers Association was formed in 1991 to meet the needs of those suffering from Gaucher disease. The Gauchers Association is the only organisation in the United Kingdom that provides information and support to those with Gaucher disease, their families and healthcare professionals.

The Association aims:
• To support families and carers and ensure all individuals with Gaucher diseases have access to best practice in diagnosis, treatment and care.

• To provide information on Gaucher disease and raise awareness of this rare disease.

• To promote research into the causes, effects and treatments of Gaucher disease.

• To represent the interests of Gaucher patients at all times to ensure that the voice of the Gaucher patient is heard.

The Association is aware of 293 Gaucher patients (adults and children that have Types 1, 2 and 3 Gaucher disease) in the UK and 17 patients in All Ireland in 2016, thus making a total of 310. This information is collated from the eight treating centres in England, Wales and Scotland and through our All Ireland Advocacy Support Worker. The Gauchers Association is in contact with 236 patients from England, Wales, Scotland and All Ireland, thus representing 76% of the total UK Gaucher patient community.

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The Association is in regular communication with all patients registered on our membership database via e-mails, our bi annual newsletter, Facebook and news feeds. The Association has an annual membership fee of £15; patients who do not pay their annual subscription continue to receive our newsletter and can access our advocacy service without prejudice.

The Association is funded through a variety of different sources, these include; annual membership fees, members' fundraising activities, charity events, individual donations, trusts and grant giving organisations and unrestricted educational grants from a number of pharmaceutical companies involved in the area of Gaucher disease.

The Association is based in Dursley, Gloucestershire. The Association originally based in London was transferred to Gloucestershire, to the home of the Executive Director in 2005 and moved into its own offices in September 2011. The Association employs a part time Chief Executive, a Charity and Information Officer, a Patient and Family Support Worker and in April 2015 appointed an administration assistant for 10 hours a week. The UK Gauchers Association offices are also home to the European Gaucher Alliance (EGA), an umbrella organisation of 42 member countries supporting Gaucher patients globally.

Are you (tick all that apply):

- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc.) – **I am the Chief Executive of the UK Gauchers Association**

How does the condition impact on patients, their families or carers?

1(i). Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition and the impact these difficulties have on patients and their families or carers.

Diagnosis:
Prior to the availability of treatment and the establishment of the Gaucher centres (see below in Treatment section), patients experienced a vast range of diagnosis journeys.

Research (online monkey survey) undertaken with our members to support this patient submission reported that the most common symptoms that led to their final diagnosis were bone pain, discovery of a large liver and/or spleen on physical examination often for other ailments, on-going fatigue, nose bleeds and bruising. The initial diagnosis of leukaemia or lymphoma is a common story in Gaucher patients, until further testing is carried out.

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Patient Research;
In 2013 the Gauchers Association supported Shire to commission a research study through a third party to explore the patient journey in detail, from initial symptoms until final diagnosis to identify how they could in the future target resources to help healthcare professionals to identify Gaucher disease symptoms in a more timely manner, and thus help patients receive an earlier diagnosis.

Results from this study were taken from 22 Gaucher patients in the UK, from a good geographical spread.

Looking back patients reported the initial signs of Gaucher disease as bleeding, bruising, bone pain and fatigue, often from a young age.

Initially the majority of patients presented to a GP and were under their care before any referral, the time ranged from 1-2 years (9% of patients interviewed) to 11+ years (18% of the patients interviewed). On average patients reported seeing 3-4 different healthcare professionals before being diagnosed. Only 1 patient reported being diagnosed with gaucher disease by the first healthcare professional seen.

The study showed that the mean time between symptoms and diagnosis was approximately 7 years, ranging from 1 month to 31 years. Only 9 patients reported their diagnosis within a year of initial symptoms.

The impact these difficulties have on patients and their families or carers;
Prior to treatment doctors managed patients' symptoms and patients report having to cope daily with often debilitating pain and fatigue and accepting that they had to adjust their lives accordingly in terms of their employment choices, the ability to socialise, whether to have children and in a number of cases were significantly limited and dependent on others for daily tasks.

Patients diagnosed more recently with Gaucher disease, since the establishment of the 8 specialist centres in England, report a shorter smoother diagnosis journey although the Association is aware of individual cases where patients have experienced periods of delay in receiving a final diagnosis or not being aware that there is a treatment as they have been managed by their GP and not referred to one of the specialist centres.

Patients with Gaucher disease face the challenge that they have an invisible disease and from the outside they look normal; they do not have a visible disability, except for a handful of older patients that use a wheelchair or walking aids. This results in patients experiencing difficulties in accessing the care, support and services they need. For example benefits and employment support i.e. rest breaks, reduced working hours, time off for appointments and treatment.

The way that patients deal with the impact of their diagnosis is vast ranging. Whether there is a short period between the initial visit to a clinician and the final diagnosis or a much longer one, the intervening period is inevitably one filled with extreme anxiety and stress for both the patients and their families as symptoms prior to diagnosis can be severe and with the availability of internet search engines many patients inevitably reach the conclusion of an incorrect self-diagnosis of cancer.

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Patients who are picked up through other illnesses or routine tests report shock being labelled with a chronic condition requiring lifelong treatment. However finding out about the treatment centres and being able to get treatment if they meet the treatment guidelines helps them to be more positive about their future. Patients diagnosed before the availability of treatment report a variety of feelings ranging from "just getting on with it" to being very depressed, having an unknown future, a poor quality of life and severe disease manifestations that impact on their day to day lives.

The diagnosis of children with Gaucher disease is devastating, whether picked up through routine testing or due to the child being very sick. Learning that a child has a rare genetic condition that has been passed on by the parents leaves the parents feeling guilty and the anxiety of the child's future health, life expectancy and quality of life are all areas that require careful handling and ongoing support from doctors, nurses and patient advocates. This is an area where close collaborative working amongst the specialist centres and the Gauchers Association can make a huge difference in the families' lives through face to face meetings, linking up with other families, sharing patient stories and attending patient meetings.

Patient quotes from Shire's research study in 2013:

"It was only once I got in touch with the Gaucher Association that I felt I had the information and support that I needed. Luckily there was not a long period between diagnosis and my contacting the Gaucher Association, but there could have been ***Patient diagnosed 1997"***

"The journey was what it was and in some ways a degree of "ignorance" in the early years when I was relatively fit may have been a protection - I cannot second guess what might have been the effect on my psychology of greater knowledge earlier…The one major factor that impacts anyone dwelling on this aspect of the lottery of genes and outcomes is having a compassionate specialist unit and Association to refer to, who both know intimately the effects on one's life and family of this genetic condition ***Patient diagnosed 1984"***

Even today there is still little known about the correlation of genotype/phenotype which is hard for patients as they do not know how their disease will manifest as they get older which brings uncertainty and anxiety about their future health and life expectancy. There is ongoing research in this area for both type 1 and 3 patients to look at the role of modifier genes and individual genome analysis, which may provide vital information relating to disease severity.

Treatment:
Our patient population fall into two categories, those that were diagnosed and lived with the disease before treatment was available and those diagnosed since treatment has been available.

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Of the members that participated in the online monkey survey in 2014 that the Association undertook to support this patient submission 60% of them (a total of 39 members who completed the survey) were diagnosed before the availability of treatment in the early 1990's. Patients diagnosed before the availability of treatment report having to take time off work due to illness, fatigue, bone pain, reduced mobility and depression. Of the patients in wheelchairs (approximately 12) and using walking aids (approximately 12), the majority of these patients were diagnosed before the availability of treatment and have suffered irreversible bone involvement. Patients diagnosed after the availability of enzyme replacement therapy and substrate reduction therapy report a different story with a significant improvement in their quality of life, being able to work, have a family, participate in outdoor and sporting activities (although in the majority of cases they were only able to do this after a period of time in consultation with their doctor).

Treatment for Gaucher disease has existed since 1991, although was not available in England until it was licensed and the Department of Health gave approval for its use in the treatment of Gaucher patients in 1994. Prior to its licensing, some Gaucher patients were prescribed treatment on an individual basis by their local primary care trusts.

Despite treatment being made available on an individual patient basis in 1992, patients and their families faced significant challenges in accessing funding through local primary care trusts due to the high cost of the treatment and the lack of knowledge of the disease.

In 1997, following much lobbying by the Gauchers Association and a handful of clinicians with an interest in this rare disease, the Department of Health granted special funding to establish three (one adult and two paediatric) Gaucher centres and then a fourth (adult centre) in 1998 to oversee the management of patients with Gaucher disease. Subsequently in 2005 central funding was approved for the treatment of Gaucher disease and other Lysosomal Storage Disorders and today there are eight specialist centres in England that look after Gaucher patients (three paediatric and five adult).

Since the development of the first enzyme replacement therapy (ERT) for Gaucher disease in 1991, two other ERTs have been developed, although one is not available in England as it was not approved for licensing by the European Medicines Agency (EMA). In addition one oral substrate reduction therapy (SRT) is licensed for mild to moderate type 1 patients for whom ERT is unsuitable.

The eight specialist treatment centres in England work collaboratively with patient groups and commissioners from the Department of Health and have developed treatment guidelines for adult and paediatric Gaucher patients. These guidelines support patients and the doctors to assess which patients are suitable for treatment. Patients who are asymptomatic and who do not receive treatment are still regularly monitored by the treatment centres.

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Patients diagnosed in the last 20 years since the first treatment was licensed report not having any issues with accessing appropriate treatment as long as they meet the national clinical guidelines. However prior to centralisation of funding in 2005 some patients did experience delays in receiving treatment due to the mechanism of decision making being made locally and timelines and processes being different depending on where a patient lived in England. Obviously where this was the case it was for many extremely distressing to know that treatment was available but potentially not accessible due to local funding issues. Fortunately geography is no longer a determinant as to whether patients receive treatment or not.

Information:

Before treatment, the establishment of the specialist centres and the advent of the internet, most Gaucher patients and their families reported being able to access very little information about the disease. The only available information was in medical journals which were not written in lay terms and therefore difficult for patients and their families to understand.

In 1991 the Gauchers Association was established. They knew of a handful of patients and started to produce a regular newsletter on the development of the new treatment for the disease. In 1992 the Association knew of 8 patients in the UK with Gauchers Disease and started to navigate them to the specialist doctors at the Royal Free Hospital, London; Addenbrooke's Hospital, Cambridge; Great Ormond Street Hospital, London and Manchester Children's Hospital.

Patients report that the establishment of the Gauchers Association and being referred to these hospitals was a turning point in their being able to understand and learn more about their disease. Today patients report that they feel well informed and get their information primarily from the staff, doctors and their teams at the specialist centres, the Gauchers Association website and the Internet

"I was given the contact details of the Gaucher Association which I then contacted, and it was only then that I was provided with all the information and support that I needed. The doctor himself only provided me with medical information rather than non-medical information or support, which I got from the Gauchers Association. This was pre- internet though so things would have been different had I been diagnosed more recently, as I could have found a lot of information myself" Patient diagnosed 1997.

"It was only once I got in touch with the Gauchers Association that I felt I had the information and support that I needed. Luckily there was not a long period between diagnosis and my contacting the Gauchers Association, but there could have been" patient diagnosed 1997.

Impacts of these difficulties have on patients and their families or carers:

Gaucher disease is a rare disease, its heterogeneity even amongst twins is not only challenging for the doctors but also for patients and their families.

Despite the vast amount of information that is now available for patients through the various channels referred to above, patients still face challenges in being able to communicate with others about their disease and have to become experts in their own right. They know more about their disease than most GPs and other medical staff they come into contact with outside of the specialist centres. They find themselves often having to repeat their story over and over again and this can lead them to feel a sense of loneliness and loss, as they often have to be the expert rather than the patient. GPs and other more local medical staff often defer any illness to their specialist even though patients could be seen locally causing undue pressure on the specialist consultant and this is often coordinated by the patient or the parents when dealing with children. This can add additional pressure on the patient and families as it may cause additional visits to the specialist centres which tend to be long distances from their home, resulting in additional financial burden, time away from work or studying and the need to organise care for other children/family members. On the other hand some local doctors are reluctant to coordinate care with the patient specialist consultant as they feel that they are best equipped to deal with the patient and this in turn can lead to issues if the local doctor is not sufficiently informed to deal with the patient properly.

(ii) ***Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects: physical health; emotional wellbeing; everyday life (including if applicable: ability to work, schooling, relationships, social functioning); other impacts not listed above***

Physical Health:
For those patients that were diagnosed before the availability of treatment the impact of the disease on their bones and having their spleens removed has left them with varying forms of disability. Some patients are wheelchair bound, are regular wheelchair users or use walking aids to get around daily. This group of pre-treatment patients still experience fractures and the need for hip replacements as a result of irreversible bone damage and report issues with fatigue which have caused them to retire or give up work or only be able to work part time.

The majority of patients who have had access to enzyme replacement therapy and substrate reduction therapy since diagnosis report a different story with a significant improvement in their quality of life, being able to work, have a family, participate in outdoor and sporting activities (although in the majority of cases they were only able to do this after a period of time in consultation with their doctor). However due to the heterogeneity of the disease some patients have continued to experience some limitations i.e. fatigue, bruising and bone pain, which has limits on their ability to participate in physical activities and hold down a job.

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Emotional Wellbeing:
The diagnosis and living with a long term condition can have a significant impact on the patients and families/carer's emotional health and wellbeing and mental health. Some patients report issues in this respect ranging from depression, anxiety, self-harming and a lack of confidence. In some cases these emotions impact on a patient's ability to physically work, cope with holding down a job, socialising with friends and family and being able to carry out day to day tasks. However, in many cases, patients are able to live a normal life and for many of them once they have started treatment and their physical symptoms subside they do not feel any emotional impact of living with Gaucher disease.

With the positive outcomes of treatment for the majority of patients and their families, patients are living longer however as a result of time, technology and medical knowledge we are learning more about the disease and there are now known links between Gaucher disease & Parkinson's disease and Gaucher disease & Multiple Myeloma with the occurrence of these conditions in Gaucher patients being higher than the general population. This has led to a number of clinical research studies for patients and their families which have heightened their awareness and anxiety for their own future health and morbidity.

Patients living with a rare disease often feel very lonely and isolated even within their own families or friendship circles. They feel that they constantly have to be the font of all knowledge about their disease and become their own advocate which is empowering but can also be exhausting and lead to depression and as one patient said "why me?". Close collaborative working amongst the specialist centres and the Gauchers Association can make a huge difference in the family's lives through face to face meetings, linking up with other families, sharing patient stories and attending patient meetings.

Patients with a genetic condition are very aware of the risks of passing on the condition to their children and the responsibility to ensure that they make informed choices for the future regarding family planning is a burden that can cause anxiety and upset in families.

Everyday Life:
Patients report the benefits of the specialist centres and the excellent care they receive but some highlight the distances they have to travel to attend these centres which can be four hours plus and requires them to take days off work not only for the patient but for a friend or spouse if they require physical or emotional support.

Except in exceptional circumstances all Gaucher patients receive their weekly, fortnightly or monthly enzyme replacement therapy infusions via a homecare service. Some patients are independent and infuse themselves or are infused by parent/carers whereas other patients have nursing support. Independent infusers will be required to receive their treatment and ancillaries monthly and be required to receive a scheduled delivery which may require time off work once a month to receive the delivery. Those patients that require nursing services will be required to a) receive monthly scheduled deliveries and b) scheduled nursing services which may require time off school, work etc. fortnightly.

The availability of homecare means that patients and their families do not have to travel to local hospitals to receive their weekly, fortnightly or monthly ERT, requiring time off work, transport and parking charges, the use of NHS services.

A number of patients that participated in our online survey reported the burden on their carer if they were involved in their treatment in accessing the vein for the cannulation which can often be very stressful i.e. multiple misses due to poor venous access.

The impact of having regular infusions on patients and their family's quality of life was highlighted by many patients including their ability to travel and work overseas, move to another country to fulfil their aspirations, the length of a holiday they can take and the constant reminder of having to schedule aspects of their life around homecare deliveries and infusions. With an increase in the number of children surviving into adulthood due to ERT, we are seeing young people being able to go to university and they report that having to have their regular infusions whilst studying away from home can be very challenging practically and also have an emotional impact. Young people have expressed that they do not want to disclose the fact that they have a medical condition as they do not want to be treated differently.

Patients with Gaucher disease report issues with employment, they have challenges with carrying out tasks required within their line of work due to experiencing fatigue and bone pain, anxieties about taking time off for appointments and having days off ill. Patients report that they do not want to disclose the fact that they have a medical condition to their employer as they fear that this will be held against them.

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

2. Advantages

(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

From the phase 3 ENGAGE clinical trial in previously untreated patients with Type I Gaucher disease and subsequent data collection from the extended trial, the new oral technology met its primary and secondary endpoint; this means that this technology for Type 1 GD addresses the following aspects of the disease;

- To increase haemoglobin, this improves anaemia and helps with fatigue.
- Increase platelets, this reduces the risk of bleeding and bruising.
- Improve bone mineral density; therefore reduces bone pain and the risk of fractures.
- Reduce the size of spleen and liver, this reduces abdominal discomfort, pain and helps to improve appetite.

Some patients are at risk of developing antibodies on ERT, patients cannot develop antibodies to this new oral technology which is a SRT and therefore this technology could be an alternative for those patients. The impact of a patient developing antibodies are either that patients will require pre-medication for allergic reasons or they may develop neutralising antibodies which may require more complex strategies to overcome these, although these are not common.

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:
- the course and outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends and employers)
- other issues not listed above

The majority of Gaucher patients that this technology would benefit are currently receiving enzyme replacement therapy by intravenous infusions either weekly, fortnightly or monthly or Zavesca which is an oral therapy licensed for patients 18 years and over with mild to moderate type 1 gaucher disease who cannot receive the standard treatment of enzyme replacement therapy.
ERT is not a cure but a management treatment and therefore some patients will have been on ERT for 20 plus years.

Many patients report difficulties with accessing their veins over such a long period of time and worry that the longer they are on ERT the more challenging venous access will become and that this will place undue pressure on them and their family especially where partners or other family members perform the cannulation for them. This new oral technology is therefore seen as having a benefit as patients would no longer have to have regular infusions and would negate the need for long term venous access.

ERT is required to be refrigerated at between 2 – 8 ^{0}C and therefore requires cold chain storage when being delivered to hospitals and patients' homes and requires patients and families to plan for monthly scheduled deliveries and weekly or fortnightly scheduled nursing support. This new oral technology will not require cold chain storage and could be delivered to patients in larger volumes (currently ERT is delivered in one month supply, whereas Zavesca an oral therapy for Niemann-Pick C is delivered once every two months) thus reducing the impact of taking a long term prescribed medication as they would not need to schedule in slots to be at home to receive their drugs and ancillaries that are often delayed or mistakes made with stocks, enabling patients and family members to carry out their daily tasks and responsibilities. In addition to deliveries some patients have support with homecare and require some level of nursing support. This also has to be timetabled and often has to be scheduled resulting in taking time off work, college.

The majority of Gaucher patients in England receive their ERT at home and this requires them to either have a separate prescribed drugs fridge supplied within the NHS homecare tender or use their own controlled fridge, monthly deliveries and space to store all the ancillaries including needles, sharps bins and often swabs containing spilt blood which therefore need to be stored securely and safely. This new oral technology would not need all of this and would mean that patients homes would no longer be like hospital once a week, fortnight or month.

Where patients are not able to have homecare, traveling on a regular basis to their infusion centre can cause financial burdens as patient do not receive any travel/parking funding unless they are in receipt of certain benefits. Often this takes up to half a day whilst staff request the ERT from pharmacy, make up the ERT and the infusion which can take up to two hours. This new oral technology would mean that patients can take the treatment without any disruption to their everyday tasks thus improving their and their families or carers quality of life.

Regular ERT infusions require patients and their families to schedule holidays, work around their infusions and limit the time patients can stay away from home. This new oral technology would enable patients to take their treatment away with them and be able to be away for as long as they want to. One patient taking the new oral technology as part of the clinical trial said “I have enjoyed the freedom of not planning my life around regular infusions”.

The new oral technology would enable students to travel more freely like other young people with a long term condition and they would not be restricted to two weeks or have to make special arrangements to have their infusion in a foreign hospital.

Young people report that having to continue with their infusions when they leave home to go to university is very challenging. Having to have a fridge at university, often a visiting nurse means that it is very hard for young people to keep their medical condition to themselves where they otherwise would want it to remain confidential.

Patients already receiving the new oral technology report;

The following are direct quotes from patients who already receiving the new oral technology:

“Taking the oral therapy is much more convenient, easy and there is no risk of local infection. I do not have to plan times to have my infusions and plan holidays around infusions or organize taking all the equipment needed with me. There is no physical discomfort with taking a pill, and no scarring as there is with regular infusions”.

“Being on the oral therapy has been a very positive experience for me and my husband, he no longer has to help me with my regular infusions, and taking a pill has made me feel like a normal person”.

"Having a tablet certainly makes me feel more independent because I am in control of when and what time I must take my tablets. Also planning holidays would be easier as I don't have to think about how long I will be abroad or on holiday without my infusion".

"Having more time to enjoy life"

"No more needles into a vein and not being able to move for a couple of hours".

"I do feel that I am a normal person again as I can take a tablet like anyone else and not be different by having to have infusions on what used to be a work day and having to have time off to have them, believe me anyone who has had infusions will tell you they are not very nice as they take at least an hour and its puts a strain on your arm and vein"

"I now have the freedom to do what I want when I want as I can take my tablets with me and have them at my regular 12 hour spots"

"It doesn't make the illness feel as serious / bad, it really does lighten my whole outlook on my illness"

"A sense of 'normality' compared to having to deal with all the equipment and time and people involved with transfusions"

3. Disadvantages
Please list any problems with or concerns you have about the technology. Disadvantages might include:
- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

The new oral technology will not be suitable for all Gaucher patients, there is no data on the oral technology in pregnant women and patients with some pre exiting conditions, e.g. cardiac conditions, will not be suitable for the oral therapy. The oral therapy will not address the neurological aspects of Gaucher disease in Type 2 and 3 patients.

The issue of compliance is a concern with this new technology; the majority of patients are on ERT which is a regular weekly, fortnightly or monthly infusion which requires planning, drugs delivery and often nursing support. The communication with the patient by the homecare company regarding deliveries requires a stock check and therefore any issues with compliance are often picked up.

The new oral technology needs to be taken once a day at the same time or twice a day at 12 hour intervals and this requires patients to remember to take the tablet. The concern is that the patient may forget and skip taking the tablet and if they do not feel unwell as a result of not taking it they may lapse into a habit of skipping treatment. There are aids available to support patients but ultimately the patients must understand the importance of compliance.

As part of the Highly Specialised LSD Service in England, the 8 expert centres all provide clinical care and treatment within approved standard operating procedures regarding treatment goals and all patients MUST attend regular appointments to monitor their response to treatment. These protocols will help support patient compliance and provide the opportunity in a timely manner for any necessary action to be taken by the treating clinician.

There is a lengthy list of medicines that the new oral technology must not be taken in combination with and patients will be required to inform their GP and other prescribing doctors of the oral technology when being prescribed other medication, the list of these medications would need to be easily accessible and updated regularly.

Patients on ERT experience very few side effects and patients report the side effects of the oral treatment are an unknown concern. Patients report that they would like to switch to the oral treatment but are unsure about the side effects and that they would need to understand these in more detail before making an informed decision.

Patients are willing to stop eating certain foods in order to take the oral treatment as they feel the benefit of an oral treatment outweighs the small list of foods they must avoid e.g. Grapefruit

Patients report through our online survey that they are keen to switch to the new oral technology however the question about switching back to ERT infusions was raised and they would want some reassurance that if the new oral technology proved unsuitable for them i.e. not being as effective, side effects, challenges with compliance, that they could switch back to ERT infusions in consultation with their treating clinician.

One patient currently on the new technology said that initially they had “An anxiety of taking an oral therapy over an infusion is it as effective?”

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

An oral therapy has been long awaited by the Gaucher community. Due to the known side effects of Zavesca, its licensing in 2002 was not followed by many patients wanting to switch from the ‘Gold’ standard ERT to this new oral therapy. In addition the conditions of use by the European Medicines Agency in 2002 was for adults (aged 18 years and above) with mild to moderate type 1 Gaucher disease who cannot receive the standard treatment of enzyme replacement therapy.

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This oral technology being appraised has been closely followed by the patient community through the Association's Newsletter and announcements of clinical trial data. Many patients report that they would like to switch to an oral therapy as it would mean no more infusions and more independence. However other patients report an infusion once a week, fortnight or month is better than having to remember to take a tablet once or twice a day every day for the rest of your life.

ERT and in particular Cerezyme has been the therapy of choice for many Gaucher patients over the past twenty years and patients trust ERT and are anxious about whether or not the oral treatment will be as effective.

Patient statements from our Members online survey:

The only criterion for me is effective disease control and possible side effects.

May not be effective, or have side effects or maybe pricier.

The possible side effects

Cerezyme has changed my life so much; I would be reluctant to change

Being diagnosed late my symptoms were at the severe extreme of all measures for type 1 GD. While my bodily structures and functions are being restored to a better state, there is still a way to go. I would be nervous of moving away from ERT for a while yet

The only disadvantage I could think of would be an adverse reaction to the oral therapy, or if it was not as effective as an infusion.

Remembering to take it would be one and the side effects another.

Depends on frequency if you had to take tablets 3 times per day compared to a one hour infusion every 2 weeks would be more of an impact

5. Are there any groups of patients who might benefit more from the technology than others? Are there any groups of patients who might benefit less from the technology than others?

The new oral technology will not be appropriate for all adult type 1 Gaucher patients, Eliglustat is metabolized by the CYP2D6 protein and therefore patients would require CYP2D6 genotyping in order to see if they were eligible to take the new oral technology. The genotyping is done by a simple blood test to identify what type of metaboliser the patient is. The new oral technology is suitable for; Extensive metabolizers (EM), Intermediate metabolizers (IM), and Poor metabolizers (PM). The new oral technology is not recommended for those patients that are Ultra-rapid CYP2D6 metabolizers or indeterminate CYP2D6 metabolizers.

The new oral technology cannot be taken with certain other medications that some patients may take for other co morbidities that are highlighted in the prescribing details.

Patients that have pre-existing cardiac diseases, moderate to severe renal impairment, hepatic impairment, pregnant women, and nursing mothers are not recommended to take the new oral technology.

Patients with a needle phobia, difficulties with regular venous access would benefit if suitable for this new oral technology as deemed by their treating clinician at of the 8 expert centres in England.

Those patients who have developed antibodies to ERT may benefit from this new oral technology depending on their level of allergic reactions, need for pre medication or those that develop neutralising antibodies.

The effects of the oral technology on the lungs were not studied as part of the clinical trials as an end point and therefore there is no clinical data available, however one type 3 young adult patient in England has been prescribed the new technology in conjunction with ERT as she has experienced ongoing lung involvement due to the accumulation of Gaucher cells in her lungs despite being on ERT since the age of 16 months of age and receiving high levels of ERT. Evidence from a clinical trial of ERT and the substrate reduction therapy Zavesca in patients with type 3 Gaucher disease 2004 - 2006 suggested a therapeutic benefit in the lungs of patients with Type 3 Gaucher disease, therefore this new technology was prescribed on a compassionate basis to explore whether it would address these on-going unmet clinical needs of this patients. This patient has experienced prolonged stays in hospital including a collapsed lung and re occurring chest infections which has impacted on her education as this has resulted in long absences from school and university on a regular basis as a result of repeated periods of illness.

Young people who are starting a life of independence such as moving away to study at University would benefit from this new oral technology as it would mean they would not have to schedule regular infusions, have a drugs fridge at university and could keep their medical condition private if they wish to.

6. Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list current standard practice (alternatives if any) used in the UK.

Patients with Gaucher disease in the UK are prescribed ERT. There are two licensed ERTs available; Cerezyme manufactured by Sanofi - Genzyme or VPRIV manufactured by Shire. All new patients are prescribed VPRIV based on the current NHS England drugs framework from 2012 - 2016. However clinicians can request that a patient receives Cerezyme on an individual case by case basis on clinical grounds.

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A small handful of patients receive Zavesca, an oral substrate reduction therapy which is licensed for Type 1 adults with mild to moderate disease who are unsuitable for ERT. This is therefore a second line treatment for Gaucher disease.

All patients are seen at one of the eight LSD Centres in England and are managed using NHS treatment guidelines which have been developed by the clinical experts from the LSD Centres, the Gaucher Association and commissioners.

All patients, except in individual cases receive three infusions in hospital on commencement of ERT and are then transferred to receive homecare with the support of one of the three homecare companies currently on the homecare framework; 1 October 2015 to 30 September 2017 with an option to extend for up to 24 months

Currently patients with type 3 Gaucher disease receive one of the two ERTs for their visceral disease, type 2 patient are not prescribed ERT and are managed using palliative care programmes.

(ii) ***If you think that the new technology has any advantages for patients over other current standard practice, please describe them. Advantages might include:***
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

The main advantages of the new oral technology over current standard practice is that it is an oral treatment taken once or twice daily rather than a weekly, fortnightly or monthly infusion and therefore there is no need for homecare service i.e. Cold chain delivery, the need for the drugs fridge and storage of ancillaries and nursing services. This technology would also enable patients to travel for pleasure e.g. a gap year, and work without having to plan them around their treatment schedule.

Patients who have had ERT infusions for a long time worry about long term venous access and scarring and the new oral technology will offer another effective treatment using a different modality.

For some patients being able to take an oral treatment would allow them to maintain their own privacy and not have to declare that they have a chronic illness requiring treatment e.g. No need to have their drugs delivered, time off for infusions, having a drugs fridge in their home or at university.

Some patients have developed antibodies to ERT and this oral technology gives them another option other than the current oral treatment Zavesca for Gaucher disease that has known side effects.

(iii) ***If you think that the new technology has any <u>disadvantages</u> for patients compared with current standard practice, please describe them. Disadvantages might include:***
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

The main possible disadvantage of the new treatment compared to the current standard practice is that compliance amongst patients may be an issue as the treatment needs to be taken once (at the same time) or twice a day and 12 hours apart, rather than a regular infusion which has in built compliance monitoring i.e. Nurses, homecare companies customer services.

7. Research evidence on patient, family or carer views of the technology
(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions.

In England, the Association is aware of only six patients receiving this new technology, four of them were on the original clinical trial, one is receiving the therapy in combination with ERT for a specific medical aspect, the lungs and one has been prescribed it on compassionate clinical grounds. The Association has undertaken a survey of these six patients and the feedback receive has been used to put this patient submission together. They report a positive experience of using the technology in terms of ease of use, gaining a new independence and feeling well on the new treatment.

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

This new oral technology is only being used by six Gaucher patients in England, four as part of the original clinical trial, one on a named patient basis for a specific aspects of their disease in combination with ERT and one has been prescribed it on compassionate clinical grounds, therefore the number of patient is very small and their time on the new oral technology is limited.

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

The Gauchers Association undertook an online targeted survey of Type 1 adult Gaucher patients currently living in England that we had emails for, we received 39 response out of 156, this equates to 25%. The survey asked for their views on their condition, their experience of diagnosis, access to treatment and information, and their thoughts on the new technology. The information collected from this survey has helped form the basis of the response to this patient statement. A copy of the survey results is attached.

8. Availability of this technology to patients
(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

The difference would be that patients would have a choice of treatment, the opportunity of having an oral treatment rather than a regular infusion would benefit those patients that experience difficulties with accessing their veins or have a needle phobia. Long term venous access causes scarring and patients experience anxiety at their veins collapsing. They would not have to have homecare deliveries and nursing services.

An oral treatment would enable patients and their families to lead a more independent life, enabling them to travel without having to schedule holidays and work trips around their infusions and for young people it would enable them to take a gap year or travel.

Some patients develop antibodies to ERT which cannot be managed through pre medication or infusion management. This new technology would enable patients if eligible i.e. CYP2D6 metaboliser, existing health conditions and drug interactions to be able to receive a licensed and effective treatment for Gaucher disease rather than just symptomatic management and palliative care.

(ii) What implications would it have for patients, their families or carers if the technology was not made available?

For those patients that develop antibodies to ERT which cannot be managed through pre medication or infusion management the only other non ERT treatment; the substrate reduction therapy licensed, Zavesca, has known side effects and if patients are unable to tolerate these then they will be untreated.

Patients who experience difficulties with long term venous access and scarring would have to continue the burden and stress of regular infusions or consider having in dwelling catheters implanted which require surgery under a general anaesthetic and must be regularly monitored to avoid infections, blockages.

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(iii) Are there groups of patients that have difficulties using the technology?

The only group of patients that may have difficulties using this technology would be those that who have a reduced mental health capacity and therefore may have issues with compliance.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which eliglustat is/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Other Issues
Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

ERT is required to be refrigerated at between 2 – 8 ^{0}C and therefore requires cold chain storage when being delivered to hospitals and patients' homes which is a cost to the NHS. This new oral technology will be more cost efficient to the NHS as it would will not require cold chain storage and could be delivered to patients in larger volumes (currently ERT is delivered in one month supply, whereas Zavesca an oral therapy for Niemann-Pick C is delivered once every two months) and also by alternative cheaper means other than complex homecare delivery companies.

Where patients are not able to have homecare, they will need to travel to their infusion centre. This often takes up a considerable amount of time for staff to request the ERT from the hospital pharmacy, make up the ERT and then have to use a bed/chair for the infusion which can take up to two hours to infuse. This new oral technology would mean that patients can take the treatment within their daily routine without any disruption to their everyday tasks thus improving their and their families or carers quality of life and for those patients that receive their ERT infusions in hospital this would reduce a burden on the NHS i.e. a bed and staffing .

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Q1 Describe your diagnosis journey, who did you see, how long did it take, was there a delay, were you diagnosed with something else before getting a diagnosis? If you were a child when you were diagnosed, it would be helpful to ask your parents to help complete this question.

Answered: 38 Skipped: 1

#	Responses	Date
1	Diagnosed at age 5, this was due to my brother aged 3 at the time being very ill due to enlarged spleen. However, it was thought he had leukemia at first but when diagnoses with Gauchers I was tested and was alos found to have the disease.	10/18/2014 4:41 PM
2	I have always been ill , as a child I would vomit, I had problems walking, I had many different diagnosis for my illnesses, by many different doctors , I was in my middle thirties when it my consultant suspected I had hepatitis because of jaundice,that at last after a liver biopsy, Gauchers was diagnosed. I did not receive any treatment (my consultant didn't know of one) , until I read on the internet about cerezyme on the Gauchers association web site. It was about another year after a mix up regarding funding, before funding was in place for me to have cerezyme. The last fifteen years of my life with treatment have been very good. I can walk , I have 2 prosthetic hips, previous to cerezyme it was deemed I was not well enough to have them replaced. I have no bleeding, no jaundice and I live almost a normal life .	10/18/2014 1:14 AM
3	At aged 20 I was feeling very tired. Blood tests showed a very low platelet count. I had bone marrow tests and was diagnosed at the Northern General Hospital in Sheffield.	10/17/2014 7:38 AM
4	Age 57 with rapidly failing health and gall stones the size of golf balls. GP took bloods (v poor) and found massive spleen and liver - rapid transfer to hospital. first thoughts were some form of blood cancer. Marrow biopsy results suggested something different - luckily haematologist aware of Gouchers (GD) so reffered me to socialists at Royal Free. Diagnosis from first visit to GP to confirmation was around 12 weeks.	10/16/2014 10:21 PM
5	My journey began when I was 11. I originally went to the my GP thinking I had a sports injury as my leg was swollen. They then sent me directly to Northwick Park Hospital where I was examined. The results showed that I had a enlarged spleen. From this diagnosis, I was then admitted to Great Ormond Street Hospital. After a couple weeks and a lot of tests, they came to the conclusion that I suffer from Gauchers Disease.	10/16/2014 9:34 PM
6	I am [redacted] I was born in Istanbul in Turkey.Doctors said to my parents i had gaucher type 1 when i was born I didnt have any treatment until i came to london.in London we contacted with [redacted] and she helped us.she referred us to [redacted] there was delay with treatment.my treatment started with 13 months ago with [redacted].i didnt get any help from turkey they didnt do anything.only i got help [redacted] and royal free hospital gaucher team.	10/16/2014 9:05 PM
7	I was diagnosed at 2 years of age, in 1979. The diagnosis took almost a year, and it was intially thought that I had Leukemia. Our local hospital was unable to offer a diagnosis, so I had to undergo several tests at Great Ormond Street.	10/16/2014 2:23 PM
8	I was diagnosed at 6 years old in 1962 after a liver biopsy	10/16/2014 2:14 PM
9	Brother was five and had another illness and was picked up then so they decided to test me and I was diagnosed at the age of 3	10/16/2014 1:56 PM
10	Diagnosed 30 years ago during pregnancy due to a low blood count this was done by bone marrow aspirate. I was not symptomatic. I was monitored during my second pregnancy and it was then decided to refer me to the haematology department for regular check ups. I was still not symptomatic. After complaining of hip pain which was dismissed I took advice to seek help elsewhere by way of support groups etc. and as a result found the Gauchers Association on line and eventually got an appointment at one of the specialist centres. They confirmed the original diagnosis and I now attend and am monitored by them.	10/16/2014 1:45 PM

11	It started in Febuary 1989 severe pain in my right hip after a week mt GP sent me to A&E at Ulster Hospital where they started doing tests on my blood and xrays, contrast M.R.I. then after about 3 weeks a bone marrow sample was taken and sent to Scotland by [redacted] after a week the results came back that I had Gauchers Disease. I was told by my Dr that I had Gauchers a rare disease and there was no cure & that all they could do was treat any symptons as and when they happened.	10/14/2014 6:09 PM
12	As a child were told about the disease but the treatment was not available in my country	10/14/2014 1:04 AM
13	Diagnosed at age 25 in Cardiff by a [redacted].Diagnosed by bone marrow test within a week of original blood test at GP.Spleen removed .Diagnosed 38 years ago.	10/10/2014 9:38 AM
14	Between the ages of 7-10years old I saw my GP several time for severe pain in my knees/hips and was sent for x-rays and told these were 'growing pains'. At the age of 11 I had another episode with severe pain in my hip and was unable to weight-bare at all. This time I was admitted to Peterborough District Hospital under an orthopedic surgeon; he put me on traction for several days and then a week of hyperbaric oxygen treatment - I was discharged after 2wks on crutches with no firm diagnosis. Around this time I had a pre-secondary school examination with the nurse, who noticed bruising on my legs and advised me to see my GP. He examined my abdomen and noticed I had an enlarged liver and spleen, so referred me to a pediatric consultant at Peterborough District Hospital; he subsequently referred me on to [redacted] at Royal Free Hospital, London. She carried out a bone biopsy and a liver biopsy resulting in a Gauchers diagnosis; I was given very little information, told there was no treatment available and certainly at this point no link with Gauchers and the bone pain I had been suffering.	10/7/2014 12:31 PM
15	Diagnois as young adult had low platelets Diagnosis after several blood tests, remeber feeling that probobly wasnt much of a problem, nil treatm,ant available at that time	10/6/2014 9:32 PM
16	I was five year old so I didn,t really know anything .	10/6/2014 3:45 PM
17	I was diagnosed when I was 6 years old, after a lumbar puncture. Very shortly after that the doctor decided to remove my spleen. After that I did not have any major health problems (except for bone paln every few years) until I was diagnosed with avascular bone necrosis at my right femur, almost 4 years ago (22 years old). Unfortunately, even after treatment was available in Romania, the doctor did not know or did not tell us about this. I started with Cerezyme treatment 2.5 years ago.	10/6/2014 1:53 PM
18	I was diagnosed aged 57 after many visits to my GP, having many broken bones, I was then treated for four years at an Arthritis Clinic at my local Hospital, no success there. I was then diagnosed with cancer. From the cancer clinic I had a bone marrow aspirate and gaucher cells were found, I was then referred to Addenbrookes Hospital speciality clinic, this took about seven years altogether.	10/4/2014 11:28 AM
19	Was poorly all the time as a young child, took several visits and saw several different GP's and eventually saw a locum GP who discovered that I had an enlarged spleen, I was 9 years old, they initially thought that I had Leukemia, my auntie just happened to be watching GMTV one morning and there was a mother and father taking about their experience of having a child with Gauchers disease, my auntie recorded it and we passed it on to the paediatrician, a stroke of luck really! I was the first child in Wales to trial the 'ceradase' at the time, my younger sister and brother were also diagnosed with Gauchers, and elder sister is a carier.	10/3/2014 11:18 PM
20	I was 8 when I was diagnosed. Despite a number of hospital admissions, and a very swollen abdomen, a number of doctors missed my enlarged spleen. Once that was diagnosed it took a week's hospital stay to get a diagnosis.	10/2/2014 5:36 PM
21	As a child i was seen by the paediatrician at my local hospital and a radiologist suggested Gauchers disease as I believe leukaemia was feared .I was referred age nine to Great Ormand Street hospital where the diagnosis was confirmed by bone marrow test I underwent a splenectomy at the same time this was 1965	10/1/2014 2:15 PM
22	My journey began five years ago when I was diagnosed with type one Gaucher. I was seen by the Royal Free Hampstead who initially thought I had cancer.	10/1/2014 12:37 PM
23	I went to the GP with tonsillitis. I hasn't been for some time as I was generally in good health. He examined my abdomen, I think to check my glands. It was very distended (due to enlarged spleen, although we didn't know that was the cause) and he was alarmed. He told us to go straight to the local hospital (the paediatric ward rather than A&E) as he thought I had a tumour in my stomach. This was very alarming. They did a barrage of tests and discounted things like leukaemia. About a week later the consultant there said he thought I might have something called Gauchers Disease which he had read about (this was in the pre internet era) but never seen. He referred me to [redacted] a Gauchers specialist, who did another barrage of tests and confirmed the diagnosis. The whole process probably took a month or two.	9/30/2014 8:53 PM
24	I had symptoms of condition since childhood, sometimes serious sometimes mild. It was only however diagnosed in my early 60s when platelet count dropped to dangerously low level and GP referred me to Hematology	9/30/2014 11:36 AM

25	From around the age of 13 I suffered excruciating bone pain and even though my sister was diagnosed with gauchers they never linked mine doctors thought ligaments and whatever tablets I was prescribed nothing came close to touching the pain.it was a number of years when my GP finally sent me for checking. I started enzyme treatment at 26 in 1996. My hips are in a bad way scan wise and will need replacing someday but the stiffness and the extremely painful bone crisis has stopped	9/29/2014 10:29 PM
26	FIrst diagnosed 20 years ago when I was 40 . I queried with my doctor that I had yellow in my eyes feeling exhausted I am non smoker and don't drink alcohol I was very fortunate that the locum doctor sent me for scans which showed enlarged spleen and liver as I had private insurance so had bone marrow biopsy and bloods taken by dr Baglin in Addenbrookes He explained that I had Gauchers Disease and his friend [redacted] was the specialist in this field.I saw [redacted] his specialist nurse. I was commenced on cerezyme therapy treatment . Which I have responded so well to treatment I was able to continue in nursing I am very fortunate to being diagnosed and responded so well to treatment. I appreciate all the work the team do to assure the funding for my treatment .	9/29/2014 4:02 PM
27	As a child I was diagnosed with perthes disease. At the age of 19 my spleen became extremely enlarged very quickly and was removed. At that time Gauchers was mentioned but nothing more. I am adopted. It wasn't until I moved from the Oldham area to the Midlands when I was 36 that I did my own research on the Internet and took my findings to my GP. He referred me straight to Addenbrooks and basically saved my life.	9/29/2014 3:58 PM
28	I was diagnosed some some 34 years ago by a haematologist, and after bone marrow biopsy. I had presented with mulitple bruising so first thoughts were of leukemia, but also had joint pains and a vertebral fracture. Enlarged spleen and aneamia were also present. There were no treatments available at that time, other than to aleviate symptoms. It was a further 11 years before I was referred to [redacted] at Addenbrookes and prescribed Cerezyme.	9/29/2014 3:45 PM
29	My brother was diagnosed first after suffering from leg pain and swollen liver & spleen. The Dr initially diagnosed him (aged 7) and I (aged 9) with leukaemia and told my parents we had approximately 10 years to live. After my brother having a bone marrow test we were both diagnosed with Type 1 Gauchers disease.	9/29/2014 1:17 PM
30	picked up on a blood test when going to theatre for gallstone operation. 2 years monitoring Dr ? told I was stable monitoring stop then 7 years on and changing from 7,8 and 9 hours shift to 12 hour shifts at work. after working 4 nights every morning had bad pains and not eating much.So I when to my doctor ([redacted]) then transfer to ([redacted]) then to [redacted] at Cambridge.	9/29/2014 1:13 PM
31	I went to my [redacted] of [redacted] Maidstone when I was 18 with symptoms but was not investigated and diagnosed with 'chronic fatigue'. In my opinion he was extremely negligent as after I received my diagnosis I contacted him (five years later) and he confirmed my blood test results had been abnormal at the time but I was never referred. I went back to the doctors aged 22 as a student in Brighton and was referred to the haematology department because my platelet count was very low. A year later I received the Gauchers diagnosis after lots of consultations, an ultra sound and a bone marrow biopsy.	9/29/2014 12:52 PM
32	I was diagnosed when I was 10 years I am now 72 . No treatment was available at that time .	9/29/2014 12:08 PM
33	Although as a child I was aware I had a slightly enlarged spleen this was put down to my having had scarlet fever. I used to get achy but never really ill and so no one looked into any underlying cause. My twin brother who trained as a doctor was one day prior to an examination (viver) palpating his own abdomen and discovered his spleen to be enlarged. He underwent various tests - Hodgkin's etc...but finally a bone marrow biopsy confirmed Gauchers. Given my own symptoms it was an odds on bet I too had Gauchers. So although I have known I had the condition form my early twenties, 1968ish, it was not confirmed until approx 1985. Marrow biopsy.	9/29/2014 11:59 AM
34	Diagnosed in 1960 at St.Thomas's Hospital London was in patient twice and 6monthly outpatient.	9/29/2014 11:35 AM
35	Diagnosed as a baby (64 years ago), after my mother suspected a problem with my large tummy, and poor health. Eventually referred to Great Ormond Street who dignosed problem.	9/29/2014 11:23 AM
36	Dr atGOSH, no delay due to brother having same complaint	9/29/2014 10:26 AM
37	Diagnosed in a follow up consultation after visiting the GP due to jaundice.	9/29/2014 10:00 AM
38	It took a long time before I was finally diagnosed, 22 years ago	9/29/2014 9:41 AM

Q2 Can you tell us what challenges you have faced living with a rare disease?

Answered: 38 Skipped: 1

#	Responses	Date
1	Operations i.e. splenectomy, hip replacements, enlarged liver causing liver failure during one of the operations on hip.	10/18/2014 4:41 PM
2	My mobility has been poor.i have generally been unwell. Fatigue. I have basically had to ignore these things as much as I possibly could as I have a large family and needed to bring them up and go to work. Even walking around a supermarket was a challenge but I had no choice but to keep on trying to ignore pain and discomfort.	10/18/2014 1:14 AM
3	Because of the treatment I am able to live a normal and productive life.	10/17/2014 7:38 AM
4	For the first 18 months since falling ill I was either hospitalised or bedridden at home. The last six months have seen a normalisation of my condition subject to the everyday impacts of GD. Now my life is organised around the treatment cycle	10/16/2014 10:21 PM
5	At first I had a few challenges. For instance, I found it impossible for me to participate with any sports or any physical expertise as I suffered from week joints and an swollen knee. This affected me for a couple years until I started to get the effects from my medication that has helped me massively. The medication has allowed me to be able to do stuff that I previously was unable to do. If i didn't have this medication i would be extremely unwell and will not be able to have a normal life as I will suffer from many disabilities.	10/16/2014 9:34 PM
6	before my treatment i had hard time i am getting better i can feel it.before i had headache,bone pain,low platelets,tiredness,small amount blinding in mouth,e.t.c.	10/16/2014 9:05 PM
7	At the time of my diagnosis there was no treatment available, so I grew up with an ever-enlarging spleen. Over than being very careful when taking part in sports activities my childhood was relatively unaffected by the condition. My spleen was removed at age twelve, and a few months later I developed Avascular Necrosis in my left hip. This has had a greater impact and has impacted on what I have been able to do over the years to a greater and lesser extent. I have only been receiving treatment for my condition for 2 years now.	10/16/2014 2:23 PM
8	Various problems as a child caused by low platelet count.	10/16/2014 2:14 PM
9	People not knowing about it. illness	10/16/2014 1:56 PM
10	Non at all.	10/16/2014 1:45 PM
11	I was never a very active prerson it was the constant pain from the hips then lower back then shoulders ,the operations to replace joints, just took over my life especially in the first few years. When I was finally reffered to Addenbrooks and put on enyzme replacement Ceradase which was a twice a week treatment it interfeared with my work. I was incapable of manual work I was lucky and was given a desk job at the company where I worked.I was finally forced to stop working as problems with my bones increased a mixtur of pain and being unable to sit in chairs for any length of time.Since Gauchers showed itself in 1989 I have had no more than a two year period of relitavely pain free existence.	10/14/2014 6:09 PM
12	Before starting taking the cerezyme treatment I was receiving blood transfusion every month more than a liter! On pain at all the time, tired always no energy, my teeth all broke, emotionally and physically affected!	10/14/2014 1:04 AM
13	Bone pain and fatigue but as I don't know any difference I have always been determined to lead as full a life as possible	10/10/2014 9:38 AM
14	After the initial diagnosis I felt very alone; even the doctors at the hospital didn't seem to know anything about what was wrong with me. I have also had difficulty in the past with obtaining travel and life insurance due to ignorance around the disease.	10/7/2014 12:31 PM
15	No one has heard of it uncertainty as how might be affected as gets older telling childrena challenge Some worry about what might happen if funding was stopped Some guilt re the cost as I work in the NHS and see how the money goes round	10/6/2014 9:32 PM
16	It was more of a impact on my parents as nothing was available to treat Gauchers. They thought I would die.	10/6/2014 3:45 PM
17	One major problem we faced, at least present in Romania, is the fact that doctors there are not very familiar with the disease and most of the times is misdiagnosed. And even if is correctly diagnosed, they don't know about the available treatment in order to recommend it very early. Removing the spleen is still a practice although this leads to more serious problems later on (bone problems).	10/6/2014 1:53 PM

18	Pain and tiredness, living with a collapsed spine, physical mobility is hard,	10/4/2014 11:28 AM
19	It's become part of life, infusing since the age of 9, it's just part of me, don't know any different really, appart from the odd occasion when feeling tired, feel quite fortunate to have been diagnosed at a fairly early age with Type 1, I lead a normal life as any other normal person.	10/3/2014 11:18 PM
20	Not knowing very much about the condition. Luckily I was believed when I complained about the pain I was suffering, even although little showed in X-rays.	10/2/2014 5:36 PM
21	I have had orthopaedic problems all of my life,pain immobility, missed schooling, time off work and then unable to work. I have lost friends because I have not been able to socialise in the normal way. This has left me feeling very socially isolated. I feel judged by people and looked down on for being disabled by acquaintances, work colleagues and even family. As I do not have a family of my own, I also feel judged by that. .	10/1/2014 2:15 PM
22	Now that I am better the main challenge is dealing with the infusion ever two or four weeks.	10/1/2014 12:37 PM
23	The main challenge was coming to terms with the diagnosis and the invasive and complex nature of the treatment. I struggled emotionally with other people's reactions and often avoided telling people.	9/30/2014 8:53 PM
24	Various symptoms and no answer to cause.	9/30/2014 11:36 AM
25	I live a normal life apart from I couldn't do contact sport now. Without treatment God knows what I would be like but I have a normal working life and family life and enjoy long walks with the dogs couldn't do this pre treatment	9/29/2014 10:29 PM
26	I struggle with fatigue I have learned to take each day as it comes.	9/29/2014 4:02 PM
27	I get so tired in general that sometimes feel like I could slip into a coma. I cope but push myself too much to the point I can't carry on.	9/29/2014 3:58 PM
28	There was little knowledge of Gauchers Disease in the medical profression generally, which is still true to a great extent, but understandable. This has at times caused minor difficulties when I've needed medical intervention of any kind. I don't consider that I've faced added challenges because of Gauchers Disease that aren't common to many with disabilities.	9/29/2014 3:45 PM
29	Doctors having no idea what it is. No one being able to give any real assurance or extra monitoring while I was pregnant. Having to have ongoing monitoring and treatment.	9/29/2014 1:17 PM
30	had to give my job up after two year on the sick, felt down and out at the time. how will we survive.	9/29/2014 1:13 PM
31	Where do I start.....apart from the physical challenges and fitting in treatment around work, I find a lot of it is psychological and to do with other people's perceptions. It's taken me a long time to accept I have a condition which can limit me at times and part of me isn't sure I will ever fully accept that. I struggle as well with other people because I 'look well' it's hard for them to understand I have a condition and that I struggle sometimes.	9/29/2014 12:52 PM
32	As a teenager I can remember not having the same energy as my sister and the eternal nose bleeds. Regular severe joint pain which often ment a spell in hospital.	9/29/2014 12:08 PM
33	Some apprehension and intimations of mortality, some ill health, splenetic and bone crisis, poor clotting, but I don't really characterise these as challenges... it is just a life - mine. I've seen greater difficulty - my experience of Gauchers might have been worse, more acute, but I have been on ERT for some 18 years and so this keeps my condition merely chronic and tolerable.	9/29/2014 11:59 AM
34	It has been a struggle as it affected my daily life	9/29/2014 11:35 AM
35	Not understood, Insurance Life Companies did not know how to assess risk. Job Medical again ignorance. Difficulty in explaining why suddenly had various bone problems at work, and reluctance to undertake physical pursuits/adventure bonding courses.	9/29/2014 11:23 AM
36	school and sport disadvantages, acceptance of an unknown problem	9/29/2014 10:26 AM
37	Balancing how open to be about it with friends, and employers, and generally. Moving internationally, due to treatment cost and complexity.	9/29/2014 10:00 AM
38	A very large spleen, acne, tired	9/29/2014 9:41 AM

Q3 Where did you go to find information on Gaucher Disease once you got your diagnosis, was it easy to find information, did it tell you everything you needed to know? Were there things you couldn't find the answer to?

Answered: 38 Skipped: 1

#	Responses	Date
1	Given information about Gaucher's association by Consultant in the Liver Unit Birmingham Queen Elizabeth Hospital who I was referred to due to liver failure.	10/18/2014 4:41 PM
2	I got my information from the Gauchers association web site. It changed my life , I will always be grateful. I couldn't believe that there were others like me, I had always felt I was insulated in having this illness, an illness no one I knew had ever heard of, most of all the best news ever was that there was a treatment!	10/18/2014 1:14 AM
3	The Gauchers Association and the team at Addenbrookes have always been great with information and support.	10/17/2014 7:38 AM
4	Internet, Royal Free staff, Gouchers Assc. I have the information I sought	10/16/2014 10:21 PM
5	When I got diagnosed, I got a huge amount of information about the disease from my Doctor at the time. Great Ormond Street Hospital was able to fill me in with a huge amount of information. I also had a huge amount of information from the Gauchers association about my condition that came in very useful when I wanted to know what was wrong with me.	10/16/2014 9:34 PM
6	i contact with tanya collin she send us to royal free.they are very helpful to me.i had all my answers about my ilness..i can say i am much happier now...everything was perfect when i diagnosed in london.	10/16/2014 9:05 PM
7	There was very little information available upon my diagnosis in 1979. Nearly all the info on Gaucher Disease that my parents received came from my GP.	10/16/2014 2:23 PM
8	There was nowhere at that time.	10/16/2014 2:14 PM
9	Many years ago, internet wasn't available so only information was from doctor at hospital. Was told treatment was too expensive.	10/16/2014 1:56 PM
10	Initially I was given a copy of the section of a medical book on the condition which was mostly medical jargon. I knew very little of the conditon but as was mainly well I didn't think much about it. Later I found much more information on line through the Gachers Association and regular updates both on line and in their newsletters. Yes, in the early days I would not have had many answers but was not concerned about it I just wanted to get on with life.	10/16/2014 1:45 PM
11	Shortly after being told I had Gauchers a friend of my mum, a nurse at Ulster told her there was a specialised clinic at Addenbrooks for Gauchers.After a lot of hassle with doctors at Ulster a letter to our local MP(at the time)meant I was finally allowed to go to the clinic and see Prof. Cox where I found out all I needed to know about Gauchers Disease, the Gauchers Ass. web site was all so quite helpful.	10/14/2014 6:09 PM
12	As soon as I came in this country I was well informed and started with treatment in 6 weeks time!!!	10/14/2014 1:04 AM
13	At the time diagnosed 38 years ago there was no information on Gauchers.When ERT was first produced I found out about it myself from seeing a child receiving treatment in USA	10/10/2014 9:38 AM
14	I was given no information other than 'it's the best liver disease you and have'! after diagnosis. There was just no information available at the time (1979). However things took an amazing turn for the better when I was contacted by Prof Cox asking me if I would consider attending his new clinic at Addenbrookes Hospital instead of Royal Free. From that first consultation I can't describe how it felt to be under the care of someone who knew what he was talking about and above all cared incredibly for his patients; wanting the very best for them. He sent me home that day with a pamphlet about Gauchers (from an American source) which filled in so many of the gaps - late onset of puberty and above all skeletal involvement to name but a couple that had been bothering me.	10/7/2014 12:31 PM
15	no problem	10/6/2014 9:32 PM
16	There was no information available in 1948, it was just only what the Doctors told you.	10/6/2014 3:45 PM

17	In Romania, there is a website and a specialized Gaucher disease center in Cluj. I got all of my information from there. In UK I got my initial information from the Gaucher association website and from the Royal Free Hospital in London which is my care center.	10/6/2014 1:53 PM
18	The Specialist Centre at Addenbrookes informed me of everything I needed to know at the time, and I found other information on the internet, and attending Gaucher Seminars.	10/4/2014 11:28 AM
19	My local paediatrician at the time had a big interest in 'Gauchers disease' and was very knowledgeable which was a great help to us.	10/3/2014 11:18 PM
20	There wasn't anything in 1963. A medical dictionary said it was "an inbuilt error of metabolism" but neither I nor my parents knew what that meant in practice. I just had to learn to live with the condition and work out what was the best course of action when pain occurred. It did mean that one time I lay at home with a fractured femur for 10 days before discovering what it was! A year later I recognised the crack when it happened again.	10/2/2014 5:36 PM
21	When I was diagnosed in 1965 with GD, there was no information available. There was no treatment available until 1992 when I was 37 and already very badly disabled. Since receiving infusions, this has helped me remain healthy, but the treatment commenced after the bone damage had already occurred. The treatment has not been able to repair the bone and joint damage already done.	10/1/2014 2:15 PM
22	The Gaucher Assocation.	10/1/2014 12:37 PM
23	The key source of information and emotional support was the Gauchers Association, the patient association. It was a lifeline during a very distressing time. Other than that the only source of information was my doctor and healthcare company/pharmaceutical company nurses. This was in the pre internet era so it was hard to get information other than via other people. I think those sources of information were satisfactory.	9/30/2014 8:53 PM
24	Internet, Gauchers clinic at Addenbrookes, Gauchers association	9/30/2014 11:36 AM
25	Gauchers association	9/29/2014 10:29 PM
26	THE Gauchers association were helpful as well an amazing team at Addenbrookes	9/29/2014 4:02 PM
27	As above, I searched on the Internet and the information I've received at clinic.	9/29/2014 3:58 PM
28	Information eventually came much later than my diagnosis, but when it did come it was first class. Referral to the clinic at Addenbrookes, and information about the Gauchers Association were literally life savers! All I needed to know and more. I was no longer on my own.	9/29/2014 3:45 PM
29	My parents had a lot of support from an oncology nurse who used to come to our house to give us our treatment as well as guidance and reassurance from [redacted] in Manchester.	9/29/2014 1:17 PM
30	Professor Cox gave me information and how to cope with my illness. he answer all my question	9/29/2014 1:13 PM
31	I found the Gauchers Association website but I did find information quite hard to come by and most of the things I read didn't feel that relevant to my case. It was a shame there wasn't a forum or an area on that people with the condition could go to and talk to each other - the main problem for me was not being able to see real people and their personal testimonies because that made me feel more isolated and like i didn;t have other people to relate to.	9/29/2014 12:52 PM
32	In the early years my Mother did not know much about the disease no where near as much as I know today . I attended an Heamatology clinic at S Bartholomews Hospital Llondonn but [redacted] who was my Cosultant at that time was a very unapproachable man .	9/29/2014 12:08 PM
33	Oddly, my brother who became a consultant paediatrician, never really laid out the implications of the disease - I assume he felt at the time I'd only worry. My aunt in North Berwick sent me an article from her Scottish paper which described aspects of the life of [redacted]. I was surprised to see she suffered the same condition as me. I wrote and she told me about the Gauchers Assoc. I got info from them. I also looked on the internet and discovered the specialist service at Addenbrookes - saw Prof Cox. Also got info off Genzyme. I got all the necessary info ... albeit the ultimate answer is 42.	9/29/2014 11:59 AM
34	Not much information as it was so rare	9/29/2014 11:35 AM
35	Once the Gauchers Association started, information availability dramatically improved. Prior to the Association, information was hidden in medical journals.	9/29/2014 11:23 AM
36	Gosh and gaucher association	9/29/2014 10:26 AM
37	Pre-internet days - spoke to doctors and looked at medical books.	9/29/2014 10:00 AM
38	How to get treatment. At the time I was borderline, and was not given treatment, which was very frustrating.	9/29/2014 9:41 AM

Q4 Can you tell us how your diagnosis impacted on you and your family?

Answered: 39 Skipped: 0

#	Responses	Date
1	Lots of hospital appointments, tests, and illness throughout childhood.	10/18/2014 4:41 PM
2	.	10/18/2014 1:46 PM
3	As I had no treatment initially, the diagnosis had no impact, I just continued trying to 'carry on'. In away it was a relief at last to know after a lifetime of illness what was wrong. My family also sort of ignored the diagnosis as my husband worked long hours, I had five children and a job to do, so life didn't really change, just because a name was at last put to my poor health. My family have always been supportive if support was needed.	10/18/2014 1:14 AM
4	There was a lot of worry at first. Having to do infusions is very draining and family life would be greatly improved if I could go over to a daily tablet.	10/17/2014 7:38 AM
5	Everything has changed in one way or another.	10/16/2014 10:21 PM
6	My diagnosis had a large impact on my family and I. The illness made my family massively upset as it was difficult to come to terms with their child being ill from a genetic disorder. Know one had really heard of this type of illness meaning it was very difficult to explain it to family and friends.	10/16/2014 9:34 PM
7	i was sad when i learned it.it was bad.it effected us very badly.but life is good i have to move on.i am trying to be pozitif every time.also i know I have to live with gaucher...	10/16/2014 9:05 PM
8	As treatment wasn't an option at the time, my family just had to accept that I had a condition that could cause complications at a later date. Other than that, everything carried on as normal.	10/16/2014 2:23 PM
9	My parents found it very difficult but tried to carry on with a normal childhood for me and my sisters.	10/16/2014 2:14 PM
10	Parents were upset. I was only young so didn't really know the full impact until I was in my teens and had to have my spleen out due to no treatment available to me.	10/16/2014 1:56 PM
11	I don't believe the diagnosis impacted on me or my family that much.	10/16/2014 1:45 PM
12	It has caused my mother and father to spend a lot of there time looking after me, especially when hips or shoulders have been realy bad.Unable to cook for myself or to get to hospital appointments without there help.	10/14/2014 6:09 PM
13	During my childhood most of the times I was in hospital unwell, very difficult situation and did not know much about the disease!	10/14/2014 1:04 AM
14	Parents upset as they thought it was there fault.Ihad to cope with my disease myself as I did not want them upset	10/10/2014 9:38 AM
15	As the doctors at the hospital didn't seem to be overly concerned following the diagnosis; only wanting to see me annually in clinic, my parents and I also weren't unduly worried. However as I got older, pain continued in my legs and I had better understanding that I did have something wrong with me, that concerned me - wondering whether I would ever be able to have children, and how it would affect any future career (wanting to go into Midwifery I was advised against this by my doctors as they felt my joints wouldn't cope).	10/7/2014 12:31 PM
16	worry re the future never been very fit (not able to keep up with my peers, not sporty) Oddly fitter now than at any time in the past	10/6/2014 9:32 PM
17	Don,t know	10/6/2014 3:45 PM

18	Except for the health issues I had when I was little, which impacted my family, as is with any family having a sick child, I did not have any major issues until a few years ago, when I had to handle all of my health issues myself, living on my own in a different town than my hometown. When I started having bone problems a few years back I researched the disease myself and addressed the Gaucher disease center in Cluj on my own. No doctor in Bucharest ever recommended treating the disease, only treating the symptoms. After that I started having my Cerezyme IVs at a center in Bucharest, but we were always seen as a problem by the hospital staff as the Cerezyme IVs must be done very often, with more time needed to prepare the medication and a longer infusion time. Considering that you could not schedule the IVs and that I always depended on the availability of the hospital staff, sometimes I waited a few hours in the hospital before the 3h necessary for the infusion. This is not something that impacts you severely when trying to hold a job and for someone who has a lot of medical expenses (MRIs performed every few months, full check up every 6 months, etc.) Things are better since I moved to UK and I have the possibility to be more independent (prepare my medication, have someone come in and cannulate me, and remove the IV myself). Having a desk job, this allows me to even take the IV (intermate /infusor) to work with me. It's not pleasant (especially for my colleagues) but it gives me more freedom.	10/6/2014 1:53 PM
19	We were all shocked as we were not sure of the outcome of a rare disease. My extended family have had tests to see if there is any impact on any children.,	10/4/2014 11:28 AM
20	I was very young at the time, I would imagined that it must of been a worrying time for my parents having 3 out of 4 of their children diagnosed with a rare disease and not knowing whether to operate to remove the spleen or to try the enzyme replacement therapy that was fortunately available, we had to travel to hospital every other sunday to have treatment via IV infusion, this just became part of life, everybody just felt relieved that the was treatment available to reduce symptoms. Unfortunately approx 6 years after commencing treatment and seeing a successful reduction in my spleen, I had an accident in the sea when abroad on holiday, I ruptured my spleen and had a splenectomy!	10/3/2014 11:18 PM
21	The impact is the same as it is for any family with a disabled member. It did get me out of doing the washing up.	10/2/2014 5:36 PM
22	My husband and I are unable to do lots of things together. He often goes to functions and also family events alone because they are held in places that are not disabled friendly. This causes me a lot of distress and guilt, although I know its not my fault. I had a strained relationship with my late mother, as I felt she resented my health problems.	10/1/2014 2:15 PM
23	My wife has been trained to provide me the infusion	10/1/2014 12:37 PM
24	Big shock and trauma because I hadn't really been ill so there was no accompanying sense of relief or a problem solved. Also bewilderment and isolation as it was so rare and we didn't know where to turn or what it all meant. Then extremely daunted by nature of the treatment. But slowly over the first year it became manageable.	9/30/2014 8:53 PM
25	Initial shock, then relief that condition is treatable, now main impact is the burden of doing the infusions	9/30/2014 11:36 AM
26	It didn't it was a relief to identify the issue and begin treatment	9/29/2014 10:29 PM
27	My husband [redacted]as been very supportive our three boys are carriers I have always been open with them nothing is hidden from them .	9/29/2014 4:02 PM
28	I am a fighter and I cope, it's not always easy but what else can you do? I have a strong will. I would say that my parents don't know so much as I was diagnosed in adulthood and with being adopted. My husband trys to understand and he supports me, but it's not always easy for him to fully understand.	9/29/2014 3:58 PM
29	For me, it was actually good to put a title on all the weird symptoms I was having. Realising I was sick and not just lazy was a relief and being in my early twenties, I still thought I was invincible anyway! For my family, on the other hand, it was more difficult, because the first indications from the haematologist suggested I might be terminally ill. I was blissfully unaware of what was going on behind the scenes.	9/29/2014 3:45 PM
30	My brother and I were too young to have much of an understanding about it at the time. My parents being told we were dying obviously had a big impact emotionally and psychologically. It has affected my brother worse	9/29/2014 1:17 PM
31	At first it was a shock to them.	9/29/2014 1:13 PM
32	Me and my mum were really relieved at first that there was an answer for all the things I'd been suffering with for years. Then the reality of the life-long condition hit home a few months later and I found it hard to come to terms with and probably still am. I find my family frustrating sometimes - for example if I have to work from home because I'm struggling that day, my mum is very judgemental and suggests I am well enough to go (I used to do a two hour commute every day which was rather energy sapping!). I was disappointed also that my brother didn't get tested to find out if he's a carrier because it would have just made me feel a bit more like he was supporting me an showing solidarity. But basically my family aren't always great because they don't really understand.	9/29/2014 12:52 PM
33	My parents were very upset at the time and very over protective but all in all life went on as normal as possible .	9/29/2014 12:08 PM

34	The major impact was with lots of 23g needles. Well- mmm ... one just factors it in... and gets on. There was nothing to be done other than take the elixir. One might say there is some impact in undergoing all the investigations etc etc... but on the other hand it is wonderful that such resources are available - in the recent past essentially one just had to bite on a bit of wood ... no cure or treatment other than analgesics and other responses to symptoms as these manifest. For me/us no drama - we are very practical and just think how wonderful that our glass has something in it --- half full at least, and capable of taking more.	9/29/2014 11:59 AM
35	We had to learn to live with it	9/29/2014 11:35 AM
36	Problem identified helped to understand cause of illness sudden bone pains and easy bruising. So able to put in place self protection.	9/29/2014 11:23 AM
37	made us stronger but difficult seeing family due to hospital trips and working	9/29/2014 10:26 AM
38	Didn't impact family too much as such. Just accept it! Impact was more on life choices for types of job etc, which impacted family indirectly.	9/29/2014 10:00 AM
39	My wife was concerned for me	9/29/2014 9:41 AM

Q5 You will be treated at one of the designated centres for your Gaucher disease, can you describe the advantages and disadvantages of this set up.

Answered: 39 Skipped: 0

#	Responses	Date
1	I am currently being treated at Addenbrookes Hospital and I am very happy with this set up.	10/18/2014 4:41 PM
2	Disadvantages It affects my work, so I have to make arrangements before I go to the designated centres. May have to avoid not going to social gatherings if I have an appointment to visit the facility.	10/18/2014 1:46 PM
3	I am at present treated by Addenbrooks, the care is really good , I live in the north if England and a team travel to Leeds twice a year for a clinic. This is wonderful as a few years ago I had to travel to Cambridge. I do find trying to communicate with the clinic hard between appointments, previously I was also managed by a haematologist locally and communicating with his clinic if I needed to was fine, since he retired I have not been told of a replacement contact. As your question is phrased in the future tense I hope I have given you the right answer, I don't know about any future changes to these clinics.	10/18/2014 1:14 AM
4	Only disadvantage for me is that it can take up to 4 hours to get there. Treatment has always been superb.	10/17/2014 7:38 AM
5	Disadvantages - a significant journey. not so much of a problem now as visits are infrequent. But a real challenge when at the lowest points Advantages - it is a rare condition, the designated centres have a depth of knowledge and understanding that could not be matched if treatment was to be provided by the local Health authority	10/16/2014 10:21 PM
6	The advantage of this is tat they are totally specialists about the disease. This therefore is much better. Another advantage is that i live in London meaning that i am able to access the centers very easy. A disadvantage is that if i am to move away from London I will find it difficult to gain access to theses areas of treatment.	10/16/2014 9:34 PM
7	my treatment is perfect.Royal free hospital gaucher team is very good,i feel very lucky.	10/16/2014 9:05 PM
8	I am lucky to live withing 30 miles of Addenbrookes and their LDU team, so for me it is an advantage having them so close. Appointments are kept to a minimum and the home support is very good. My treatment is administered at home, which is also of great benefit. I can't really think of any disadvantages for me of this set up.	10/16/2014 2:23 PM
9	It is brilliant so much better than having doctors who do not really know about the disease. The only problem is travel.	10/16/2014 2:14 PM
10	Not sure	10/16/2014 1:56 PM
11	I believe there are huge advantages of attending the designated centres. I have never worried about the condition but unlike attending my local hospital it is treated seriously at the centres and I don't feel like or am treated like a fraud. They check that that there is no deterioration in my condition and they look for emerging symptoms/other related illnesses. One disadvantage is the long journey to the centre but I feel it is more than outweighed by the care and treatment there.	10/16/2014 1:45 PM
12	As I am only person wth Gauchers in Northern Ireland needing treatment I dont think there will be a designated centre here.	10/14/2014 6:09 PM
13	Since, Dec/1998 started with a cerezyme treatment easy to get a treatment in hospital to start with and year after been delivered at home and receiving treatment at home Trained to receive infusion by our self Ordering and receiving a delivery on time at home Easy to get contact with health care at home or hospital Disadvantages: difficulty sometimes to find a veins to infuse	10/14/2014 1:04 AM
14	The treatment I have had at Addenbrookes has been amazing and I would not want to change that.It is a centre of excellence for Gauchers diseaseand there have been no disadvatages.Iam prepared to travel for such dedicated treatment from all staff	10/10/2014 9:38 AM
15	As far as I'm concerned there are only advantages. Being cared for by a team of professionals who are experts in the field who know and care for their patients. They are aware of new treatments available and always willing to discuss concerns in a very honest and easy to understand way - I have the utmost respect for the team I am under at Addenbrookes and would never be able to thank them enough for the care they have shown me over many years.	10/7/2014 12:31 PM
16	travel to london , whole day off struggle to cover work, without having to discuyss the reason im away	10/6/2014 9:32 PM
17	I find it ok.	10/6/2014 3:45 PM

18	The only disadvantage I see with this set up is if you are a person that has to travel a lot and you might prefer to have the possibility to address any center for your treatment. For this disease you have to have stability in administering your treatment and this would cause problems.	10/6/2014 1:53 PM
19	The centres are excellent forms of knowledge within a safe and caring group of doctors and nurses. The only disadvantage is having to travel to the centre 50 miles away.	10/4/2014 11:28 AM
20	.	10/3/2014 11:18 PM
21	I already go to a designated centre every 6 months to see my specialist. That way the management of my condition is overseen by someone who is a leader in the field.	10/2/2014 5:36 PM
22	I have been treated at Addenbrooks Hospital in Cambridge for nearly 23 years. From my first consultation the relief I had by seeing people who really understood my disease was immeasurable. The advantages are that I can now contact someone at any time with a query, and my local medics have also had reason to do so as well. The only disadvantage for me is that this is an 900 mile round trip approximately away every six months for myself and my husband.	10/1/2014 2:15 PM
23	I think this question has not asked correctly.	10/1/2014 12:37 PM
24	Great advantage of access to true medical specialists in the field. Logistical advantage that the centres form a network which is centralised eg for purposes of information distribution.	9/30/2014 8:53 PM
25	The arrangement works well. I see people who are of excellent levels of competence and knowledge of my condition, I am treated as an individual rather than a number, if the there are a problems I can speak to people who are knowledgeable and helpful	9/30/2014 11:36 AM
26	Advantage is consistency always see the same specialist year in year out who know you and the care is second to none. There are no disadvantages and you always know they are there anytime to help	9/29/2014 10:29 PM
27	When I lived in England I was seen every three months now I live in the west of Scotland I see them once a year for the last 5years.I Am most grateful for their expertise I know they are there if I need them.I am blessed and appreciate the team at Addenbrookes .	9/29/2014 4:02 PM
28	The team at Addenbrooks are great and I feel well taken care of. It's a 240 mile round trip though and I can no longer drive that far, it tires me out. So I have to rely on someone to take me and I have to use holiday days at work for appointments.	9/29/2014 3:58 PM
29	In a word 'wonderful'. I've been attending Addenbrookes for 24 years now, and it's been a massive benefit to have been seeing many of the same faces in all that time. I have total confidence in the care and treatment I receive from these wonderful people. The only disadvantage is the 3 hours each way the journey takes, but worth it.	9/29/2014 3:45 PM
30	Advantages- I'd no longer have to have needles which I hate. Disadvantages- travel time, cost, disruption to my family/newborn baby, time off work as the nearest centre is far away, not as convenient as managing my own treatment at home currently	9/29/2014 1:17 PM
31	York hospital is pain to get to at busy times and the distance travelling. when passing Selby Hospital on the way. Cambridge hospital is a long way to travel	9/29/2014 1:13 PM
32	I'm treated at home by BUPA nurses at the moment. They're great and I feel really comfortable and supported with them. It's also been good to become semi-independent recently so that I can get on with other things during the treatment.	9/29/2014 12:52 PM
33	I was transferred from the Norfolk and Norwich Hospital to Addenbrooks in 1997 to the Lyosomal Dept . The dept is excellent very helpful extremely kind knowledgeable and have made my condition so much more manageable as I have got older . The only disadvantage is the distance from my home it is over 4 hours driving from where I live now . however my son drives me for my clinic appointments and we can manage the trip in a day .	9/29/2014 12:08 PM
34	Addenbrookes. Cambridge - 3 hours drive. Better if it were nearer, but then I would seldom see one of my dear friends in Cottenham near the hospital and in any case the staff there are excellent and Prof Cox and I can share bad puns. Seems to me being treated is the ultimate advantage - all else is insignificant.	9/29/2014 11:59 AM
35	Will be ok but would be better if it could be local	9/29/2014 11:35 AM
36	Going to a specialist centre means that the medical staff know what they are dealing with, rather than me having to teach a new person each time I contact the medical profession. Able if needed to share experience with other patients.	9/29/2014 11:23 AM
37	travel and work life balance. specialised care	9/29/2014 10:26 AM
38	ensure have proper professional support who understand the condition.	9/29/2014 10:00 AM
39	Very good and helpful, with all thye expertise available	9/29/2014 9:41 AM

Q6 Can you tell us how having Gaucher Disease affects your daily life, have you had to adapt the way you live in anyway? e.g. physical, emotional, ability to go to school, work, college, go out to social gatherings etc.

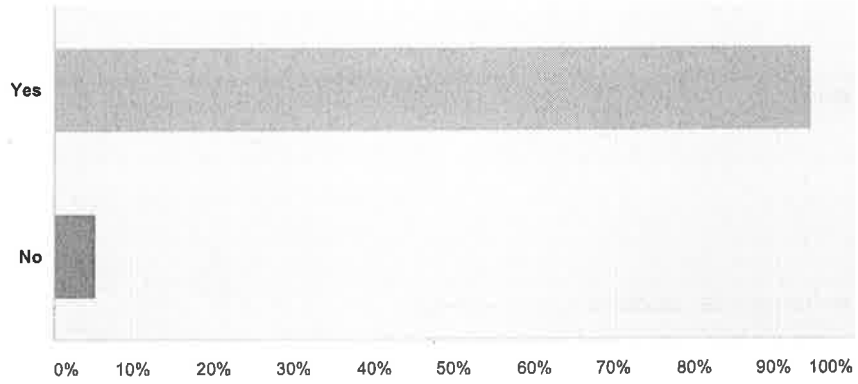
Answered: 39 Skipped: 0

#	Responses	Date
1	Do have problems with some physical activities but it has not prevented me from working (i am now retired) due to having the treatment.	10/18/2014 4:41 PM
2	.	10/18/2014 1:46 PM
3	I live almost a normal life. I retired from work a few years ago, this has really helped me. I don't have the worry if going to work and trying to function when I'm not well. I walk very slow, I fall asleep a lot and am generally weak, but it doesn't really have any impact in my life.	10/18/2014 1:14 AM
4	With treatment there is little or no impact.	10/17/2014 7:38 AM
5	All of the above except school/college. GD impacts on my physical health in terms of fatigue and general aches and pains and this in tern impacts on the way life is lived	10/16/2014 10:21 PM
6	At first it did as it took me a while to feel better from my medication. I have also had to adapt to having an infusion every week. Now that I have had this medication I am able to do stuff i might not have been able to do without it. Having a tabet will be a lot easier as i am able to do things i previously wouldn't have been able to. For instance i may be able to travel more or work abroad. If i was to have a tablet, my lifestyle will be vastly improved and different.	10/16/2014 9:34 PM
7	i am 33 years old.i am young.it doesnt effect me.in future i dont know what will happen to me.but i am having treatment.i think i will be fine...I am sad because of gaucher.i am not like the others...i have to have this tratment and accept my illness...	10/16/2014 9:05 PM
8	Other than arrange some time off for appointment, and the necessity of having an ERT infusion at home once a fortnight, having Gaucher Disease does not have any adverse effects upon my daily life.	10/16/2014 2:23 PM
9	I have have never really known any different. Now as I see older friends having to limit what they do I realise that I have always done so.	10/16/2014 2:14 PM
10	Not been to bad.	10/16/2014 1:56 PM
11	I am not affected in my daily life.	10/16/2014 1:45 PM
12	In last 25 years I have sent over 3 years in hospital then add up to 8 more waiting for then recovering from hip & shoulder opertions and the bone crisis.I am unable to work and I have had long periods where I can not even enjoy my two main interests of Coarse Angling in warmer months and playing Snooker and 8 Ball Pool.The not kowing if I will ever be able to do either of my hobbies again is always on my mind as without these I have no standard of life.	10/14/2014 6:09 PM
13	Affects physically and emotionally some how managed to qualify but very difficult to keep up work!	10/14/2014 1:04 AM
14	Yes physically I have adapted to the fact that I can not do much exercise and emotionally I deal with my disease as much as I can rather than involve other people	10/10/2014 9:38 AM
15	Although I had to alter my initial career plans I have gone on to enjoy my working life with very little impact from my health. Now that I am stable with ERT Gauchers really doesn't affect my daily life, other than once a fortnight when I have to home infuse.	10/7/2014 12:31 PM
16	Not v sporty nil else	10/6/2014 9:32 PM
17	Gauchers has never stopped me doing any thing but sport I was never any good at.	10/6/2014 3:45 PM
18	I am in a more delicate situation as I have bone issues that prevent me from having a very active life (performing most sports, walking a lot) but I replaced these with other activities (swimming, stationary bike). Otherwise I can have all the normal social activities done in the normal way.	10/6/2014 1:53 PM

19	I am physically not strong and get depressed because I cannot do the things I would like to do. I need a walking stick for standing, but try to get out as much as possible	10/4/2014 11:28 AM
20	Quite fortunate to say that it doesn't disrupt daily life, able to participate in sports, social gatherings, work etc, although fatigue can be a problem at times especially when having 2 young children to look after!	10/3/2014 11:18 PM
21	I am now a permanent wheelchair user so have all the difficulties that entails.	10/2/2014 5:36 PM
22	I am a good mixer but Gauchers Disease has always been in the way in every aspect of my life. This includes when at school, when at work or at social gatherings. I cannot do what other people are able to do, and cannot do what I would like to do. The guilt I feel at times can be overwhelming as I just want to be, and do, the same as others.	10/1/2014 2:15 PM
23	Now that I am on ERT I am 100% fine. Been able to run marathons, etc.	10/1/2014 12:37 PM
24	Doesn't really affect daily life luckily. At school I dropped some PE classes. Only adaptation has related to the treatment, for example arranging delivery, setting aside time and private location to administer it, occasional need for on call nurse to help out. This can be a bit of a hassle/embarrassing or distressing, especially when in shared accomodation for example university or flat shares.	9/30/2014 8:53 PM
25	The condition effected my whole life - until I was diagnosed. Since being on Enzyme Therapy I feel 10 years younger. Main issue now is the stress and disruption of having to do the infusions. There are some residual issues now eg bone conditions mean I need to avoid activities that could increase risks of falls.	9/30/2014 11:36 AM
26	Only carnt do contact sport too risky for the hips everything normal life since treatment	9/29/2014 10:29 PM
27	at fifty with GAuchers disease and the menapause I needed to stop working but thankful For the 30 plus years I was able To nurse. I	9/29/2014 4:02 PM
28	I try to live my life how I want. Sometimes when I get home from work I have to go straight to bed. I get down sometimes, depressed, frustrated and 'WHY ME'.	9/29/2014 3:58 PM
29	In the early days, when my health was very poor, I had to give up work and with bouts of illness or disability over the years I've never got back to working. I've still managed to have a family and the usual life that goes with that, and my social life is as busy as I want it to be (with or without crutches). Adaptations have happened, but not life diminishing in any way. I concentrate on what I am able to do, rather than what I can't do.	9/29/2014 3:45 PM
30	Time off work for hospital appointments, storage space in my house for treatment stores & a medicine fridge, anaemia	9/29/2014 1:17 PM
31	Did at first had to give up lots things work, going out could not face people no get up and go. but now things was getting better untill 1 year ago landed up with bad ulcers on one of my legs	9/29/2014 1:13 PM
32	As above really - I tihnk it affects me quite a lot at the moment but I'm trying to get over it and remind myself it's still early days. The main problems are other people's perceptions and me being hard on myself and admitting to myself I might have limit how much I want to do to fit with how much I am able to do.	9/29/2014 12:52 PM
33	Well I am limited in what I can do but my friends all know and adapt our activities accordingly my walking distance is limited and I have a lot of help in the house and garden .	9/29/2014 12:08 PM
34	I have some issues of energy levels and some joint problems but I am 68 and some lessening of powers goes with the territory - Having said that recently I have been managing a bit of land we are acquiring so have chainsawed some 70ft trees, built a bridge across the stream using 12ft reinforced concrete beams ... I just move slightly slower and assess more carefully. There's always a way.	9/29/2014 11:59 AM
35	Physically yes I have to use a wheelchair,I live in a ground floor flat,I can't use a bath so have had to have a shower installed	9/29/2014 11:35 AM
36	Whilst working, I avoided any job that meant long periods abroad (not trusting foreign hospitals with my care if I had a flare up). Inability to emigrate as worry for medical expenses if a problem occurred. Seeking a large employer who would accept sudden long periods of absences for such as hip replacements.	9/29/2014 11:23 AM
37	adapt to what my body can allow	9/29/2014 10:26 AM
38	has altered type of job i would do (now work independently), and also has limited some forms of exercise that i can do (no running, for example).	9/29/2014 10:00 AM
39	Little now apart from fornightly infusions, and waiting in for the drugs to be delivered	9/29/2014 9:41 AM

Q7 Are you on Enzyme Replacement Therapy?

Answered: 39 Skipped: 0



Answer Choices	Responses	
Yes	94.87%	37
No	5.13%	2
Total		39

Q8 If you answered yes to Q7 do you still have any unmet medical needs that you feel ERT has not helped with?

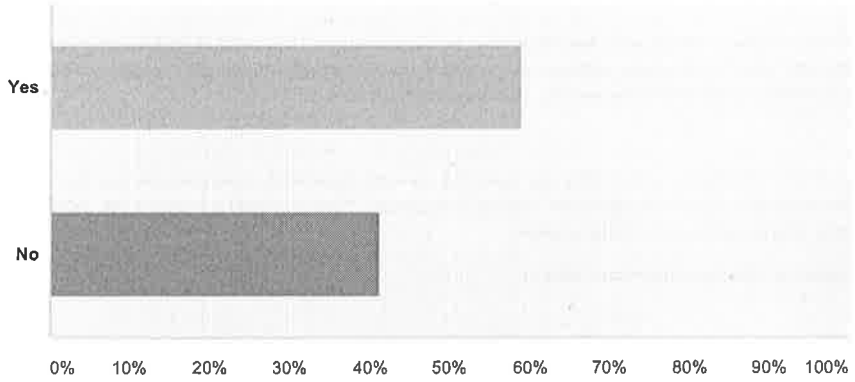
Answered: 39 Skipped: 0

#	Responses	Date
1	No	10/18/2014 4:41 PM
2	No.	10/18/2014 1:46 PM
3	No	10/18/2014 1:14 AM
4	No.	10/17/2014 7:38 AM
5	No. ERT has had a huge, beneficial impact on my wellbeing.	10/16/2014 10:21 PM
6	No	10/16/2014 9:34 PM
7	i am ok.i havent got any problem...	10/16/2014 9:05 PM
8	No.	10/16/2014 2:23 PM
9	No	10/16/2014 2:14 PM
10	No	10/16/2014 1:56 PM
11	N/A	10/16/2014 1:45 PM
12	No I am sure the ERT has halterd or slowed the progression of my disease.	10/14/2014 6:09 PM
13	Joint and lower back pain, feeling tired all the time	10/14/2014 1:04 AM
14	Still have bone crisis.	10/10/2014 9:38 AM
15	No	10/7/2014 12:31 PM
16	No The treatment has far exceeded ny expectations Obviously i cant say how I would be with out treatment	10/6/2014 9:32 PM
17	No	10/6/2014 3:45 PM
18	The only disadvantage of this medication is that it needs to be stored in special conditions, to be prepared in a certain way and to be administered over a longer period of time. This does not allow you a lot of flexibility of your schedule (every month you have to be home to receive your medication and infusion equipment), every two weeks you have to be able to cut from your work schedule or other activities to have your treatment administered. From medical point of view, I know that ERT does not have a great effect when bone disease sets in.	10/6/2014 1:53 PM
19	No	10/4/2014 11:28 AM
20	No	10/3/2014 11:18 PM
21	I still break my bones as a result of a trauma (such as falling out of my wheelchair) which can require a long hospital stay.	10/2/2014 5:36 PM
22	Damage done to skeleton before enzyme replacement therapy became available, making me very disabled.	10/1/2014 2:15 PM
23	No.	10/1/2014 12:37 PM
24	No	9/30/2014 8:53 PM
25	Not sure	9/30/2014 11:36 AM
26	No	9/29/2014 10:29 PM
27	No	9/29/2014 4:02 PM
28	Not sure how to answer this one.	9/29/2014 3:58 PM

29	I have major skeletal involvement with the illness, and was many years on bisphosphonates, however, the fractures were still happening. I'm now on Strontium Renalate, and the change really seems to have helped prevent more spinal fractures. The only difficulties I have now is controlling the bouts of discomfort in joints where the damage has already been done.	9/29/2014 3:45 PM
30	No	9/29/2014 1:17 PM
31	no	9/29/2014 1:13 PM
32	I have really profound fatigue which has always been my worst symptom. I said at the Royal Free recently that I felt like the ERT wasn't really helping and they said the fatigue was very unusal for Gauchers. I recently got diagnosed with depression so that may be the problem. I'm trying to sort that out too!!!	9/29/2014 12:52 PM
33	No	9/29/2014 12:08 PM
34	I think that is impossible to answer either way, assuming you mean those needs connected with Gauchers.. I suppose an oral medication might be thought better - but only if as effective. Other than that I am happy to rely on my medical team for advice regarding any related problems.	9/29/2014 11:59 AM
35	Yes because I also have Rheumatoid Arthritis	9/29/2014 11:35 AM
36	No	9/29/2014 11:23 AM
37	no	9/29/2014 10:26 AM
38	Yes, but marginal e.g. some bone involvement.	9/29/2014 10:00 AM
39	No	9/29/2014 9:41 AM

Q9 Were you diagnosed before Enzyme Replacement Therapy was available?

Answered: 39 Skipped: 0



Answer Choices	Responses	
Yes	58.97%	23
No	41.03%	16
Total		39

Q10 If you answered Yes to Q9 then please describe to us the physical and emotional challenges of living with a condition that did not have a treatment.

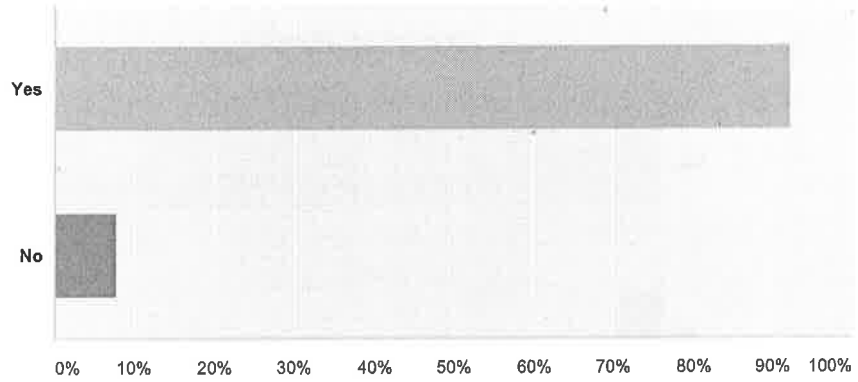
Answered: 28 Skipped: 11

#	Responses	Date
1	Enlarged spleen and liver causing varices resulting in liver failure after one of my hip operations	10/18/2014 4:41 PM
2	As I stated in a previous question, I felt it was best to try to deny the illness in my mind so I could carry on with family life. It was sometimes daunting, my health has been very poor at certain times of my life. The worst episodes being affected by my poor liver function, which was very hard to deal with and look after our five children. Pain and poor mobility were also a hindrance, I was becoming so weak, it was a great worry . We took out a life insurance policy, I was worried what would happen to our children if I died, as my husband needed to work to look after them financially. (This was before the internet and as the doctor I saw from the insurance company didn't know much about Gauchers it was granted) We were aware if the seriousness if my illness, but carried on best we could.	10/18/2014 1:14 AM
3	This was a very worrying time but I remained optimistic that a treatment would become available and luckily it did.	10/17/2014 7:38 AM
4	i was in turkey and i had nothing.Of course it was hard without treatment...i had pregnancy as well.doctors alwasy looked after me when i was pregnant...i had really difficult time.	10/16/2014 9:05 PM
5	As treatment wasn't an option at the time, I just had to accept that I had a condition that could cause me complications at a later date. Other than that, I carried on as normal.	10/16/2014 2:23 PM
6	I expected to die young which was very hard when my children were young.	10/16/2014 2:14 PM
7	health problems	10/16/2014 1:56 PM
8	none	10/16/2014 1:45 PM
9	I was started on ERT in febuary 1994 and as only got to permission to attend Gauchers Clinic Addenbrooks in 1993 I know this was before to ERT was approved by B.M.A. I didnt even know a treatment was available till1993,had I been able to visit clinic earlier I dont know I might have not have lost my spleen or my left hip. This was due to Dr at Ulster not allowing me access to Gauchers clinic I (I only got permission after letter to MP)	10/14/2014 6:09 PM
10	Hospitalised most of the time receiving blood transfusion and analgesia for the pain Isolates, unable to attend school, surgical operations during childhood such as splenectomy, knee and many teeth surgery!	10/14/2014 1:04 AM
11	It was debilitating. I had my spleen removed and had serious bleeding problems after giving birth ,very severe bone crisis,fatigue.It was very distressing for my family as no ongoing treatment was available	10/10/2014 9:38 AM
12	Physically I had a lot of pain in my joints/bones and had an enlarged abdomen due to my liver/spleen. Emotionally I am a reasonably strong person who tends to think positively most of the time, although suppose the greatest concern was the unknown; how the disease would continue to progress.	10/7/2014 12:31 PM
13	easy bleeding	10/6/2014 9:32 PM
14	Never knew any different.	10/6/2014 3:45 PM
15	When I was diagnosed, it was believed that removing the spleen was a cure for the disease. Therefore, considering that I didn't have any severe health issues after that, it did not influence my life in a negative way. Unfortunately, removing the spleen is not a cure, and you end up living in ignorance until you discover that you did not have enough information to prevent the more severe consequences of the disease (bone disease).	10/6/2014 1:53 PM
16	I had prepared myself that I would probably require full time care before the age of 50. I'm now almost 60 and don't expect to need full time care until I reach old age!	10/2/2014 5:36 PM
17	I have suffered agonising bone pain over the years and also fever. I have been unable to get out of bed and walk unaided when having a bone crises. I have been hospitalised for long periods of time on a number of occasions, and had to wear callipers, wear splints and had radiotherapy for pain relief as a child. I have always put on a cheerful face when in the company of others, when sometimes all I want to do is cry.	10/1/2014 2:15 PM
18	I feel let down cheated and angry that nothing was done for me until I took information to my GP in Stafford in 2001.	9/29/2014 3:58 PM

19	Probably answered this earlier. I was in my early twenties when diagnosed, and other than the symptoms; didn't give it too much thought. Went on to have three babies before treatment, and had health and mobility issues most of that time. Symptoms were dealt with as they arose and I was happy with that.	9/29/2014 3:45 PM
20	NA	9/29/2014 1:17 PM
21	N/A	9/29/2014 1:13 PM
22	My body was stiff so and painful and both hips were replaced when my husband was alive he was a great help to me and I got on with living to the best of my ability .	9/29/2014 12:08 PM
23	One or two minor challenges, splenetic infarct - bone too but these resolved with rest. Clearly one does ponder one's lot but apart from occasional 'down' days no real difficulties as I perceive my life. I was fortunate in that the symptoms were tolerable and when the level became acute, by then, treatment was available. Phew!	9/29/2014 11:59 AM
24	Getting depressed because the physical challenges We're a big problem	9/29/2014 11:35 AM
25	See above	9/29/2014 11:23 AM
26	undescribable paln. pressure put on parents.	9/29/2014 10:26 AM
27	Was mentally exhausting and a little depressing. Vomited out stomach contents every morning on awakening. did not expect to live well for many years, reduced willingness and desire to get married and have kids.	9/29/2014 10:00 AM
28	But not able to have treatment, which concerned me.	9/29/2014 9:41 AM

Q11 Have you heard about the new oral therapy that Genzyme have developed for Type 1 adults with Gaucher disease?

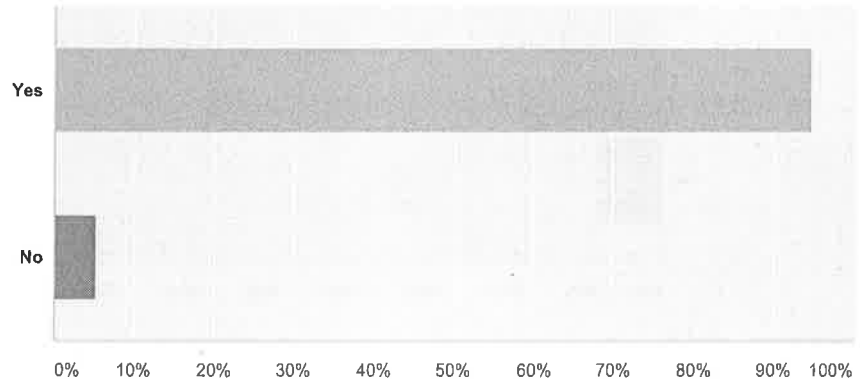
Answered: 39 Skipped: 0



Answer Choices	Responses	
Yes	**92.31%**	36
No	**7.69%**	3
Total		**39**

Q12 Would you consider taking an oral treatment for your Gaucher disease rather than regular enzyme replacement therapy infusions, subject to a full consultation with your doctor?

Answered: 39 Skipped: 0



Answer Choices	Responses	
Yes	94.87%	37
No	5.13%	2
Total		39

Q13 What do you consider to be the advantages of taking an oral therapy? What difference do you think it would make to you?

Answered: 39 Skipped: 0

#	Responses	Date
1	Not having to infuse	10/18/2014 4:41 PM
2	It makes my life easier at work and personal. Regarding career, I can consider taking many jobs which I like to do. For example, I can take offshore jobs which involve a lot of travelling. In that situation, I no need to worry about the treatment as I could take the medicines with me. Personally, I will have more time to spend with the family and friends because I no need to worry about my appointment for the treatment.	10/18/2014 1:46 PM
3	I travel twice a year for a month outside the uk. Oral therapy would mean I could stay away longer, apart from this I am happy with my infusions.	10/18/2014 1:14 AM
4	This would be amazing. To stop infusions would be a major improvement to my life. Doing infusions is not at all pleasant.	10/17/2014 7:38 AM
5	Not being tied to the cycle of ERT and drug receipt and control (assuming that home storage of the drug will not be temperature critical) would restore a degree of flexibility.	10/16/2014 10:21 PM
6	My lifestyle will be completely different. I will be able to do stuff I cant do at the moment. If i was to go onto a tablet, this would help me massively if the future as i will be able to travel more or even get a job where I am able travel to other countries for a long period of time.	10/16/2014 9:34 PM
7	i will be more happier,i do not need to having injections every 2 weeks.that is gonna be amazing for me...but this decision belongs to my doctor.if they say you can take oral treatment i will be fine...	10/16/2014 9:05 PM
8	Fortnightly infusions are time consuming, and as with all procedures, carry risks (such as infection or adverse reactions). My wife carries out my treatment, and it is very stressful for her, putting her under pressure to carry out everything correctly. Taking an oral therapy would alomost completely remove these issues.	10/16/2014 2:23 PM
9	I already take Zavesca and to be released from the stress of an infusion in 'tired' veins is wonderful.	10/16/2014 2:14 PM
10	Time, easier	10/16/2014 1:56 PM
11	It would currently make no difference to me because I don't get emzyme replacement but I would imagine that it would be easier in all sorts of ways if you could just take this orally.	10/16/2014 1:45 PM
12	I have a problem with needles i always have,plus a lot of my viens have become hard to find. It would a big differnce but I wold be worried that it might be as effictive as infused enzyme.	10/14/2014 6:09 PM
13	Easy to take it, no need for infusion and big treatment order	10/14/2014 1:04 AM
14	Better for my veins and not so invasive for both me am nd my family	10/10/2014 9:38 AM
15	I suppose the main advantage would be no cannulation.	10/7/2014 12:31 PM
16	after 18years of treatment im worried i may run out of venous access, at some point	10/6/2014 9:32 PM
17	I feel it would stop the tension my wife sometimes feels when doing the infusions.	10/6/2014 3:45 PM
18	As long as the medical efficiency of the oral treatment is as good or better then the infusion version, I would like to benefit from this oral alternative. As explained above, using the infusion version means that the medication needs to be stored in special conditions, to be prepared in a certain way and to be administered over a longer period of time. This does not allow you a lot of flexibility of your schedule (every month you have to be home to receive your medication and infusion equipment), every two weeks you have to be able to cut from your work schedule or other activities to have your treatment administered. I don't expect for the oral treatment to eliminate all of these steps but I expect it to make the life easier for people with this disease.	10/6/2014 1:53 PM
19	A massive advantage, freedom and stress from the logistical problems of home medication removed, and costs could be less, no more home nurses/equipment/deliveries,which are often incorrect. Refrigeration checking etc.	10/4/2014 11:28 AM
20	It would be easier but then again it's become part of life doing the IV infusions.	10/3/2014 11:18 PM

21	It is getting harder and harder to get a vein for my infusion. An oral therapy will be much, much easier to administer , and will mean I can go abroad on holiday for more than a week at a time.	10/2/2014 5:36 PM
22	It would be a boon to me as my veins have really suffered over the last 23 years, and the nurses sometime have great difficult in canulating me before my infusion. I also have to travel to my local hospital every two weeks as I am unable to self infuse at home because of my vein problems. Oral therapy would involve no travel to hospital and my veins no longer being punished.	10/1/2014 2:15 PM
23	Not having infusions.	10/1/2014 12:37 PM
24	Enormous difference! I would jump at the chance and would be unimaginably relieved after 15 years of an invasive, sometimes distressing and complex treatment.	9/30/2014 8:53 PM
25	Infusions are a major issue and getting rid of the process would remove an enormous burden. I am independent (ie we do them ourselves at home) but infusions are still very time consuming and stressful. I do infusion preparation etc but my wife inserts cannula. She suffers from epilepsy and if she has recently had a seizure we have to postpone the infusion and the stress is not good for her.. On top of the stress and hassle we need to allocate a half day to the process (general disinfection of work areas, infusion prep, infusion, clean up etc). To help getting the cannula in correctly I need to make sure I am well hydrated and warm and this tends to mean an infusion around mid day. If the first couple of attempts fail we then need to put things to one side and try again later. This then means that we avoid making any commitments on the day of the infusion.	9/30/2014 11:36 AM
26	Wouldn't have to sore treatment or organise people being in	9/29/2014 10:29 PM
27	I have been infusing for 20 years since 1994 It would be great not have to and have oral medication instead	9/29/2014 4:02 PM
28	I would feel almost free, we set aside every other Tuesday evening to do my medication. Taking it orally would mean no refrigerated meds delivered to work, no storage and freedom when away.	9/29/2014 3:58 PM
29	22 years of infusions into the same blood vessels have started to take its toll. I home infuse and don't like admitting that I sometimes have to make more than one attempt to access a blood vessel and they are getting pretty scarred up! The convenience of an oral tablet would be great.	9/29/2014 3:45 PM
30	More convenient and manageable, less stress on my narrow veins, less time consuming, I'd no longer have to have room taken up with boxes of treatment stock or a medicine fridge	9/29/2014 1:17 PM
31	save going to York Hospital every fortnight fighting traffic and waiting for drugs to be made up.	9/29/2014 1:13 PM
32	Less disruptive - able to travel for longer.	9/29/2014 12:52 PM
33	Every other Wednesday I would be free !	9/29/2014 12:08 PM
34	The only advantage so far as I am concerned is not having to infuse with all that implies. I am not sure what difference it might make to me - assuming no side effects - like turning green with red dots. Daily pills can be perceived as equally onerous as fortnightly infusions. A fine balance perhaps.	9/29/2014 11:59 AM
35	I don't mind the infusions but it would be marvellous to take a pill	9/29/2014 11:35 AM
36	Less risk than putting needles into the body, and the eventual accumulated damage to veins. Not being reliant on timly drug delivery and nurse availability. Not being tied to a location every 2 weeks (I could take holidays when I want and for longer than 1 to 2 weeks without missing an infusion).	9/29/2014 11:23 AM
37	no more injections	9/29/2014 10:26 AM
38	Easier to integrate into busy lifestyle. Veins are getting hard after many years of infusions!	9/29/2014 10:00 AM
39	Simpler, and will avoid infusions and the potential dangers attached to them	9/29/2014 9:41 AM

Q14 What disadvantages do you consider an oral therapy would have?

Answered: 39 Skipped: 0

#	Responses	Date
1	Easier to take medication	10/18/2014 4:41 PM
2	None.	10/18/2014 1:46 PM
3	Cerezyme has changed my life so much , I would be reluctant to change.	10/18/2014 1:14 AM
4	If it is as effective then I do not see any.	10/17/2014 7:38 AM
5	Being diagnosed late my symptoms were at the severe extreme of all measures for type 1 GD. While my bodily structures and functions are being restored to a better state, there is still a way to go. I would be nervous of moving away from ERT for a while yet	10/16/2014 10:21 PM
6	The oral medication would be great but there is also the risk of side effects that i'm sure i'm willing to consider unless i'm convinced otherwise.	10/16/2014 9:34 PM
7	i think is gonna be useful for all of us...if it works perfectly.	10/16/2014 9:05 PM
8	The only disadvantage I could think of would be an adverse reaction to the oral therapy, or if it was not as effective as an infusion.	10/16/2014 2:23 PM
9	As above	10/16/2014 2:14 PM
10	Maybe not do the same as infusion	10/16/2014 1:56 PM
11	Remembering to take it would be one and the side effects another.	10/16/2014 1:45 PM
12	No needles	10/14/2014 6:09 PM
13	The side effects?I	10/14/2014 1:04 AM
14	None as long it maintains my condition	10/10/2014 9:38 AM
15	Remembering to take it at the right time. I would personally not choose to have the new oral therapy because I am fortunate to have no problems with infusing myself at home and this is only fortnightly, rather than remembering to take a tablet daily. However my main concern would be taking another new treatment and being a 'guinea pig' again. I currently use velaglucerase from Shire; following the problems with Genezyme a few years ago I have lost my confidence in them as a company.	10/7/2014 12:31 PM
16	may not be effective, or have other side effects may be pricier	10/6/2014 9:32 PM
17	None	10/6/2014 3:45 PM
18	As long as the medical efficiency of the oral treatment is as good or better then the infusion version, I see no disadvantages to the oral treatment.	10/6/2014 1:53 PM
19	None that I know of if successful.	10/4/2014 11:28 AM
20	It would depend if it has the same effect/benefits as doing the IV infusion, if so then all good.	10/3/2014 11:18 PM
21	Can't think of any.	10/2/2014 5:36 PM
22	Assuming I have the same results as with infusions, and that I can tolerate the new oral therapy, I can foresee no disadvantages at all.	10/1/2014 2:15 PM
23	Concern if the oral therapy will work.	10/1/2014 12:37 PM
24	None! Unless there were side effects.	9/30/2014 8:53 PM
25	Possible side effects. The infusion process is a major operation for us but so far I have had no adverse side effects	9/30/2014 11:36 AM
26	Depends on frequency if you had to take tablets 3 times per day compared to a one hour infusion every 2 weeks would be more of an impact	9/29/2014 10:29 PM
27	None	9/29/2014 4:02 PM
28	Don't know as of yet.	9/29/2014 3:58 PM

29	Hopefully none. So long as there are no adverse effects on the stomach (I tried an oral bisphosphonate once, and was as sick as a dog!!).	9/29/2014 3:45 PM
30	Worried it wouldn't be as effective	9/29/2014 1:17 PM
31	If there's any side affects with oral therapy. I have had oral therapy before and add bad experience with them would not like to have them again	9/29/2014 1:13 PM
32	I'd be a bit concerned about possible side effects	9/29/2014 12:52 PM
33	I could take it on holiday wherever I went . At the moment my life revolves around my treatment I do a lot of family visiting driving myself but always around my treatment days .	9/29/2014 12:08 PM
34	You tell me. The only real criterion for me is effective disease control, possible side effects. Without such info can't say.	9/29/2014 11:59 AM
35	None	9/29/2014 11:35 AM
36	Frequency of taking pills (remembering to take them).	9/29/2014 11:23 AM
37	remembering to do it	9/29/2014 10:26 AM
38	none, unless there are side effects.	9/29/2014 10:00 AM
39	None	9/29/2014 9:41 AM

Q15 Is there anything else that you would like to share with us that would provide a unique perspective on what it is like for you and your family living with Gaucher disease?

Answered: 30 Skipped: 9

#	Responses	Date
1	No	10/18/2014 4:41 PM
2	I am always worried about Parkinson's as carriers of the disease are more likely to develop it. Some of my family in the past has had it, I am worried about my children, incase they develop Parkinson's .	10/18/2014 1:14 AM
3	Just very glad to be living in a country that provides this treatment.	10/17/2014 7:38 AM
4	not at this time	10/16/2014 10:21 PM
5	This has an impact on my family as well as me as they have been trained to give me my treatment infusions. When they get older and so do I there may have to be a change meaning that i will have to learn to infuse myself or seek other help. This is inconvenience and it would be easier if i was able to have a tablet.	10/16/2014 9:34 PM
6	my husband and my daughter always help me.we dont think much about my gaucher...	10/16/2014 9:05 PM
7	No.	10/16/2014 2:23 PM
8	I have been very lucky as my symptoms have never been severe but the emotional aspects have been hard. I never shared how I felt because no one even knew what this disease was.	10/16/2014 2:14 PM
9	No because it doesn't really affect my life.	10/16/2014 1:45 PM
10	Nothing i can think off	10/14/2014 6:09 PM
11	It affects my life every day physically and emotionally difficult to cope with daily activities, also financially, Sadly, I just give up my best job I ever had in my life due to joints & lower back pain!	10/14/2014 1:04 AM
12	im very grateful for the availability of any treatmant i dont like the bother of the infusion, but a small proice to pay id like a drug holiday !!	10/6/2014 9:32 PM
13	I have the disease and I just have to live with it.	10/6/2014 3:45 PM
14	My life is governed by a monthly delivery service, and a two weekly infusion,although cerezyme is a wonderful treatment and am grateful for it, the oral therapy would be heaven sent.	10/4/2014 11:28 AM
15	Just feel very fortunate to have treatment that keeps my symptoms at bay and to have an amazing medical team who are extremely dedicated and knowledgeable, this gives me peace of mind knowing that I am in good hands.	10/3/2014 11:18 PM
16	Within a month of being on ERT the exhaustion I had experience most of my life had lifted. It made it possible for me to move from a fairly demanding job as a teacher to an even more challenging one which has long hours and involves a lot of travelling. Had ERT not come along when it did I would not be leading the full life I do, indeed I wouldn't have even been able to contemplate doing what I do now.	10/2/2014 5:36 PM
17	My only regret is that ERT treatment was not available at the time of my diagnosis, and take great comfort that, by not having a family of my own, I am not passing this disease onto future generations for someone to suffer as I have suffered.	10/1/2014 2:15 PM
18	No.	10/1/2014 12:37 PM
19	Impact on decision re whether to have children due to genetic nature of the disease (my husband is of the same ethnic background as me). Had carrier testing before getting married.	9/30/2014 8:53 PM
20	If I was not on Enzyme therapy I would probably now be very seriously ill. Far from my health continuing to deteriorate the Enzyme therapy has in fact meant that my general health has significantly improved since I started on it and I have much more energy. Hence I have much to be thank the NHS for. It would though remove an enormous burden from our lives if I could switch to an effective oral therapy	9/30/2014 11:36 AM
21	Don't think so	9/29/2014 10:29 PM

22	I am thankful to be diagnosed and treated	9/29/2014 4:02 PM
23	I suppose with the amount of major health issues throughout my life I just 'get on with it' but nobody sees the me that sometimes feels it's just not fair. I've just had my third hip replacement and I feel cheated because my first replacement was left far too long, and then I had to go private. I get so down.	9/29/2014 3:58 PM
24	There have been times over the years since my symptoms started that I have felt very poorly, and during bone crises when I've felt very sorry for myself because of the pain. But, with treatment, I've come through that and despite the odd set back (or fracture), probably now feel as well as I've ever felt. For me, Gauchers desease is something I have, much like some have diabetes, some have epilepsy, and so on. I know my limitations and work around them. For my family I think its just something they've grown up with and they don't give it a thought unless it comes up on a medical history questionnaire. Life's pretty good despite Gauchers Disease.	9/29/2014 3:45 PM
25	Informing and telling more people that there is a disease called Gaucher because its very rare it is kept quiet make it public knowledge will help family's living with Gaucher	9/29/2014 1:13 PM
26	It's a bit pants really!!!	9/29/2014 12:52 PM
27	I am eternally grateful for the treatment so are my family . I can still live on my own and do most things for myself . That is so important to me as I get older.	9/29/2014 12:08 PM
28	Every body's life is unique - what can I say - in the spectrum of possible types and effects of Gauchers I have been fortunate in that I am medicated and that seems effective with no side effects to speak of and my symptoms so far are relatively easy to tolerate, i.e. could be worse so we/I don't really obsess over it. Tell me when I can be a GMO - and whether, if being one, I will be allowed in Safeways.	9/29/2014 11:59 AM
29	no	9/29/2014 10:00 AM
30	I am very very grateful for being able to live an almost normal life	9/29/2014 9:41 AM

Appendix G – NHS England statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Commissioners provide a unique perspective on the technology, which is not available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Commissioner's perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: [redacted]

Name of your organisation: NHS England

Please indicate your position in the organisation: Public health adviser

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

What is the expected place of the technology in current practice?

Eliglustat is not currently commissioned by NHS England. The appropriate use would be as an alternative to enzyme replacement therapy or substrate reduction therapy in patients with Gaucher disease.

Potential impact on the NHS if NICE recommends the technology

In what setting should/could the technology be used – for example, expert centres only, homecare? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

This oral therapy potentially replaces intravenous infusion, but it will be important for patients to remain under the care of expert centres for initiation and monitoring of eliglustat therapy (if recommended)

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Other Issues

Please include here any other issues you would like the Evaluation Committee to consider when evaluating this technology?

Current clinical practice in England is to titrate the dose of enzyme replacement therapy against the patient's clinical condition and use the lowest effective dose. The economic evaluation will need to take account of this.

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: Royal College of Physicians (RCP)

- **Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None**

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

There are approximately 400 patients in the UK
I would expect 50-100 to receive treatment with the technology

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Gaucher disease is an inherited disorder which is largely diagnosed in the UK in patients once they have become symptomatic as a result of the clinical presentation of those symptoms. There is often a delay between the onset of clinical manifestations of the condition and diagnosis. A minority of patients are diagnosed before the onset of symptoms as a result of screening of the siblings of a symptomatic index case. As a result most patients fulfil the criteria for Gaucher -specific therapy as specified by the NHS England Standard Operating Procedure from diagnosis. All patients with a confirmed diagnosis of Gaucher disease are evaluated through one of 5 adult or 3 paediatric specialist centres in England all of whom work to the NHS England SOP eliminating geographical variation. Patients deemed eligible for Gaucher-specific therapy receive intravenous enzyme replacement therapy (ERT) as first line. Two ERT products have marketing approval in the EU, imiglucerase and velaglucerase. Recently patients new to ERT in England receive Velaglucerase as a result of an NHS England tender and a cost advantage. Patients receiving ERT prior to the establishment of the current framework continue to be prescribed both imiglucerase or velaglucerase. ERT is initiated in the hospital setting and transferred to home care after 1-3 hospital infusions. Home care is facilitated through an NHS England framework with BUPA and Healthcare at home administering the home care process and providing nurses for those patient who require nursing input for cannulation or during the total infusion. Some patients or their relatives reconstitute and administer ERT themselves and depend on home care only for deliveries and provision of a fridge for storage of enzyme. Oral substrate reduction therapy is currently available with Miglustat which is approved for patients with mild to moderate Gaucher disease in whom ERT is unsuitable. It has been considered in patients in whom cannulation is difficult, infusions are impractical and theoretically those with infusion reactions. Its use in type 1 Gaucher disease has been limited by moderate efficacy and concern regarding side effects of gastrointestinal symptoms and peripheral neuropathy.
It is anticipated that the place of eliglustat in clinical practice will be as an alternative first line therapeutic option to naïve or enzyme- experienced adult patients with type 1 Gaucher disease without limitation by severity or suitability for enzyme replacement therapy.

Physicians in England at the Lysosomal Disease Service (LSD) centres all work to the National SOP with minimal variation in practice.

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Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

The potential advantage of the technology, eliglustat, is the availability of an effective oral alternative to enzyme therapy for adult patients with type 1 Gaucher disease who are either naïve or experienced with therapy. Unlike miglustat, clinical trial data suggests that eliglustat has comparative efficacy to ERT without the medical, quality of life and health economic implications of an intravenous therapy. Enzyme replacement therapy is highly effective but necessarily requires upwards of 1 hour intravenous infusion every two weeks. Whilst this can be self-administered or nurse administered at home it is associated with a burden or time and medical equipment. Some patients report a social burden related to having to take time off work or school,and/or a psychological burden associated with cannulation. Currently patients are supplied with a dedicated refrigerator at home which reduces space, creates noise and as a result of daily temperature checking is a constant reminder of their condition. Whilst ERT is generally well tolerated a small proportion of patients develop anti-drug antibodies, the significance of which is unknown, and some infusion reactions. The administration of home care is an additional expense for the health economy and burden for specialist centre nurses and physicians, who retain clinical responsibility for the patients, dealing with complaints, queries and adverse reactions. Refrigerator failure is not infrequent and can result in loss of doses for the patient. None-the-less some patients do prefer the intermittent nature of enzyme infusions with comparative normality for the intervening 2 weeks. Disadvantaged of eliglustat are the requirement for cytochrome p450 2D6 genetic testing as a result of its metabolism by this route, plasma level monitoring and avoidance of drugs which may potentially interact through this pathway.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Type 1 Gaucher disease is a heterogenous condition and whilst a number of severity scores to assess disease burden have been developed a prognostic scoring system is lacking. Some phenotype/ genotype correlations can be made but modifying factors exist and predictions of severity are not absolute. Clinical trial data does not suggest the existence of subgroups of GD1 patients who would benefit heterogeneously from eliglustat. Patients with a rare subtype of Gaucher disease, resulting from deficiency of the activator protein saponsin C, cannot respond to exogenous enzyme therapy. Although eliglustat has not been tested in this subtype, theory suggests it should have a salutary biological effect through reducing production of substrate.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?

Since most UK patients diagnosed with GD are eligible for treatment and currently receive ERT the delivery of care with eliglustat would not generate

increased treated patient numbers or require additional specialist nurses or physicians. Other than for delivery of the drug it is likely that home nursing and storage requirements will reduced.
Genetic testing for cyt p450 2D6 genetic status will be required and possible consideration of plasma drug monitoring at the initiation of therapy or if an interacting medication is initiated.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Eliglustat is currently only available to patients who participated in the clinical trials and possibly some patients to whom it has been made available by compassionate access

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

No guidelines currently exist for the use of eliglustat in clinical practice in adult type 1 Gaucher patients.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Please see the initial response outlining the advantages of the therapy.

Eliglustat is indicated for use in patients who are cytochrome P450 (CYP) 2D6 extensive, intermediate, or poor metabolizers, as identified by a genetic test but is contraindicated in patients who are ultra-rapid CYP2D6 metabolizers and may not achieve therapeutic concentrations of eliglustat, and those whose CYP2D6 metabolic rate is undetermined and so a specific dose cannot be recommended.

Eliglustat is substrate of CYP2D6 and CYP3A; According to the US prescribing information concomitant use of medicines that are inhibitors of either enzyme (e.g.the CYP2D6 inhibitors paroxetine and terbinafine and the CYP3A inhibitors ketoconazole, fluconazole and ranitidine) could significantly increase exposure to eliglustat, causing prolongation of PR ,QTc and/or QRS intervals and hence cardiacarrhythmias. Eliglustat may also interact with grapefruit juice. Concomitant use of eliglustat with CYP3A inducers such as

rifampin, carbamazepine, phenobarbital, St.John's Wort and phenytoin decreases eliglustat exposure. Eliglustat inhibits P-glycoprotein(P-gp)andCYP2D6; concomitant administration of eliglustat could increase the concentrations of drugs that are substrates of P-gp (e.g. digoxin, phenytoin, colchicine and dabigatranetexilate) or CYP2D6 (e.g.metoprolol, tricyclic anti-depressants and phenothiazines). However none of the mentioned medications are expected concomitant medication in Gaucher disease. Vigilance will be required but drug interactions are not expected to be problematic in most patients.

Eliglustat is also not recommended in patients with severe hepatic or renal impairment due to lack of data . Severe hepatic and renal impairment are rarely features of GD with a minority of patient presenting with hepatic abnormalities due to liver infiltration of Gaucher cells. In this instance if hepatic impairment was severe first line therapy would be ERT until hepatic dysfunction was considered to have improved sufficiently to permit eliglustat.
According to the US prescribing information eliglustat is pregnancy category C and therefore ERT which is used with confidence during pregnancy would be considered ahead of eliglustat in pregnant females and in women contemplating pregnancy.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

The technology has not as yet been used in clinical practice outside of clinical trials in England. The entry criteria for the trials broadly reflect the starting criteria for Gaucher specific therapy in the NHS England SOP and it would be anticipated that this SOP would not differentiate starting criteria for the current alternatives and eliglustat . Current stopping criteria include patients specific outcomes such as non-compliance, development of a co-existing life-threatening condition, movement out of NHS eligibility, disease –specific outcomes such as failure of the treatment to improve or maintain stable multiple aspects of the condition and treatment specific outcomes such as unmanageable infusion reactions. It is anticipated that the patient and disease-specific outcomes would be consistent for any new technology but the treatment specific outcomes will require consideration based on the specifics of the technology.
Genetic testing for cyt p450 2D6 genotypes will be required at initiated to confirm eligibility and dose.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Eliglustat for treating type 1 Gaucher disease

The evidence presented in phase 2 and 3 clinical trials is consistent with UK practice for patients starting therapy and the outcome measure relevant, meaningful and those used to monitor patients in the UK according to the NHS England SOP.

The results in treatment-naïve patients at 1, 2 and 4 years of an open-label phase 2 study have been reported (1, 2, 3), with 19 of 26 patients completing 4 years . Eliglustat (50 or 100 mg based on plasma drug concentrations) was orally self-administered twice per day. At 1 year statistically significant improvements in mean haemoglobin (1.62 g/dL) and platelet count (40.3%) are consistent with current expectations with the existing standard of care in clinical practice.
At 2 years mean haemoglobin level increased 2.1 g/dL overall and 3.1 g/dL in 10 patients with baseline anaemia (2) The mean haemoglobin at 4 years increased by 2.3±1.5g/dL and platelet count by 95% . At 4 years the mean spleen volume decreased by 63% and liver volumes by 28%. The median chitotriosidase and CCL-18 , biomarkers correlating with overall substrate burden, each decreased by 82%. The report also described normalisation of plasma glucosylceramide the relevant substrate in Gaucher disease.

The effect of a therapy for GD can also be assessed in terms of patients achieving targets in various haematological, visceral and other domains, the so-called therapeutic goals At 2 years seventeen (85%) patients met published therapeutic goals for ≥ 3 of the 4 haemoglobin, platelet , liver and spleen volume parameters.

Effects on Gaucher-related bone disease were reported separately in 19 patients up to 4 years (4) Lumbar spine T-scores were reported to increase significantly from a mean of -1.6 to -0.9 whilst mean femur T-score remained normal . MRI of the femurs showed that 10/18 patients had decreased Gaucher cell infiltration compared to baseline; and there were no lumbar spine or femoral fractures and no reported bone crises. At year 4, one new asymptomatic, indeterminate bone lesion was discovered that subsequently resolved.

In the phase 3 engage study 40 patients aged 16 years or older with splenomegaly and thrombocytopenia and/or anaemia were randomized to receive placebo or eliglustat (50 mg bd initially and then 100 mg bd from week 4 depending on plasma concentrations. After 9 months there was a greater reduction in spleen volume with eliglustat than placebo (-27.8 vs 2.3%)(5). Significant differences were also seen for change in Hb, change in liver volume change in platelet count, improvement in bone marrow burden score and DS3 disease severity score. The difference in total spine bone mineral density was not statistically significant.

An endpoint of non-inferiority is reported in the open label ENCORE study which included 159 patients who had ERT for 3 year and met certain goals at

baseline Patients were randomised to Eliglustat 50mg or 100mg bd depending on plasma concentrations of imiglucerase for 12months. Eliglustat demonstrated non-inferiority to imiglucerase for the composite primary endpoint of stability in spleen liver volume haemoglobin level and platelet count from baseline to 12months Therapeutic goals were maintained in 12 of 15 eliglustat recipients (6)

Data from the engage study and the phase 2 study has been compared with matched patients from the Genzyme International Collaborative Gaucher Group Registry (patients treated in routine clinical practice including the UK). indicating similar effects or haematological and visceral parameters at 9 12 and 48 months (7) The increase in lumbar spine Z score was greater than that seen with imiglucerase

1: Lukina E, Watman N, Dragosky M, Pastores GM, Arreguin EA, Rosenbaum H, Zimran A, Angell J, Ross L, Puga AC, Peterschmitt JM. Eliglustat, an investigational oral therapy for Gaucher disease type 1: Phase 2 trial results after 4years of treatment. Blood Cells Mol Dis. 2014 Dec;53(4):274-6. doi: 10.1016/j.bcmd.2014.04.002. Epub 2014 May 15. PubMed PMID: 24835462.

2: Lukina E, Watman N, Arreguin EA, Dragosky M, Iastrebner M, Rosenbaum H, Phillips M, Pastores GM, Kamath RS, Rosenthal DI, Kaper M, Singh T, Puga AC, Peterschmitt MJ. Improvement in hematological, visceral, and skeletal manifestations of Gaucher disease type 1 with oral eliglustat tartrate (Genz-112638) treatment: 2-year results of a phase 2 study. Blood. 2010 Nov 18;116(20):4095-8. doi: 10.1182/blood-2010-06-293902. Epub 2010 Aug 16. Erratumin: Blood. 2011 May 19;117(20):5551. PubMed PMID: 20713962; PubMed Central PMCID PMC2993616.

3: Lukina E, Watman N, Arreguin EA, Banikazemi M, Dragosky M, Iastrebner M, Rosenbaum H, Phillips M, Pastores GM, Rosenthal DI, Kaper M, Singh T, Puga AC, Bonate PL, Peterschmitt MJ. A phase 2 study of eliglustat tartrate (Genz-112638), an oral substrate reduction therapy for Gaucher disease type 1. Blood. 2010 Aug 12;116(6):893-9. doi: 10.1182/blood-2010-03-273151. Epub 2010 May 3. PubMed PMID: 20439622; PubMed Central PMCID: PMC2924227.

4: Kamath RS, Lukina E, Watman N, Dragosky M, Pastores GM, Arreguin EA, Rosenbaum H, Zimran A, Aguzzi R, Puga AC, Norfleet AM, Peterschmitt MJ, Rosenthal DI. Skeletal improvement in patients with Gaucher disease type 1: a phase 2 trial of oral eliglustat. Skeletal Radiol. 2014 Oct;43(10):1353-60. doi:10.1007/s00256-014-1891-9. Epub 2014 May 10. PubMed PMID: 24816856; PubMedCentral PMCID: PMC4141971.

5 PackmanS,AmatoD,DasoukiM,etal.ENGAGE:Aphase3, randomized,double blind,placebo-controlled,multi-centerstudy to investigate the efficacy andsafety of eliglustatin adults with gaucher disease ype1(GD1):9 monthresults [abstractno. 2276F].In:63rdAmericanSociety of Human Genetics Annual Meeting;22October2013

6. BurrowTA,BalwaniM,CoxTM,etal.Encore:arandomized, controlled,open-labelnon-inferioritystudycomparingeliglustat toimiglucerase in gaucher diseasetype1 patients on enzyme replacement therapy who have reached therapeutic goals[abstract no.3468].In:55thAnnualMeetingandExpositionofthe AmericanSocietyofHematology;7December2013:New Orleans

7 MankoskiR,TaylorJS,MarulkarS,etal.Clinicalresponseto eliglustatintreatment-naivepatientswithgaucherdiseasetype1:posthoccomparisontoimigluceraseinareal-worldsetting [abstractno.130].In:AmericanCollegeofMedicalGenetics AnnualClinicalGeneticsMeeting;25May2014:Nashville

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Three phase 1 studies of eliglustat evaluated the safety, tolerability, and pharmacokinetics in health volunteers after escalating single doses (n = 99), escalating multiple doses (n =36), and food (n = 24) (8). Eliglustat tartrate was said to be well tolerated at single doses ≤ 20 mg/kg and multiple doses ≤ 200 mg bid, with 50 mg bid producing plasma concentrations in the predicted therapeutic range. No serious adverse events occurred. The authors report mild to moderate events of nausea, dizziness, and vomiting increased in frequency with escalating single and multiple doses. Single doses ≥ 10 mg/kg caused mild increases in electrocardiogram PR, QRS, and QT/QTc intervals. In the 12 month phase 2 study in naïve Gaucher patients. The current US SPC includes warnings and precautions regarding use in patients with cardiovascular disease and long QT syndrome and those taking anti-arrhythmic medication due to ECG changes in clinical trials.
In the phase 2 study to 12 months 7 mild, transient adverse events in 6 patients were considered treatment-related (5).Most adverse events occurred early and few were considered treatment related. 3% patients discontinued due to adverse events.

Clinical interpretation of the trial data is that these side effects are generally mild and not out with the experience with other therapies. Care will need to be taken with patients with cardiac conditions / medication however cardiac involvement is not a specific manifestation of adult type 1 GD.

8: Peterschmitt MJ, Burke A, Blankstein L, Smith SE, Puga AC, Kramer WG, HarrisJA, Mathews D, Bonate PL. Safety, tolerability, and pharmacokinetics of eliglustat tartrate (Genz-112638) after single doses, multiple doses, and food in healthy volunteers. J Clin Pharmacol. 2011 May;51(5):695-705. doi: 10.1177/0091270010372387. Epub 2010 Sep 23. PubMed PMID: 20864621

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from

registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I am not aware of any other evidence

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Other than cytochrome p450 2d6 genotype testing, which could be made available through industry, no further resources additional to the LSD specialist centres will be required.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which eliglustat is/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

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To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation:
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?xxxx yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes xx
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? no
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
none

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition.
Around 350 Gaucher patients in the UK

How many of them would be expected to receive treatment with the technology?

I think perhaps 50

How is the condition currently treated in the NHS?
Most diagnosed patients are on enzyme replacement therapy but at doses of 20-40 Units/kg (children are on 60 Units/kg)

Is there significant geographical variation in current practice?

No
Are there differences of opinion between professionals as to what current practice should be?
No – there are national SOPs on the NHS England web site
What are the current alternatives (if any) to the technology
Enzyme replacement. Pro – well known tested, effective at visceral manifestations
Cons – intravenous, does not access CNS, does not access bone very well
, and what are their respective advantages and disadvantages?

Also there is 1 form of SRT – miglustat – licensed, but this is poorly tolerated (diarrhoea) and can cause peripheral neuropathy

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?
Yes – the (predominantly) children with lower residual enzyme have type 3 Gaucher and neurological disease.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Occasional patients cannot tolerate any of the currently available treatments

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?

The new technology requires testing to see if the patient is a rapid or slow metaboliser; this is all additional testing and there is a need for a 24 hour help line to advise re drug interactions.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There is an SOP formulated by UK experts from the designated centres which is on the NHS England web site

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Easier (because oral); but more difficult (because of interactions)
Additional testing required – but this is all easily managed

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Most of these are covered by the current SOP
The new drug should not be given to children, those contemplating pregnancy, those with cardiac disease or on cardiac drugs

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice.

Yes they do

Do the circumstances in which the trials were conducted reflect current UK practice, Yes they do
and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials?

These are some of the ones measured – Hb level, platelet count, organ volumes

If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Impact on bone disease is difficult to measure in a short time frame

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Generally well tolerated. Concerns about cardiac toxicity were generally not realised and the drug looks to be very safe

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which eliglustat is/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

It is important that patients with rare diseases should not be disadvantaged
Many patients with Gaucher are from ethnic minorities

Appendix G - professional organisation statement template

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Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: Royal Free London NHS Foundation Trust, Lysosomal Storage Disorders Unit
Are you (tick all that apply):

- **Yes** a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)
- **No Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco**

Appendix G - professional organisation statement template

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Eliglustat for treating type 1 Gaucher disease

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

There are approximately 400 patients in the UK
I would expect 50-100 to receive treatment with the technology

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Gaucher disease is an inherited disorder which is largely diagnosed in the UK in patients once they have become symptomatic as a result of the clinical presentation of those symptoms. There is often a delay between the onset of clinical manifestations of the condition and diagnosis. A minority of patients are diagnosed before the onset of symptoms as a result of screening of the sibings of a symptomatic index case. As a result most patients fulfil the criteria for Gaucher -specific therapy as specified by the NHS England Standard Operating Procedure from diagnosis. All patients with a confirmed diagnosis of Gaucher disease are evaluated through one of 5 adult or 3 paediatric specialist centres in England all of whom work to the NHS England SOP eliminating geographical variation. Patients deemed eligible for Gaucher-specific therapy receive intravenous enzyme replacement therapy (ERT) as first line. Two ERT products have marketing approval in the EU, Imiglucerase and velaglucerase. Recently patients new to ERT in England receive Velaglucerase as a result of an NHS England tender and a cost advantage. Patients receiving ERT prior to the establishment of the current framework continue to be prescribed both imiglucerase or velaglucerase. ERT is initiated in the hospital setting and transferred to home care after 1-3 hospital infusions. Home care is facilitated through an NHS England framework with BUPA and Healthcare at home administering the home care process and providing nurses for those patient who require nursing input for cannulation or during the total infusion. Some patients or their relatives reconstitute and administer ERT themselves and depend on Home care only for deliveries and provision of a fridge for storage of enzyme. Oral substrate reduction therapy is currently available with Miglustat which is approved for patients with mild to moderate Gaucher disease in whom ERT is unsuitable. It has been considered in patients in whom cannulation is difficult, infusions are impractical and theoretically those with infusion reactions. Its use in type 1 Gaucher disease has been limited by moderate efficacy and concern regarding side effects of gastrointestinal symptoms and peripheral neuropathy.
It is anticipated that the place of eliglustat in clinical practice will be as an alternative first line therapeutic option to naïve or enzyme- experience adult patients with type 1 Gaucher disease without limitation by severity or suitability for enzyme replacement therapy.

Physicians in England at the LSD centres all work to the National SOP with minimal variation in practice.

Appendix G - professional organisation statement template

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The potential advantaged of the technology , eliglustat, is the availability of an effective oral alternative to enzyme therapy for adult patients with type 1 Gaucher disease who are either naïve or experience with therapy. Unlike miglustat clinical trial data suggests that eliglustat has comparative efficacy to ERT without the medical, quality of life and health economic implications of an intravenous therapy. Enzyme replacement therapy is highly effective but necessarily requires upwards of 1 hour intravenous infusion every two weeks. Whilst this can be self-administered or nurse administered at home it is associated with a burden or time and medical equipment. Currently patients are supplied with a dedicated refrigerator at home which reduces space, creates noise and as a result of daily temperature checking is a constant reminder of their condition. Whilst ERT is generally well tolerated a small proportion of patients develop anti-drug antibodies, the significance of which is unknown, and some infusion reactions. The administration of home care is an additional expense for the health economy and burden for specialist centre nurses and physicians, who retain clinical responsibility for the patients, dealing with complaints, queries and adverse reactions. Refrigerator failure is not infrequent and can result in loss of doses for the patient. None-the-less some patients do prefer the intermittent nature of enzyme infusions with comparative normality for the intervening 2 weeks. Disadvantaged of eliglustat are the requirement for cytochrome p450 2D6 genetic testing as a result of its metabolism by this route, plasma level monitoring and avoidance of drugs which may potentially interact through this pathway.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Type 1 Gaucher disease is a heterogenous condition and whilst a number of severity scores to assess disease burden have been developed a prognostic scoring system is lacking. Some phenotype/ genotype correlations can be made but modifying factors exist and predictions of severity are not absolute. Clinical trial data does not suggest the existence of subgroups of GD1 patients who would benefit heterogeneously from eliglustat.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?

Since most UK patients diagnosed with GD are eligible for treatment and currently receive ERT the delivery of care with eliglustat would not generate increased treated patient numbers or require additional specialist nurses or physicians. Other than for delivery of the drug it is likely that home are nursing and storage requirements will reduced.
Genetic testing for cyt p450 2D6 genetic status will be required and possible consideration of plasma drug monitoring at the initiation of therapy or if an interacting medication is initiated.

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If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Eliglustat is currently only available to patients who participated in the clinical trials and possibly some patients to whom it has been made available by compassionate access

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

No guidelines currently exist for the use of elglustat in clinical practice in adult type 1 Gaucher patients.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Please see the initial response outlining the advantages of the therapy.

Eliglustat is indicated for use in patients who are cytochrome P450 (CYP) 2D6 extensive, intermediate, or poor metabolizers, as identified by a genetic test but is contraindicated in patients who are ultra-rapid CYP2D6 metabolizers and may not achieve therapeutic concentrations of eliglustat, and those whose CYP2D6 metabolic rate is undetermined and so a specific dose cannot be recommended.

Eliglustat is substrate of CYP2D6 and CYP3A; According to the US prescribing information concomitant use of medicines that are inhibitors of either enzyme (e.g.the CYP2D6 inhibitors paroxetine and terbinafine and the CYP3A inhibitors ketoconazole, fluconazole and ranitidine) could significantly increase exposure to eliglustat, causing prolongation of PR ,QTc and/or QRS intervals and hence cardiacarrhythmias. Eliglustat may also interact with grapefruit juice. Concomitant use of eliglustat with CYP3A inducers such as rifampin, carbamazepine, phenobarbital, St.John's Wort and phenytoin decreases eliglustat exposure. Eliglustat inhibits P-glycoprotein(P-gp)andCYP2D6; concomitant administration of eliglustat could increase the concentrations of drugs that are substrates of P-gp (e.g. digoxin, phenytoin, colchicine and dabigatranetexilate) or CYP2D6 (e.g.metoprolol, tricyclic anti depressantsand phenothiazines). However none of the mentioned medications

are expected con-commitant medication in Gaucher disease. Vigilance will be required but drug interactions are not expected to be problematic in most patients.

Eliglustat is also not recommended in patients with severe hepatic or renal impairment due to lack of data . Severe hepatic and renal impairment are rarely features of GD with a minority of patient presenting with hepatic abnormalities due to liver infiltration of Gaucher cells. In this instance if hepatic impairment was severe first line therapy would be ERT until hepatic dysfunction was considered to have improved sufficiently to permit eliglustat.
According to the US prescribing information eliglustat is pregnancy category C and therefore ERT which is used with confidence during pregnancy would be considered ahead of eliglustat in pregnant females and in women contemplating pregnancy.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

The technology has not as yet been used in clinical practice outside of clinical trials in England. The entry criteria for the trials broadly reflect the starting criteria for Gaucher specific therapy in the NHS England SOP and it would be anticipated that this SOP would not differentiate starting criteria for the current alternatives and eliglustat . Current stopping criteria include patients specific outcomes such as non-compliance, development of a co-exisiting life-threatening condition, movement out of NHS eligibility, disease –specific outcomes such as failure of the treatment to improve or maintain stable multiple aspects of the condition and treatment specific outcomes such as unmanageable infusion reactions. It is anticipated that the patient and disease-specific outcomes would be consistent for any new technology but the treatment specific outcomes will require consideration based on the specifics of the technology.
Genetic testing for cyt p450 2D6 genotypes will be required at initiated to confirm eligibility and dose.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The evidence presented in phase 2 and 3 clinical trials is consistent with Uk practice for patients starting therapy and the outcome measure relevant, meaningful and those used to monitor patients in the UK according to the NHS England SOP.

The results in treatment-naïve patients at 1 , 2 and 4 years of an open-label phase 2 study have been reported (1, 2,3), with 19 of 26 patients completing 4 years . Eliglustat (50 or 100 mg based on plasma drug concentrations) was orally self-administered twice per day. At 1 year statistically significant improvements in mean haemoglobin (1.62 g/dL) and platelet count (40.3%) are consistent with current expectations with the existing standard of care in clinical practice.
At 2 years mean haemoglobin level increased 2.1 g/dL overall and 3.1 g/dL in 10 patients with baseline anaemia (2) The mean haemoglobin at 4 years increased by 2.3±1.5g/dL and platelet count by 95% . At 4 years the mean spleen volume decreased by 63% and liver volumes by 28%. The median chitotriosidase and CCL-18 , biomarkers correlating with overall substrate burden, each decreased by 82%. The report also described normalisation of plasma glucosylceramide the relevant substrate in Gaucher disease.

The effect of a therapy for GD can also be assessed in terms of patients achieving targets in various haematological, visceral and other domains, the so-called therapeutic goals At 2 years seventeen (85%) patients met published therapeutic goals for ≥ 3 of the 4 haemoglobin, platelet , liver and spleen volume parameters.

Effects on Gaucher-related bone disease were reported separately in 19 patients upto 4 years (4) Lumbar spine T-scores were reported to increase significantly from a mean of -1.6 to -0.9 whilst mean femur T-score remained normal . MRI of the femurs showed that 10/18 patients had decreased Gaucher cell infiltration compared to baseline; and there were no lumbar spine or femoral fractures and no reported bone crises. At year 4, one new asymptomatic, indeterminate bone lesion was discovered that subsequently resolved.

In the phase 3 engage study 40 patients aged 16 years or older with splenomegaly and thrombocytopenia and/or anaemia were randomized to receive placebo or eliglustat (50 mg bd initially and then 100 mg bd from week 4 depending on plasma concentrations. After 9 months there was a greater reduction in spleen volume with eliglustat than placebo (-27.8 vs 2.3%)(5). Significant differences were also seen for change in Hb, change in liver volume change in platelet count, improvement in bone marrow burden score and DS3 disease severity score. The difference in total spine bone mineral density was not statistically significant.

An endpoint of non-inferiority is reported in the open label ENCORE study which included 159 patients who had ERT for 3 year and met certain goals at baseline Patients were randomised to Eliglustat 50mg or 100mg bd depending on plasma concentrations o imiglucerase for 12months. Eliglustat demonstrated non-inferiority to imiglucerase for the composite primary endpoint of stability in spleen liver volume haemoglobin level and platelet count from baseline to 12months Therapeutic goals were maintained in 12 of 15 eliglustat recipients (6)

Data from the engage study and the phase 2 study has been compared with matched patients from the Genzyme International Collaborative Gaucher Group Registry (patients treated in routine clinical practice including the UK). indicating similar effects or haematological and visceral parameters at 9 12 and 48 months (7) The increase in lumbar spine Z score was greater than that seen with imiglucerase
1: Lukina E, Watman N, Dragosky M, Pastores GM, Arreguin EA, Rosenbaum H, Zimran A, Angell J, Ross L, Puga AC, Peterschmitt JM. Eliglustat, an investigational oral therapy for Gaucher disease type 1: Phase 2 trial results after 4years of treatment. Blood Cells Mol Dis. 2014 Dec;53(4):274-6. doi: 10.1016/j.bcmd.2014.04.002. Epub 2014 May 15. PubMed PMID: 24835462. **2: Lukina E, Watman N, Arreguin EA, Dragosky M, Iastrebner M, Rosenbaum H, Phillips M, Pastores GM, Kamath RS, Rosenthal DI, Kaper M, Singh T, Puga AC, Peterschmitt MJ. Improvement in hematological, visceral, and skeletal manifestations of Gaucher disease type 1 with oral eliglustat tartrate (Genz-112638) treatment: 2-year results of a phase 2 study. Blood. 2010 Nov 18;116(20):4095-8. doi: 10.1182/blood-2010-06-293902. Epub 2010 Aug 16. Erratumin: Blood. 2011 May 19;117(20):5551. PubMed PMID: 20713962; PubMed Central PMCID PMC2993616.** **3: Lukina E, Watman N, Arreguin EA, Banikazemi M, Dragosky M, Iastrebner M, Rosenbaum H, Phillips M, Pastores GM, Rosenthal DI, Kaper M, Singh T, Puga AC, Bonate PL, Peterschmitt MJ. A phase 2 study of eliglustat tartrate (Genz-112638), an oral substrate reduction therapy for Gaucher disease type 1. Blood. 2010 Aug 12;116(6):893-9. doi: 10.1182/blood-2010-03-273151. Epub 2010 May 3. PubMed PMID: 20439622; PubMed Central PMCID: PMC2924227.** **4: Kamath RS, Lukina E, Watman N, Dragosky M, Pastores GM, Arreguin EA, Rosenbaum H, Zimran A, Aguzzi R, Puga AC, Norfleet AM, Peterschmitt MJ, Rosenthal DI. Skeletal improvement in patients with Gaucher disease type 1: a phase 2 trial of oral eliglustat. Skeletal Radiol. 2014 Oct;43(10):1353-60. doi:10.1007/s00256-014-1891-9. Epub 2014 May 10. PubMed PMID: 24816856; PubMedCentral PMCID: PMC4141971.** **5 PackmanS,AmatoD,DasoukiM,etal.ENGAGE:Aphase3, randomized,double blind,placebo-controlled,multi-centerstudy to investigate the efficacy andsafety of eliglustatin adults with gaucher disease ype1(GD1):9 monthresults [abstractno. 2276F].In:63rdAmericanSociety of Human Genetics Annual Meeting;22October2013** **6. BurrowTA,BalwaniM,CoxTM,etal.Encore:arandomized, controlled,open-labelnon-inferioritystudycomparingeliglustat toimiglucerase in gaucher diseasetype1 patients on enzyme replacement therapy who have reached therapeutic goals[abstract no.3468].In:55thAnnualMeetingandExpositionofthe AmericanSocietyofHematology;7December2013:New Orleans** **7 MankoskiR,TaylorJS,MarulkarS,etal.Clinicalresponseto eliglustatintreatment-naivepatientswithgaucherdiseasetype1:posthoccomparisontoimigluceraseinar eal-worldsetting [abstractno.130].In:AmericanCollegeofMedicalGenetics AnnualClinicalGeneticsMeeting;25May2014:Nashville**

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What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Three phase 1 studies of eliglustat evaluated the safety, tolerability, and pharmacokinetics in health volunteers after escalating single doses (n = 99), escalating multiple doses (n =36), and food (n = 24) (8). Eliglustat tartrate was said to be well tolerated at single doses ≤ 20 mg/kg and multiple doses ≤ 200 mg bid, with 50 mg bid producing plasma concentrations in the predicted therapeutic range. No serious adverse events occurred. The authors report mild to moderate events of nausea, dizziness, and vomiting increased in frequency with escalating single and multiple doses. Single doses ≥ 10 mg/kg caused mild increases in electrocardiogram PR, QRS, and QT/QTc intervals. In the 12 month phase 2 study in naïve Gaucher patients. The current US SPC includes warnings and precautions regarding use in patients with cardiovascular disease and long QT syndrome and those taking anti-arrhythmic medication due to ECG changes in clinical trials.
In the phase 2 study to 12 months 7 mild, transient adverse events in 6 patients were considered treatment-related (5).Most adverse events occurred early and few were considered treatment related. 3% patients discontinued due to adverse events.

Clinical interpretation of the trial data is that these side effects are generally mild and not out with the experience with other therapies. Care will need to be taken with patients with cardiac conditions / medication however cardiac involvement is not a specific manifestation of adult type 1 GD.

8: Peterschmitt MJ, Burke A, Blankstein L, Smith SE, Puga AC, Kramer WG, HarrisJA, Mathews D, Bonate PL. Safety, tolerability, and pharmacokinetics of eliglustat tartrate (Genz-112638) after single doses, multiple doses, and food in healthy volunteers. J Clin Pharmacol. 2011 May;51(5):695-705. doi: 10.1177/0091270010372387. Epub 2010 Sep 23. PubMed PMID: 20864621

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I am not aware of any other evidence

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Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Other than cytochrome p450 2d6 genotype testing, which could be made available through industry, no further resources additional to the LSD specialist centres will be required.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which eliglustat is/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

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Eliglustat for treating type 1 Gaucher disease [ID 709]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: Patient expert nominated by the Gauchers Association

Brief description of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

N/A

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology? √
- a carer of a patient with the condition for which NICE is considering this technology?
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)
- other? (please specify)

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How does the condition impact on patients, their families or carers?

Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

As Gaucher disease often isn't detected until there is a problem it is common that there is a delay with diagnosis and its rare so can be easily misdiagnosed, as I was. Therefore the wrong treatment could also be given. Because it is rare there are few articles /websites etc. about it, which is frustrating and can be quite terrifying.

My diagnosis journey was very challenging, I was admitted to hospital in late 1989 for a pain in my hip, actually it was broken and I didn't realise. They did x-rays but couldn't find anything, so they took bloods. Initially they thought the blood results were wrong so did them again and then said I had leukaemia. They then scheduled me for a bone marrow transplant and started to try and match my family members. It was only because another doctor saw me and thought it might be something else that then diagnosed me with Gaucher disease. At this time there was no treatment available to patients in the UK but there was a treatment on the horizon but it was very expensive and my parents spent a lot of time fighting for me to get access to it, which I eventually did in 1991.

This was a very difficult time for my family as we had had an aunt that had had a bone marrow transplant for another condition and she had sadly died and my parents were very scared that I would not survive.

Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:
- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above

My life was changed irrevocably for both me and my family. Initially my treatment meant twice weekly hospital visits stays so my mum had to give up work.

Finding out you have a serious illness destroys emotional well-being. Personally I went from a 16 year old school leaver starting work to a disabled person with a death sentence overnight.

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This was a lot of years ago and it is very different now, but it has a serious effect on me mentally as well as physically.

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

Advantages
Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

Tablets instead of enzyme replacement therapy make an unquestionable amount of difference. It is like getting your life back. Holidays, everything you don't need to even think about it. It is having options again which one didn't have before.

Please list any short-term and/or long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends, employers)
- other issues not listed above.

With an oral treatment there will be no further need to use a homecare service, staying in for deliveries and storing bulky ancillaries and a drugs fridge.

You won't need to take time off school or work to receive deliveries and for fortnightly infusions.

You don't have to plan your holidays around your treatment and if you wanted to travel abroad for a period of time this would be possible.

Taking an oral treatment has changed my attitude to my condition, when I had regular infusions I had a portacath device on my ribs and when people used to hug me they would feel it and this was a constant reminder of having a chronic condition.

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Now I feel like a normal person not having to attend hospital regularly. Before having my portacath fitted I had terrible problems with accessing my veins every fortnight.

Disadvantages
Please list any problems with or concerns you have about the technology.
Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

None that I can think of as I take my tablet twice a day like clockwork and I have had no side effects.

Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

N/A

Are there any groups of patients who might benefit more from the technology than others? Are there any groups of patients who might benefit less from the technology than others?

The oral tablet may benefit young people who may want to study away from home or abroad.

The oral tablet would benefit patients who either have a needle phobia or have problems accessing their veins.

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Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

Please list any current standard practice (alternatives if any) used in the UK.

In the UK if you have Gaucher disease you can have ERT or for some patients that are not able to have ERT they can have Zavesca, this is another oral treatment but there are known side effects of this tablet.

If you have Gaucher disease you have to be seen at one of the eight specialist centres in England, usually you visit every 6 months or once a year and have to undergo a whole batch of tests to see how your disease is being controlled with the treatment.

If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

Taking a tablet twice a day is much easier than having a fortnightly infusion and having all of the necessary planning and preparation that goes into it, for example; storage of ancillaries, having a drugs fridge in your home, fitting in regular deliveries.

Before I started taking this new tablet I had previously taken Zavesca but because I developed peripheral neuropathy I had to stop taking this treatment and was without treatment for almost a year. Since taking this new tablet my blood counts have almost stabilised and my peripheral neuropathy has gone.

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If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

For some people it may be easier to have a set fortnightly infusion than remembering to take a tablet twice a day.

Research evidence on patient or carer views of the technology

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine care reflects that observed under clinical trial conditions.

N/A

Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

N/A

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Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies. N/A

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Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients, their families and/or carers if this technology was made available?

That patients' would have options, either ERT or to take an oral tablet if they wanted to, especially if they have problems accessing their veins from long term infusions.

For some people ERT may not help with all their Gaucher symptoms and this new tablet may help address some of these which would make them feel better and improve the quality of their life.

What implications would it have for patients, their families and/or carers if the technology was **not** made available?

For me this would be a death sentence.

For those patient unable to have ERT because of needle phobia, bad veins or if they react to it, this would mean that the only other option would be Zavesca which has side effects, therefore this may mean that they would not be able to have any treatment for their disease.

Are there groups of patients that have difficulties using the technology?

Not that I know of.

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Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Other Issues

Please include here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

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Eliglustat for treating type 1 Gaucher disease [ID 709]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: Gaucher's Association

Brief description of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

Please refer to Gaucher's Association Website

Are you (tick all that apply):

- ✓a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)
- other? (please specify)

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I was diagnosed with Gaucher disease by the team at Addenbrooke's Hospital some time ago. I was put on enzyme therapy by intravenous infusion – twice a week administered at home by my wife. As [redacted] was no longer in a position to administer this drug. Furthermore, with my busy professional and charitable work an oral therapy was considered mandatory and as such I was put on miglustat (capsule taken 3 times a day,365 days a year). I believe there is evidence that this drug is no longer controlling my Gaucher disease. I believe, I have the understanding and expertise as a patient to provide important witness information that would guide NICE towards a positive decision for a drug which appears to be safe and effective alternative to enzyme therapy in Gaucher disease

How does the condition impact on patients, their families or carers?

Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

Speaking about myself, it took a long time for the diagnosis to be confirmed. Once confirmed it impacted on family life, social association with friends, implications at work and the added burden of going away or abroad or going on holiday or being posted abroad for long period of time through work. There was also a social stigma because of lack of understanding of this disease by the common person.

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Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:
- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above

To start with it impacted on family emotional wellbeing as things had to be scheduled around my IV infusion times. It also impacted on my social and personal life as I wasn't allowed to play contact sports with my friends or family members due to massively enlarged spleen, implications on my travel etc

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

Advantages
Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

I believe the new drug will offer much more freedom as an individual and enhance the quality of life and control the disease better than the present drug which needs to be taken 3 times a day x365 days a year. This needs a strict routine and discipline plus the drug is not every effective in controlling my Gauchers condition.

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Please list any short-term and/or long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends, employers)
- other issues not listed above.

Mentioned above.

Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to

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accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

I believe every drug has side effects but as a patient one has to make compromises to improve their quality and the welfare of their family and friends.

Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

I believe not, as it will make a difference to my quality of life.

Are there any groups of patients who might benefit more from the technology than others? Are there any groups of patients who might benefit less from the technology than others?

Don't know

Comparing the technology with alternative available treatments or technologies

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NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

Please list any current standard practice (alternatives if any) used in the UK.

If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

Advantages will be improvement of the condition, quality of life, ease of use.

If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

Don’t know.

Research evidence on patient or carer views of the technology

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If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine care reflects that observed under clinical trial conditions.

Don't know

Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

Don't know

Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

Don't know

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Highly Specialised Technology Evaluation

Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients, their families and/or carers if this technology was made available?

Better quality of life, ease of use plus the benefits described above

What implications would it have for patients, their families and/or carers if the technology was **not** made available?

In my case it would impact on quality of life, deteriorate the present condition.

Are there groups of patients that have difficulties using the technology?

Don't know.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

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- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

To do clinical trials and evaluate results.

Other Issues

Please include here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

Benefits to the patients and their quality of life, ease of use etc.

CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Report
Eliglustat for treating type 1 Gaucher disease

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD

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Rider on responsibility for report

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Contributions of authors

Robert Hodgson and Philip Morgan undertook the critique of the cost-effectiveness submission and conducted the ERG exploratory analyses: Robert Hodgson took overall responsibility. Nerys Woolacott, Huiqin Yang and Alex Hodkinson undertook the critique of the clinical effectiveness submission. Melissa Harden critiqued the literature searches in the submission. Nerys Woolacott took overall responsibility the critique of the clinical effectiveness and the project as a whole.

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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List of abbreviations

AE	Adverse event
BMB	Bone marrow burden
BMD	Bone mineral density
BPI	Brief Pain Inventory
CI	Confidence interval
CS	Company submission
CSR	Clinical study report
DXA	Dual-energy X-ray absorptiometry
EMA	European Medicine Agency
EM	Extensive metaboliser
ERT	Enzyme replacement therapy
ERG	Evidence review group
EPAR	CHMP European Public Assessment Report
FSS	Fatigue severity scale
GD-DS3	Gaucher Disease Type 1 Severity Scoring System
GD1	Gaucher disease type 1
Hb	Haemoglobin
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IgG	Immunoglobulin G
ITT	Intention to treat
IM	Intermediate metaboliser
LOCF	last observation carried forward
LSD	Lysosomal storage disorder
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical benefits advisory committee
PM	Poor metaboliser
MRI	Magnetic resonance imaging
PPP	Per protocol population
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RD	Risk difference
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	Short Form 36 Health Survey

SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SRT	Substrate reduction therapy
TEAE	Treatment-related adverse event
URM	Ultra-rapid metaboliser

1 Summary

This report represents the ERG's assessment of the company's (Sanofi Genzyme) submission to NICE on the use of eliglustat for the treatment of adult patients with Gaucher disease type 1 (GD1). The report includes an assessment of both the clinical and cost effectiveness evidence submitted by the company. The report also includes a summary of additional submissions received from patients, patient organisations, clinicians and NHS England: submissions from Addenbrooke's Hospital Cambridge UK, Royal Free lysosomal storage disorder (LSD) unit, Royal College of Physicians, NHS England; and Gauchers Association Limited.

The company's evaluation of clinical efficacy included evidence relating to eliglustat therapy versus placebo, evidence relating to eliglustat therapy versus enzyme replacement therapy (imiglucerase), an indirect comparison of relative efficacy between eliglustat, imiglucerase and velaglucerase, and a decision analysis assessing the cost-effectiveness of eliglustat compared with enzyme replacement therapy (imiglucerase and velaglucerase).

1.1 Critique of the decision problem in the company's submission

The company's decision problem reflects the population specified in the NICE scope: adult patients with symptomatic GD1. The evidence presented in the Company's submission was derived from patients who were treatment naive or not currently on ERT, and others who were stable on ERT.

The submission presented data on therapy initiated with eliglustat tartrate 50 mg or 100 mg once or twice daily for oral administration, which is not precisely reflective of the product licence. The current licensed dose of eliglustat is 84 mg (equivalent to 100mg eliglustat tartrate) twice daily or once daily depending on the CYP2D6 metaboliser status. The EMA licence is granted for patients with PM, IM and EM metabolism status. The majority of patients in the eligible eliglustat trials in the CS are IM or EM status. Approximately 3% of the GD population are ultra-rapid metabolisers and are excluded currently from the treatment with eliglustat.

Imiglucerase and velaglucerase alfa were the comparators of interest addressed in the company submission, reflecting the NICE scope. However, the submission excluded miglustat as a relevant comparator, stating that it was only used in a very small proportion of adult GD1 patients for whom ERT was not suitable. The ERG suggests it is likely that, if recommended, eliglustat would be used in place of miglustat, as it is better tolerated.

The company's decision problem addressed each of the relevant outcomes: GD1 therapeutic goals (based on four measures: haemoglobin level, platelet count, spleen volume and liver volume), mortality, adverse effects of treatment, and patients' health-related quality of life (HRQL). The primary outcome of the key trial of eliglustat (ENCORE) was proportion of patients who remained

stable for the GD1 therapeutic goal (based on the composite measure of platelet count, haemoglobin level, liver and spleen volumes).

The primary measure of cost-effectiveness was incremental cost per quality-adjusted life year (QALY) gained.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company submission presented three RCTs (ENCORE, ENGAGE and EDGE) and one single arm Phase II study to demonstrate clinical efficacy and safety of eliglustat.

ENCORE is a phase III RCT comparing eliglustat with imiglucerase for treating adults with symptomatic GD1 already controlled by ERT therapy. ENGAGE is another phase III RCT comparing eliglustat with placebo in untreated patients. Supporting long-term evidence was provided from a Phase II, single-arm trial of eliglustat. Single-arm data are also presented from the lead-in phase of a third RCT (EDGE) that assessed once daily with twice daily dosing with eliglustat.

The synthesis of adverse effects in the company's submission comprised a summary of adverse effects from ENCORE, ENGAGE, EDGE and the Phase II study.

ENCORE

ENCORE, an open-label RCT, conducted in 159 ERT stable patients demonstrated that when patients switched from ERT therapy, eliglustat maintained haematological and organ volume stability over 52 weeks. At 52 weeks eliglustat met the criteria of being non-inferior to imiglucerase in terms of the primary outcome and maintaining stability, as the non-inferiority lower 95% CI was -17.6% which was within the pre-specified threshold of -25% (lower 95% CI for the composite endpoint confirmed non-inferiority at the 20% acceptance margin).

The results for individual outcomes of spleen and liver volume, haemoglobin levels and platelet counts indicate a small reduction in efficacy with eliglustat, although this reached statistical significance only for haemoglobin levels (-0.28 (95% CI (-0.52, -0.03)). There were no significant changes in DS3 scores or measures of bone health. Eliglustat was not associated with any improvement in quality of life despite patients expressing a marked preference for an oral therapy. A post hoc analysis showed that eliglustat efficacy was similar both post-imiglucerase and post-velaglucerase treatment.

Long-term follow-up data from ENCORE demonstrated that for patients who remain on eliglustat stability on all four composite parameters is maintained over 4 years. Although very few patients withdrew due to adverse events the number of patients in the analysis at 4 years was only 44 out of an original 159 patients: the unexplained loss of patients from follow-up raises a question of how to

interpret these long-term results. As treatment for GD1 is life-long, there is uncertainty regarding the long-term implications of a possible small reduction in efficacy with eliglustat compared with ERT.

ENGAGE

ENGAGE was a placebo-controlled RCT in 40 patients who were not treated with ERT. At 39 weeks, eliglustat was associated with a reduction in spleen volume of 27.8% compared with an increase of 2.3% on placebo (statistically significant mean difference of -30.03%; 95% CI -36.82% to -23.24%). Eliglustat was also associated with a reduction in liver volume of 55.2% compared with an increase of 1.4% on placebo (statistically significant mean difference of -6.64%; 95% -11.37% to -1.91%). The effect sizes of point estimates for spleen and liver volumes were moderate to large, implying that these treatment effects could be clinically significant. Compared with placebo eliglustat achieved a statistically significant increase in haemoglobin level (1.22 g/dL; 95% CI 0.57 to 1.88) and platelet count (41.06%; 95% CI 23.95% to 58.17%). Nineteen out of the 20 patients in the eliglustat treatment group met at least one of the 1-year therapeutic goals established for Gaucher patients (9 met 2 goals, and 2 met 3 goals). Improvements were also seen in DS3 scores, though none achieved the minimum clinically significant threshold for improvement. At 39 weeks, eliglustat also demonstrated beneficial effects on a number of bone-related outcomes and some reached statistical significance. Eliglustat showed some positive effects on health-related quality of life measures, being associated with a significant improvement in disease-specific quality of life outcome (fatigue severity score 0.7; 95% CI 0.02 to 1.33) compared with placebo but there was no statistically significant difference in brief pain inventory (BPI)(average pain) (-0.2; 95% CI -0.81 to 0.36) between the treatment and placebo groups nor for the SF-36 general health score (-2.4; 95% CI -9.84 to 4.94), physical component score (3.3; 95% CI -0.67 to 7.29) or mental component score (-2.2; 95% CI -7.01 to 2.59) at week 39.

The open-label extension data indicated that the beneficial effects on organ volumes, haemoglobin level and platelet count were sustained at 78 weeks; there were no drop outs. There was also an indication of continued small improvements in some but not all bone parameters. Results for DS3 scores, biomarker measures and health-related quality of life outcomes at 78 weeks were not reported.

Supporting evidence

The results of the two RCTs are supported by a single-arm phase II study which included 26 patients. At year 1, 77% of the 26 patients achieved a composite outcome requiring improvements from baseline in at least two of spleen volume, haemoglobin level and platelet count. At year 2, this was 85% of 20 patients remaining in the analysis. At 4 years all 19 patients included at this point met their therapeutic goals for spleen volume and haemoglobin level, 94% met the goal for liver volume and 47% met the goal for platelet count. Bone parameter and HRQL data suggested some small improvements by 2 years, but were not reported at 4 years. Due to the lack of control group in this

study, the small sample size and the unexplained loss of patients from the later time points, the treatment effects observed over the four year follow-up are uncertain.

Supportive evidence also came from the single-arm open label lead-in period trial EDGE, in which 83% of the 170 patients achieved all five therapeutic goals during the lead-in period.

The adverse effects profile from all four of these trials suggests that eliglustat is well tolerated. There were no deaths reported, very few discontinuations and few eliglustat related SAEs. Most AEs were reported as mild (78%) or moderate (44%). The most common AEs were headache, arthralgia, nasopharyngitis, diarrhoea, most were of mild severity.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The clinical effectiveness evidence in the company's submission was based on a systematic review of eliglustat for the treatment of adult patients with GD1. The ERG is confident that all relevant trials (including trial extensions) were included in the submission.

ENCORE was a well conducted trial with a clinically relevant composite primary outcome based on four measures: haemoglobin level, platelet count, spleen volume and liver volume. The primary efficacy endpoint was the percentage of patients whose organ volumes and haematological variables remained stable after 12 months. This outcome reflects the targeting of therapeutic goals used in clinical practice. However, because the comparator imiglucerase is administered by infusion and eliglustat is an oral therapy, the trial was open label. This means that the trial was at high risk of bias for any subjective outcomes.

Whilst eliglustat met the criteria of being non-inferior to imiglucerase in terms of the primary outcome and maintaining stability, this non-inferiority margin is somewhat wider than would normally be accepted: a margin of 15% would have been more robust. Furthermore, the 25% non-inferiority margin assumes that a 10% reduction in efficacy is clinically insignificant, an assumption that was not justified by any clinical argument. The ERG notes the EMA accepted the broader margin due to the rare nature of the disease: the conduct of a larger trial (as would be necessary with a 15% margin) would not be feasible.

Although the long-term follow-up data from ENCORE demonstrated that for patients who remain on eliglustat stability on all four composite parameters is maintained over 4 years the unexplained loss of patients from follow-up (only 44 out of 159 remaining at 4 years) raises a question of how to interpret these long-term results. As treatment for GD1 is life-long, there is uncertainty regarding the long-term implications of a possible small reduction in efficacy with eliglustat compared with ERT.

ENGAGE was a well conducted placebo-controlled RCT in patients not being treated with ERT. However the sample size was small (40 patients), the primary outcome was spleen volume, rather than a more clinically relevant composite outcome, and the randomised phase was only 39 weeks. It should be noted that in the company submission the trial population are referred to as treatment naïve, but this was not the case for all patients: the inclusion criteria encompassed those who had had previous, though terminated at the time of recruitment, treatment with ERT.

As far as can be determined from limited data sets, the generalisability of findings from the two main Phase III trials (ENGAGE and ENCORE) to routine practice in England is adequate. There is nothing to suggest that the beneficial effects observed in these trials would not be reflected in practice except for a lack of information on the treatment of ERT stable patients with very large spleens and some question over the ERT dosing.

No data comparing eliglustat with imiglucerase or veleglucerase in treatment naive or untreated patients were presented, nor any making a direct comparison of eliglustat with velaglucerase in ERT stable patients. There are no pertinent data to enable an indirect comparison analysis to be performed. It is generally accepted that imiglucerase and velaglucerase are equivalent, though the trial data to support this are limited to one small non-inferiority trial with haemoglobin levels as the primary outcome.

Due to the lack of control group in both the Phase II trial and the lead-in phase of the EDGE trial the results from these trials cannot be considered robust, but are supportive of the findings from the RCTs. In addition, the small sample size and the unexplained loss of patients from the later time points add to the uncertainty of the Phase II results. The treatment effects observed over the four year follow-up are uncertain.

The adverse effects of eliglustat were based on the limited available evidence from ENCORE, ENGAGE and the Phase II trial. The evidence from ENCORE shows a higher number of patients experiencing treatment related AEs and severe TEAEs. However, this apparent difference in tolerability may be due to the fact that patients were stable on ERT at recruitment into the trial. The evidence was mostly limited to the short-term data although some data up to 4 years demonstrate that eliglustat is generally well tolerated.

1.4 Summary of cost effectiveness submitted evidence by the company

The *de novo* economic analysis presented by the company consisted of a cost-consequence and budget impact analysis. The models compared eliglustat with two enzyme replacement therapies: imiglucerase and velaglucerase, in the treatment of Gaucher disease. Four different populations were considered in the cost-consequence model:

- Intermediate and extensive metabolisers initiated on treatment for the first time;
- Poor metabolisers initiated on treatment for the first time;
- Intermediate and extensive metabolisers stable on ERT treatment;
- Poor metabolisers stable on ERT treatment.

The model used a ten health state model based on the GD1 DS3 score, a validated measure of disease severity. For treatment naïve patients transition probabilities were based on the ENGAGE trial in the first year and then on the DS3 score study in subsequent years. Importantly, for this population no difference in clinical effectiveness was assumed between eliglustat and the ERT treatments. For stable patients transition probabilities were derived from the ENCORE trial in the first years and then on the DS3 score study for subsequent years. For this patient group, the model assumed differential clinical effectiveness in the first year and then equal effectiveness in subsequent years.

Quality of life data were derived from the DS3 score study which collect SF-36 quality of life data in cohort of 101 patients (though only 50 were included in the QoL analysis due to missing data). The SF-36 scores collected in the DS3 were mapped to EQ-5D utilities using a published algorithm. To calculate the health state utilities a regression model for utility was fitted using a generalised estimating equation (GEE) regression model. Costs were assessed from an NHS and personal and social services perspective and incorporated drug acquisition, administration, and monitoring and management costs.

The company presented both deterministic and probabilistic analysis. The deterministic results for the two comparator treatments for each population are summarised in Table 1.

Table 1: Deterministic results for the company's cost consequences analysis

Comparison	Incremental costs	IncrementaQALYs
ERT stable patients, IM and EM		
Patients switching from imiglucerase	-£147,394	2.28
Patients switching from velaglucerase	-£1,288,963	2.28
ERT stable patients, PM		
Patients switching from imiglucerase	-£2,116,154	2.28
Patients switching from velaglucerase	-£3,323,218	2.28
Treatment naïve patients, IM and EM		
Patients who would otherwise initiate on imiglucerase	-£212,299	2.43
Patients who would otherwise initiate on velaglucerase	-£1,352,367	2.45
Treatment naïve patients, PM		
Patients who would otherwise initiate on imiglucerase	-£2,297,310	2.43
Patients who would otherwise initiate on velaglucerase	-£3,437,379	2.45
Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; PM, poor metaboliser.		

Total costs primarily consisted of drug acquisition costs which made up more than 80% of total costs. QALY differences between treatments were primarily driven by a QALY increment assigned to eliglustat patients to represent the benefits of oral treatment. In addition to the base-case analysis presented, the company also presented a series of one-way sensitivity analyses and scenario analyses to assess the impact of uncertainty around key input variables and assumptions on incremental costs and QALYs. The results of these indicated that the base-case results were relatively insensitive to most input parameters.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The economic model submitted by the company is considered by the ERG to meet the NICE reference case and is broadly in-line with the decision problem specified in the scope. The NICE scope, however, included a further comparator treatment milglustat which was not included in the economic analysis presented by the company.

In its review of the company model the ERG identified a number of uncertainties surrounding assumptions made in the cost-consequence model presented in the CS which have a significant impact on estimated costs and benefits. These most significant of these are outlined in brief below:

1. *Incorporation of clinical data in the economic model*

   The structure of the economic model along with a number of assumptions made about the comparative long term effectiveness of eliglustat means that the model does not incorporate uncertainty regarding any long-term differences in the relative effectiveness of eliglustat with

ERT and makes the strong assumption that long-term effectiveness will be equal between eliglustat and the comparator ERT treatments.

2. *Dosing of ERT therapies*

   The company model assumes the dose of ERT therapy used will be the same as that used in the ENCORE trial. This dose is, however, significantly higher than is typically used in the UK and as such the economic model significantly overestimates the drug acquisition costs associated with ERT treatments.

3. *Benefits of oral therapy*

   The company model assumes an incremental utility benefit of 0.12 QALYs per year to represent the benefits of oral therapy. While the ERG acknowledges that there may be some HRQoL benefits resulting from oral therapy, the ERG considers the magnitude of these benefits to be unreasonably large when compared with QALY decrements from adverse events and QALY benefits of other oral therapies estimated in previous NICE submissions.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

1.6.1.1 Clinical effectiveness evidence

The company's systematic review of the literature used appropriate search methods to identify the relevant evidence of eliglustat for the treatment of adult patients with GD1. The ERG considers that the evidence identified and included in the submission is generally appropriate to the decision problem and NICE scope. The ERG is confident that all relevant trials (including trial extensions) were included in the submission. The key findings were derived from an open-label phase III RCT (ENCORE) for treatment-stable patients and a double-blind phase III RCT (ENGAGE) for untreated patients, which were conducted in a relevant population. Both trials were of reasonably good quality, in relation to their study design, conduct and analysis.

Furthermore, the company adequately applied the intention-to-treat approach for the efficacy analysis for the ENGAGE trial (a superiority trial). The results from the 39 week data analysis of the ENGAGE trial was considered to be robust. For the ENCORE trial, the company appropriately applied the per protocol approach for the efficacy analysis, which is considered as an optimal analysis method for non-inferiority trials

1.6.1.2 Cost-effectiveness evaluation

There is a lack of published evidence on the cost-effectiveness of eliglustat; the only studies, identified being comparisons of ERT treatments either with each other or best supportive care. The

ERG therefore considers company's model to provide the most relevant evidence for the decision problem. The strength of the model present include the use of a validated measure of disease severity to model disease progression; the use of long term registry data to model long term effectiveness; the inclusion of all major costs associated with the treatment of Gaucher disease including a comprehensive assessment of the monitoring and management costs associated with Gaucher disease; and, the separation of population groups to account for differences in costs and benefits according to patients metaboliser status and whether patients have received treatment previously. The analysis also includes a number of sensitivity analyses, the majority of which did not alter incremental costs and QALYs substantially.

1.7 Weaknesses and areas of uncertainty

1.7.1.1 Clinical effectiveness evidence

A key concern for the ENCORE trial, was the lack of adequate justification for the choice of the non-inferiority margin used in the data analysis. The non-inferiority margin of 25% was higher than the more usual 15%. This and the assumption that a lower efficacy with eliglustat of up to 10% compared with imiglucerase is not clinically important, were not justified, statistically or clinically. Therefore, whether eliglustat is clinically non-inferior to imiglucerase in treating ERT-stable patients remains uncertain.

Data for the effectiveness of eliglustat in untreated patients is limited. Whilst the results from the ENGAGE placebo controlled RCT and single-arm Phase II studies are positive, the number of patients studied is small, only 66 (40 (ENGAGE) and 26 (Phase II)) in total.

Data for the effectiveness of eliglustat in the long-term is limited. The 4 year follow-up data from ENCORE and the Phase II trial are based on only small number of patients (63 in total), with no clear information regarding patients not included in the analysis. Furthermore, as GD1 is a lifelong condition 4 years follow-up is short compared to life-long administration. This uncertainty is compounded by the long-term implications of a possible small reduction in efficacy with eliglustat compared with ERT.

The evaluation of the adverse effects of eliglustat was primarily limited to the short-term data from two RCTs of adult GD1 patients. Long-term adverse effect data were from on a single arm Phase II trial with a small sample size. While the short-term adverse effect data indicate that eliglustat appears to be generally well tolerated, the long-term adverse effect profile remains uncertain because the company failed to provide longer term follow-up data from controlled studies.

There is uncertainty regarding the doses of ERT used in clinical practice. This has implications for the generalisability of the findings of the ENCORE trial: in ENCORE 58% of patients were receiving

doses of at least 35 U/kg every two weeks. SPCs for imiglucerase and velaglucerase recommend higher starting dose of 60U/kg every two weeks however the SOP, developed by expert consensus reports that a maintenance dose of 15-30 U/kg is appropriate for most patients on either imiglucerase or velaglucerase, though this may be increased to 60 U/kg. Expert opinion suggests typical doses of 25 U/kg (range: 15-28 U/kg) or 20-40 U/kg (practitioner submission to NICE). Across the observational studies mean doses of ERT reported ranged from 34.2 U/kg/4 weeks to 67.5 U/kg/ 4 weeks.

1.7.1.2 Cost-effectiveness evaluation

The economic model presented in CS contained a number of significant weaknesses. The most significant of these relates to the structure of the model and assumptions made regarding the comparative effectiveness of eliglustat and ERT treatments. The model structure adopted by the company is based on the GD1 DS3 score. While the DS3 score is a validated measure of disease severity, the ERG questions the appropriateness of using this scoring system as the basis of the model structure as the DS3 score system appears to be a relative insensitive measure of disease severity and as such apparent differences in the clinical effectiveness of eliglustat and ERT observed in the ENCORE trial are not observed as differences in DS3 score. Furthermore, the model makes the very strong assumption of equal effectiveness in the long-term, basing long term transitions on those observed in a registry study. This assumption is not supported by any clinical data other than the 12 month trial data from the ENCORE which, as discussed above, appears to indicate a small difference in clinical effectiveness in favour of the ERT treatment, imiglucerase.

In addition to the significant structural issues noted above the, the ERG did not consider that the company had adequately justified a number of critical assumptions underpinning their base-case analysis. The most significant of which related to the dose of ERT assumed and the HRQoL benefits associated with oral treatment. Both of these assumptions have a significant impact on estimated cost benefits estimated by the model.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has a number of concerns regarding the company's base-case analysis and consider it overoptimistic with respect to a number of assumptions. The ERG therefore carried out a significant number of additional analyse exploring a number of alternative assumptions. The results of these analyses are summarised in Table 2 below for treatment stable IM/EM patients (note these results are based on list prices and do not include any discounts). The ERG also presented an alternative base-case based on a combination of a number of these scenario analyses. The ERG base-case made the following assumptions:

- Additional administration costs for eliglustat;
- Revised administration costs for ERT treatments;
- Revised estimate of the QALY benefits of oral therapy;
- Revised modelling of mortality to allow for increased mortality risk for marked and severe patients;
- Reduction in dose of ERT to bring it in-line with UK practice;
- Using ENCORE effectiveness data in the treatment naïve population during the first cycle

Table 2: Summary of results from additional analyses carried out by the ERG (list prices)

	Immiglucerase		Velaglucerase	
Analysis	**QALYs**	**Costs**	**QALYs**	**Costs**
CS's Base-case	**2.28**	**-£147,394**	**2.28**	**-£1,288,963**
ERG's Base-case	**1.05**	**£ 1,712,502**	**1.05**	**£ 923,621**
Additional administration costs for Eliglustat	2.28	-£ 144,095	2.28	-£ 1,351,158
Revised administration costs for ERT treatments	2.28	-£ 25,013	2.28	-£ 1,232,077
Revised estimate of the QALY benefits of oral therapy;	0.94	-£147,394	1.01	-£1,288,963
Revised modelling of mortality to allow for increased mortality risk for marked and severe patients;	2.53	-£ 163,517	2.53	-£ 1,501,459
Reduction in dose of ERT to bring it in-line with UK practice;	2.28	£ 1,530,403	2.28	£ 818,691

In the ERG's base-case analysis the estimated incremental costs of implementing eliglustat compared with imiglucerase are £1,712,502 and incremental QALYS are 1.05. Incremental costs of implementing eliglustat compared with velaglucerase were £ 923,621 in the ERG's base-case. Incremental benefits were estimated to be 1.05 QALYs.

Using these revised estimates of the costs the five year budget impact of implementing eliglustat in the NHS is to increase costs by £27,818,534 assuming the company's estimate of the size of the GD1 population.

1.9 Conclusions

The ERG considers that the clinical evidence supporting the non-inferiority of eliglustat is weak and conclusions are highly dependent on the non-inferiority margin selected. Evidence on the long-term comparative effectiveness of eliglustat is also lacking and therefore the health benefits of

implementing eliglustat in the NHS are highly uncertain. These uncertain benefits are set against potentially significant increases in costs to the NHS, which based on the ERG's base-case budget impact analysis approaches £28 million over five years.

2 Background

2.1 Critique of company's description of underlying health problem

This section presents an overview of the underlying health problem in the company's submission. The company provided a brief summary of the key issues relating to Gaucher disease, including details of the underlying course of the disease, the disease morbidity and the impact of the disease on patients' quality of life.

The Company Submission (CS) stated that Gaucher disease is an inherited metabolic disease that primarily affects organs where tissue macrophages are prevalent. This disease is a rare, autosomal recessive lysosomal glycolipid storage disease, which is caused by a deficiency in activity of the lysosomal enzyme acid β-glucosidase.[1] This enzyme deficiency can result in an accumulation of its substrate, glucosylceramide, an intermediate metabolite in the synthesis and catabolism of more complex glycosphingolipids, in cells derived from the monocyte/macrophage system.[1]Defects in acid β-glucosidase function are caused by mutations in the acid β-glucosidase gene (GBA) which is located on region q21 of chromosome 1. There are four common genetic defects (N370S, L444P, 84GG and IVS2+1) being identified. These genetic defects account for 89% to 96% of the mutant alleles being found in the Ashkenazi Jewish population.[2, 3]

There are three subtypes of Gaucher disease: type 1 (non-neuropathic), type 2 (acute neuronopathic) and type 3 (subacute neuronopathic).[4] In the absence of primary central nervous system involvement, Gaucher disease type 1 (GD1) is the most common subtype in the Europe, US and Canada, representing approximately 94% of the Gaucher disease population.[5]If Gaucher disease is left untreated, lipid-engorged macrophages (Gaucher cells) can accumulate primarily in the liver, spleen and bone marrow, and secondarily in the lungs, kidneys, and intestines, which leads to debilitating visceral, haematological, and skeletal manifestations with a wide range of severity, including extensive morbidity and a shortened life expectancy in many patients.[1]

Gaucher disease is associated with a range of clinical manifestations, including anaemia, thrombocytopenia, splenomegaly, hepatomegaly, bone pain and bone crises.[6] There is a higher risk of parkinsonism and Parkinson's disease in GD patients due to GBA gene mutations. Although the relationship remains unclear, there is also a higher risk of myeloma, leukaemia, glioblastoma, lung cancer, and hepatocellular carcinoma in GD patients.[6]

The CS indicates that Gaucher disease has a significant impact on patients' health-related quality of life (HRQoL). The CS cites haematological, bone and visceral symptoms as key factors affecting patients' HRQoL; the HRQoL of patients is reduced when patients progress into severe disease. In

particular, anaemia and thrombocytopenia, which are haematological consequences of Gaucher disease, can impact patients' physical functioning and mobility. When patents progress to more severe disease, there is increased bone damage and corresponding pain, as well as incidence of fragility fractures, leading to a further reduction in patients' HRQL.[7]

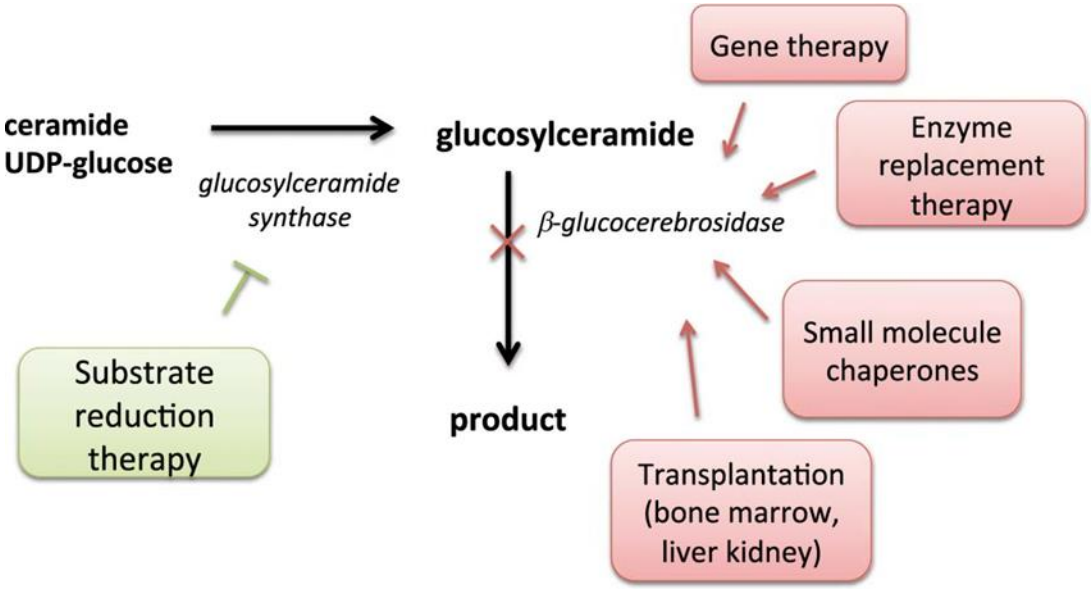
Overall, the company's description of the underlying health problem appears to be appropriate and generally relevant to the decision problem under consideration. It provided a brief but accurate overview of the disease for which the technology is being considered in the scope issued by NICE. The CS included some estimates for the number of patients with GD1 in England: 214 and [redacted]. The practitioner submissions included estimates of 300 to 400 known patients with Gaucher disease in England though estimated that only 50 to 100 patients would receive eliglustat. In their response to the ERG the Company provided further estimates of patients diagnosed with Gaucher disease in the UK of 272 (2012), 276 (2013), 283 (2014), 293 (2015).

2.2 Critique of company's overview of current service provision

2.2.1 Current management options

Current management options for patients with GD1 in Europe are three therapies that have been approved for Gaucher disease by the European Medicines Agency (EMA): two enzyme replacement therapies (imiglucerase and velaglucerase alfa) and the substrate reduction therapy (miglustat). Figure 1 presents the treatment pathways for patients with GD1.The enzyme replacement therapies (ERTs) are indicated for both children and adults with GD, while miglustat is indicated only for adults with GD1 for whom ERT is unsuitable. The ERT replaces the defective acid β-glucosidase enzyme with a functioning version derived from recombinant technology. The substrate reduction therapy inhibits the creation of the substrate for acid β-glucosidase, glucosylceramide, which accumulates in the organs of those patients affected by Gaucher disease.

Figure 1 Treatment pathways for GD1



The introduction of ERT therapy for patients with GD1 has had a substantial impact in decreasing the haematological, visceral and bone manifestations, consequently extending patients' life expectancy. The use of ERT enables patients to live a life with fewer (or no) symptoms within a short period of initiating appropriate management. The aim of ERT is to achieve therapeutic goals in the following symptom areas: anaemia, thrombocytopenia, hepatomegaly, splenomegaly, skeletal pathology, pulmonary involvement, functional health and HRQL.

The CS recognises that ERTs are very effective in reducing symptoms, controlling disease, and improving patients' HRQL. The clinical advisor to the ERG concurs with this opinion of ERT. The CS highlights the negative impact on patients of the requirement for ERT to be administered as an infusion therapy every two weeks. The CS also noted that, despite the ERT treatment, bone manifestations may still be difficult to manage and the frequency of new bone complications is decreased but not eliminated in patients with GD1 in the UK setting.[8] Furthermore, about 10-15% of patients with GD1 treated with imiglucerase develop immunoglobulin G (IgG) antibodies to the enzyme protein, which can impair enzyme activity.[9] The CS also raises the issue of how production of ERT can be interrupted due to contamination of the mammalian cell culture, causing shortage of supply. This reflects an event that occurred in June 2008; the ERG is unclear how significant this issue is in terms of current and continuing risk. The company claims that there is unmet need for a convenient, well-tolerated therapy with demonstrated efficacy in terms of patients achieving or maintaining therapeutic goals, but also a therapy that could improve the quality of life for patients. The clinical advisor to the ERG advised that the main anticipated benefit of eliglustat would be that associated with it being an oral medication.

Overall, the company's submission provided an accurate overview of the treatment pathway for GD1. The company provided details of which ERT therapies (imiglucerase and velaglucerase alfa) are currently used for the treatment of patients with GD1 in UK clinical practice. However, the company did not give details of what proportion of patients receive each therapy in routine practice.

2.2.2 Outcome measures

The ERG investigated the relevant outcomes in GD1. When a diagnosis of Gaucher disease is confirmed, a comprehensive assessment of all disease domains is important to establish baseline disease characteristics and to develop personalized therapeutic goals and monitoring strategies.[10] An important premise in the management and monitoring of Gaucher disease is that it is a progressive chronic disease, ultimately leading to reduced life-expectancy.[11]

Currently the published treatment guidelines and therapeutic goals for Gaucher disease are primarily based on the experience with enzyme replacement therapy (e.g. velaglucerase and imiglucerase), which is used as a benchmark for all other treatment therapies.[12, 13] Methods have been developed to measure the volumes of liver and spleen using magnetic resonance imaging and X-ray computed tomography images.[14] Platelet counts and blood haemoglobin concentration reflect disease severity of haematological manifestations for Gaucher disease; treatment response relating to these two outcomes can be measured by standard technology. An accurate skeletal assessment is also essential because bone-related disease such as fragility fractures are the most disabling and irreversible complications of this disease. The skeletal assessment will comprise taking history of bone crises (avascular necrosis or fracture, assessment of bone mineral density (BMD)/risk of osteoporosis, and assessment using MRI scanning of the extent of bone marrow involvement (Bone marrow burden (BMB) score).[15] Additionally, a number of biomarkers are used to measure the effects of therapies in adult patients with GD1. These biomarkers include chitotriosidase (a biomarker indicative of the bodily burden of Gaucher cells), plasma glucosylceramide (which indicates if there is a substantial reduction of the synthesis of glucosylceramide, thereby preventing glucosylceramide accumulation and alleviating clinical manifestations), plasma GM3 ganglioside (a measure of the inhibition of glucosylceramide synthesis), plasma macrophage inflammatory protein (indicative of an effect on GD1-related bone activity), plasma sphingomyelin (which indicates an effect of eliglustat on other glycosphingolipids that are synthesised from this same substrate (sphingomyelin) and plasma ceramide.

The chronic nature of type 1 Gaucher disease with heterogeneous symptoms requires an individualized disease management model relating to therapy dose and therapeutic goals in each disease domain. There is an international consensus on therapeutic goals in the treatment of Gaucher disease (Table 3: An international consensus on therapeutic goals in the treatment of Gaucher disease

[13]). [13]This provides the UK national guideline for the use of these therapeutic targets to guide initiation and adjustment of therapy.[12, 16]

Table 3: An international consensus on therapeutic goals in the treatment of Gaucher disease [13]

Disease domain	Therapeutic goals
Anaemia	•Increase haemoglobin levels within 12 to 24 months to ➢ ≥11g/dL for women ➢ ≥12g/dL for men • Eliminate blood transfusion dependency • Reduce fatigue, dyspnoea, angina • Maintain improved Hb values achieved after the first 12 to 24 months of therapy
Thrombocytopaenia	• All patients: increase platelet counts during the first year of treatment sufficiently to prevent surgical, obstetric and spontaneous bleeding. • Splenectomised patients: normalisation of platelet count by 1 year of treatment. • Patients with intact spleen: ➢ Moderate baseline thrombocytopaenia (60-120 X 109/L): the –platelet count should increase by 1.5 to 2-fold by year 1 and approach low-normal levels by year 2. ➢ Severe baseline thrombocytopaenia (<60 X 109/L): the platelet count should increase by 1.5-fold by year 1 and continue to increase slightly during years 2 to 5 (doubling by year 2), but normalisation is not expected. ➢ Avoid splenectomy (may be necessary during life-threatening haemorrhagic events) ➢ Maintain stable platelet counts to eliminate risks of bleeding after a maximal response has been achieved.
Hepatomegaly	•Reduce and maintain the liver volume to 1.0 to 1.5 times normal (according to body weight) • Reduce the liver volume by 20% to 30% within year 1 to 2 and by 30% to 40% by year 3 to 5
Splenomegaly	•Reduce and maintain spleen volume to ≤2 to 8 times normal • Reduce the spleen volume by 30% to 50% within year 1 and by 50% to 60% by year 2 to 5 • Alleviate symptoms due to splenomegaly: abdominal distension, early satiety, new splenic infarction. • Eliminate hypersplenism
Skeletal Pathology.	•Lessen or eliminate bone pain within 1 to 2 years • Prevent bone crises • Prevent osteonecrosis and subchondral joint collapse • Improve BMD Adult patients: Increase trabecular BMD by 3 to 5 years
Pulmonary Involvement	•Reverse hepatopulmonary syndrome and dependency on oxygen • Ameliorate pulmonary hypertension (ERT plus adjuvant therapies) • Improve function status and quality of life • Prevent rapid deterioration of pulmonary disease and sudden death • Prevent pulmonary disease by timely initiation of ERT and avoidance of splenectomy
Functional Health and Well-being	•Improve or restore physical function for carrying out normal daily activities and fulfilling functional roles • Improve scores from baseline of a validated quality of life instrument with 2 to 3 years or less depending on disease burden.

Gaucher Disease Type 1 Severity Scoring System (GD-DS3)

The GD1 Severity Scoring System (GD-DS3) is a validated measure established to score the severity of GD1 has been developed by an expert physician group using the nominal group technique of consensus formation.[17, 18] The domains assessed cover haematological (including items for anaemia

and thrombocytopenia), visceral (including splenomegaly and hepatomegaly) and bone. The specific assessments used for the scoring are:

- Lytic lesions, avascular necrosis or bone pathology (present or absent)
- Chronic bone or joint pain (scale of severity – none to extreme)
- Bone crisis in past 12 months
- Bone marrow infiltration (MRI BMB Score)
- BMD (lumber spine DXA Z-score)
- Thrombocytopaenia (platelet count)
- Bleeding (mild – moderate bruising; moderate – no transfusions; severe – transfusions needed)
- Anaemia (Hb measure)
- Spleen volume (MN)
- Liver volume (MN)
- Gaucher-related pulmonary disease. (present or absent).

The DS3 scoring system classifies patients into categories of disease severity:

- Severe (DS3 9 – 19)
- Marked (DS3 6 – <9)
- Moderate (DS3 3 – <6)
- Mild (DS3 <3).

A minimally clinically important improvement in response to treatment of -3.1 has been determined, although patients who commence therapy in the mild category cannot achieve this.[18] The clinical advisor to the ERG advised that this scoring system is not used in clinical practice; patients need only to have one or more recognised Gaucher complication to be eligible for treatment. The decision to treat is not guided by a numerical scoring system.

Quality of life measures

Quality of life measures and severity scores of patients are of importance in making treatment decisions. The clinical advisor to the ERG advised that in clinical practice the validated pain (Brief Pain Inventory (BPI)) and quality of life (SF-36) scores are most commonly used measures to assess quality of life.

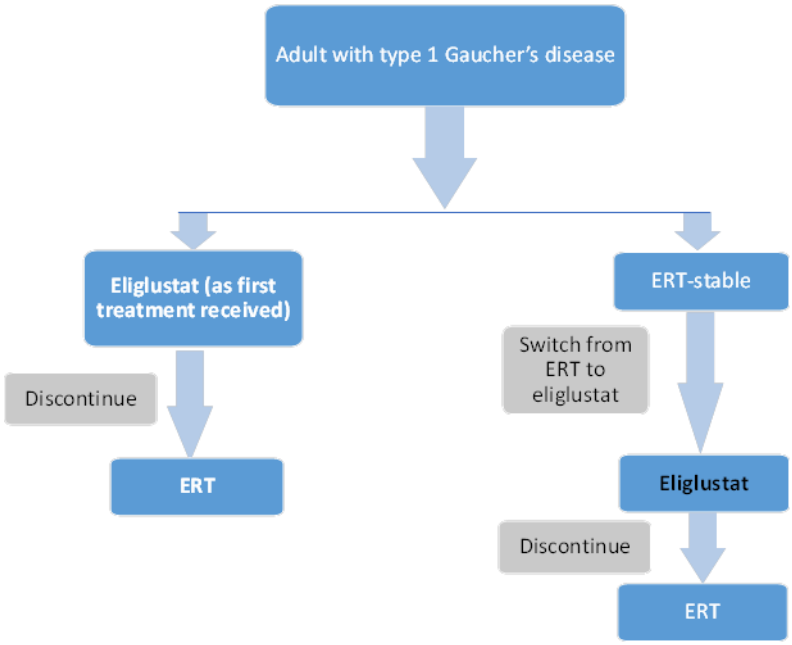
2.3 Description of the technology under assessment

Eliglustat (Cerdelga™) is a new oral substrate reduction therapy (SRT), which acts by mimicking the glucosylceramide synthase (the enzyme responsible for the synthesis of glucosylceramide), thereby reducing synthesis of glucosylceramide and preventing glucosylceramide accumulation. Eliglustat

received marketing authorisation from the European Medicines Agency (EMA) on 19 January 2015, and the anticipated launch date in the UK as stated by the company is December 2016.[19]Eliglustat is indicated for the long-term treatment of adult patients with GD1, who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs). Eliglustat is an oral treatment administered twice daily over the course of a patients' lifetime. Before initiation of treatment with eliglustat, patients should be genotyped for CYP2D6 to determine the CYP2D6 metaboliser status; this is necessary because eliglustat is extensively metabolised by CYP2D6. Eliglustat is not indicated in patients who are CYP2D6 ultra-rapid metabolisers (URMs) or indeterminate.[19]

The company provides a brief overview of the anticipated positioning of eliglustat in the treatment pathway (see Figure 2). The company indicates that the availability of the oral therapy, eliglustat, may be used as a first-line alternative treatment option to the intravenously administered ERTs in patients with GD1. Eliglustat may also offer an alternative treatment in those patients who are stable on ERT but who have a preference for oral treatment. In addition, the company indicates that oral administration will also alleviate the NHS burden associated with frequency of visits, and preparing and administering infusion treatment (including staff time). The ERG notes that eliglustat is also likely to offer an alternative to miglustat for those few patients for whom ERT is unsuitable.

Figure 2 Eliglustat's positioning in clinical practice



3 Critique of company's definition of decision problem

3.1 Population

In the statement of the decision problem, the company specified the relevant population as adult patients with symptomatic GD1.This exactly reflects the population specified in the NICE scope. All the clinical study evidence presented in the Company's submission was derived from predominantly adult patients with symptomatic GD1, some patients who were treatment naive and others who were stable on ERT.

3.2 Intervention

The intervention specified in the company's decision problem is eliglustat. This reflects the NICE scope; although the scope did not specify the dose of eliglustat. The submission presented data on therapy initiated with eliglustat 50 mg or 100 mg once or twice daily for oral administration. This is not precisely reflective of the product licence: the current licensed dose of eliglustat is 84 mg twice daily or once daily depending on the CYP2D6 metaboliser status.[19] However 84 mg eliglustat base is equivalent to 100 mg eliglustat tartrate.

3.3 Comparators

The decision problem addressed in the company submission generally reflects the NICE scope and specifies imiglucerase and velaglucerase alfa as the comparators of interest. However, the submission excluded miglustat as a relevant comparator, stating that it was only used in a very small proportion of adult GD1 patients in England for whom ERT was not suitable (<2% (4) patients in 2015). The exclusion of miglustat was not in line with the final scope issued by NICE.

The company submission (page141) further states that eliglustat is expected to be used in ERT-unsuitable patients instead of miglustat. The ERG requested the company to provide a comparison of eliglustat with miglustat in this specific population or provide further clarification as to why such a comparison is not relevant, or should not have been presented. In the company's response it stated that the sentence on page 141 contains a typographical error and it should read "In the very small number of patients for whom ERT is unsuitable, miglustat is used at present and eliglustat would not be expected to be used in place of it". As stated earlier the ERG doubts that this is the case and suggests it is likely that in practice eliglustat would be used in place of miglustat.

3.4 Outcomes

In the statement of the decision problem, the company's submission addressed each of the following outcomes: GD1 therapeutic goals, mortality, adverse effects of treatment, and patients' health-related quality of life. The primary outcome of the key trial of eliglustat (ENCORE) was proportion of

patients who remained stable for the GD1 therapeutic goal (a composite measure). Secondary outcomes included changes in haemoglobin level, platelet count and organ volumes. The health-related quality of life was measured by the Short Form 36 Health Survey (SF-36) and the disease specific quality of life measure (fatigue severity score). The safety outcomes were mortality and the incidence of adverse events. In the supporting ENGAGE trial there was only one primary outcome spleen volume which differed to the composite endpoint in ENCORE involving four key measures.

The primary measure of cost-effectiveness was incremental cost per quality-adjusted life year (QALY) gained.

3.5 Other relevant factors

Equity issues were not specified in the NICE scope nor in the decision problem. The submission states that no equity issues relating to socio-economic status, ethnicity and gender are anticipated for the appraisal of eliglustat. Other factors relating to patients' metabolism status and dosing in clinical practice were presented in this section.

3.5.1 Metabolism status

The EMA licence is granted for patients with PM, IM and EM metabolism status. The majority of patients as were found in the eligible eliglustat trials in the CS are IM or EM status. Approximately 3% of the GD population are ultra-rapid metabolisers and are excluded currently from the treatment with eliglustat.

4 Clinical Effectiveness

This section presents a critique of the methods of the review of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results and the results of any synthesis of studies.

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company's submission described the search strategies used to identify relevant studies. This is explained in CS Section 17.3 of Appendix 3 of the CS.

The CS described the search strategies used to identify relevant articles of the efficacy and safety of enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) for the treatment of Gaucher disease type 1. The search strategies were briefly described in the main body of the submission in CS Section 9.1.1 and full details were provided in Appendix 1 of the CS.

The electronic databases MEDLINE via PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched on 6th February 2013. Update searches were performed on the same set of databases on 5th January 2014 and 14th August 2015. The searches were limited by date from 1990 onwards. A restriction to limit to English language studies in MEDLINE and EMBASE was applied.

The manufacturer clarified that a separate search of the Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE) was carried out outside of the formal review. The search strategies for this were missing from the original submission but were provided in the manufacturer's response to the points for clarification. The manufacturer also clarified that the update searches of 14th August 2015 included searches for CDSR and DARE using the strategy reported under CENTRAL (CS section 17.1.4 Appendix).

To supplement the electronic database searches, the manufacturer checked the reference lists of all accepted studies, relevant systematic reviews, meta-analyses and treatment guidelines. Unpublished studies were sought from conference abstracts and posters presented at the following meetings held between 2012-2015: European Working Group on Gaucher Disease, American Society of Human Genetics, Society of Inborn Errors of Metabolism and the Lysosomal Disease Network annual meeting.

The methods used to identify both published and unpublished studies for the systematic review were appropriate for the most part. However some of the limits applied to the search strategies were not appropriate and could have caused relevant studies to be missed. The reporting of the searches was

fairly clear, though some minor details were missing: the interface/provider for EMBASE was not reported and a full description of how the conference proceedings were searched was not provided.

The structure used for the search strategies was appropriate, using terms for Gaucher disease to allow for maximum retrieval of studies of all interventions for Gaucher disease. However several limitations were noted with the search strategy which could have led to relevant studies not being identified: relevant subject heading searches for Gaucher disease were missing from the strategies for EMBASE and CENTRAL; a limit to human studies was applied in most of the strategies presented, therefore potentially missing those records of studies in humans which are awaiting indexing; searches were limited to English language only studies, therefore relevant foreign language papers would not have been identified by the searches; searches in EMBASE were limited to records which have an abstract.

The search strategy for CENTRAL included terms to remove any systematic reviews, meta-analyses or indirect/mixed treatment comparisons from the results. However this limit is unnecessary as CENTRAL only contains clinical trials. In addition, the same search strategy was used to search DARE and CDSR for relevant reviews, therefore this strategy would fail to identify relevant reviews.

The manufacturer did not search the Health Technology Assessment database which could have contained relevant studies, nor did they search the major clinical trials registers such as Clinicaltrials.gov or the WHO International Clinical Trials Registry.

4.1.2 Inclusion criteria

The detailed inclusion and exclusion criteria for the systematic review were not clearly specified in the submission though they did generally reflect the decision problem. The submission appropriately used a PRISMA diagram showing the number of included and excluded studies at each stage of the systematic review.

Clinical efficacy: The evaluation of clinical efficacy included randomised controlled trials (RCTs) (including trial extensions) assessing eliglustat for the treatment of adults or mixed (adult and paediatric) with symptomatic GD1, and reporting relevant efficacy and quality of life outcomes (e.g. fatigue severity score, SF-36). The ERG notes that despite the inclusion criteria specifying RCTs, additional study designs were included in the review (and accommodated for in the methods for quality assessment). Whilst RCTs are most appropriate to determine the efficacy of a treatment, the inclusion of other study designs as supporting and complementary evidence is appropriate. Studies involving only paediatric patients were excluded. The submission specified that participants relating to mixed (adult and paediatric) with symptomatic GD1 were eligible for inclusion. However, this inclusion criterion is not strictly in line with the product licence, which specifies that eliglustat is not specifically licensed for paediatric use. Although adults with symptomatic GD1 were the population

of interest, it would have been beneficial if the disease of interest was defined using explicit criteria, for example, clearly specify whether the diagnosis of GD1 was confirmed by documented deficiency of acid β-glucosidase activity or whether the eligible patients have one or more GD1 related disease manifestations including haematological complications, skeletal disease or gastrointestinal complications due to enlarged liver or spleen.

The submission did not differentiate clearly between the intervention and comparators in the inclusion criteria: the submission listed both the intervention (eliglustat) and other comparators as interventions. The inclusion criteria specified that eligible comparators were imiglucerase, velaglucerase alfa, miglustat, alglucerase, and taliglucerase alfa. The ERG noted that two of these comparators (alglucerase, and taliglucerase alfa) were not in line with those relevant comparators specified by the NICE scope nor the company's decision problem, and it is unclear why these two comparators were included in the inclusion criteria, although the company did not present the evidence relating to them.

The ERG noted that miglustat was included as a relevant comparator in the systematic review. This is in line with the NICE scope, but not consistent with the company's statement of their decision problem in the submission: "miglustat was not considered a relevant comparator as it was only used in a very small proportion of adult GD1 patients in England for whom ERT is unsuitable (<2% [4 patients] in 2015)". Given this statement, it was unclear why miglustat was included as a relevant comparator in the systematic review. No data on miglustat were presented in the CS.

The eligible outcomes were any outcomes relating to clinical efficacy in the submission. In particular, the submission did not explicitly specify the primary outcomes and secondary outcomes for inclusion. The ERG requested further information on eligible outcomes for inclusion. In their clarification the company stated that, while the inclusion criteria were broad for efficacy outcomes, the data extraction focused on main outcomes such as spleen and liver volume, haemoglobin level and platelet counts, skeletal pathology such as bone marrow burden (BMB) score and bone crises, and patient reported outcomes such as general quality of life.

Safety evaluation: The inclusion and exclusion criteria in the company's submission for the evaluation of safety did not appear to correspond with the synthesis of safety data presented. In the submission the company specified that only randomised controlled trials were eligible; however, other study designs such as the phase II non-controlled study were included. Although it appears to be appropriate to include evidence from longer-term non-randomised controlled trials for the safety evaluation, a lack of transparent approach in the inclusion and exclusion criteria could threaten the reproducibility of the findings from the systematic review.

The ERG requested further details for eligible outcomes for the evaluation of safety in the points for clarification. In their clarification the company stated that, while any safety outcomes were eligible, data extraction focused on any adverse events reported (including but not limited to neurologic, gastrointestinal, cardiovascular, especially cardiac arrhythmias and syncopal episodes) and treatment discontinuations (due to adverse events or due to lack of efficacy).

In addition, only English language studies were included, thereby introducing the potential for language bias.

Study selection: In their response, the company stated that abstracts identified during the literature searches were screened by one reviewer, and articles accepted at the abstract level were retrieved in full text and screened for inclusion by two reviewers independently. Any discrepancies were resolved by a third reviewer. Study selection of abstracts was not performed in duplicate, so it may have introduced errors and biases during this process.

4.1.3 Critique of data extraction

The submission stated that data extraction was performed by one reviewer and then checked by a second reviewer. Any disagreements were resolved by a third reviewer. Therefore, data extraction was appropriately performed in order to minimise the risk of errors and bias. However, the submission did not provide any information on whether authors of primary studies were contacted to provide missing or additional data during the data extraction process.

4.1.4 Quality assessment

The validity assessment tool used to appraise the included trials in the submission was based on the quality assessment criteria for RCTs as suggested by the NICE guideline template for companies. The criteria used were appropriate and in line with Cochrane risk of bias tool for RCTs, including randomisation method, concealment of allocation, blinding of participants, investigators and outcome assessors, drop-outs, similarity in terms of prognostic factors at baseline, measuring more outcomes than reported, and intention-to-treat analysis. For non-RCTs, the submission used the Downs and Black checklist to assess the quality of the single arm Phase II study. For further discussion of study quality of individual studies, see Section 4.2.

The submission did not state whether quality assessment was performed in duplicate to reduce potential bias. The ERG requested further details in the points for clarification and the Company confirmed that Two levels of study screening were performed using the exclusion and inclusion criteria below. Abstracts identified during the literature searches were screened by one reviewer. Articles accepted at the abstract level were retrieved in full text and screened for inclusion by two

reviewers working independently. Any discrepancies with regard to inclusion or exclusion of an article were resolved by a third reviewer.

4.1.5 Evidence synthesis

The company did not undertake a formal meta-analysis mainly because of the diverse nature of the clinical and methodological characteristics of the included studies, for example, considerable heterogeneity relating to patient population (e.g. treatment-naïve and treatment stable), study design and intervention. As a result, the company performed a narrative synthesis of the evidence. Despite the lack of a transparent pre-specified approach to the narrative synthesis, the ERG considers that theapproach undertaken by the company was acceptable.

4.1.6 Summary statement

Although the company's search strategies were likely to have identified all the evidence relevant to the decision problem, the ERG had concerns about how the studies were selected in the submission. For the evaluation of clinical efficacy, it appears that all relevant trials have been included. The ERG identified one additional relevant article, [20] which was published after the company's literature search in their review. This study provides a descriptive comparison of patients receiving eliglustat or miglustat after switching from ERT. Details are given in Section 4.5.There was a lack of clarity regarding the study selection for the safety evaluation, as the company did not clearly pre-specify the study design in their inclusion criteria. Appropriate criteria were used to assess the study validity. Limiting a systematic review to English language studies may have introduced the potential for language bias. There was also a lack of transparency on the selection of outcomes being considered. A narrative synthesis approach undertaken by the company was considered appropriate.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 The included trials of eliglustat

Table 4 presents the included trials of the evaluation of clinical efficacy and safety of eliglustat, including three RCTs (ENCORE, ENGAGE and EDGE) and one single arm Phase II study.

Table 4: The included studies of the evaluation of clinical efficacy and safety

Study	Study Design	Intervention and comparator
ENCORE	RCT	Eliglustat versus imiglucerase
ENGAGE	RCT	Eliglustat versus placebo
EDGE	RCT	Eliglustat versus Eliglustat (once daily vs. twice daily)
Phase II trial	Non-randomised,, single arm trial	A single arm of eliglustat (no comparator)

Direct trial evidence of the efficacy of eliglustat: ENCORE is a phase III RCT comparing eliglustat with imiglucerase for treating adults with symptomatic GD1 already controlled by ERT therapy. ENGAGE is another phase III RCT comparing eliglustat with placebo in patients not on therapy. Supporting long-term evidence was provided from a Phase II, single-arm trial of eliglustat. Further single-arm data are presented from the lead-in phase of a third RCT (EDGE) trial that assessed once daily with twice daily dosing with eliglustat.

Safety evaluation: The synthesis of adverse effects in the company's submission comprised a pooled descriptive summary of adverse effects from ENCORE, ENGAGE, EDGE and the Phase II study.

4.2.2 Outcomes in the trials

There were some variations in the outcomes used in the trials. In particular, the included trials used different primary outcomes. Table 5 presents the primary outcomes in measuring the achievement of therapeutic goals in individual trials. These outcomes will be discussed further in the individual trial sections.

Table 5 Primary outcomes in measuring the achievement of therapeutic goals in trials

	ENCORE	ENGAGE	EDGE	Phase II
Type of endpoint	Composite	Single	Composite	Composite
Primary outcome	Percentage of patients who remained stable for 52 weeks on the composite endpoint of a combination of haematological parameters and organ volumes defined as: Haemoglobin level does not decrease >1.5g/dl from baseline; platelet count does not decrease >25% from baseline; spleen volume does not increase >25% from baseline; liver volume does not increase >20% from baseline	The primary efficacy endpoint was the percentage change in spleen volume (MN) from baseline (Mean baseline spleen volume 13.89 MN) to Week 39 of treatment.	The lead-in period therapeutic goals included: ≤1 bone crisis and no symptomatic bone disease during previous 6 months of the lead-in period Haemoglobin ≥11 g/dL for females and ≥12 g/dL for males Platelet count ≥100,000/mm^3 Spleen volume ≤10 MN (if applicable) Liver volume ≤1.5 MN	Improvement from baseline to Week 52 in at least 2 of the 3 main efficacy parameters: - Spleen volume - Haemoglobin level - Platelet count

However it should be noted that a composite primary outcome of haemoglobin level, platelet count, spleen volume and liver volume is more applicable to routine practice since therapy dosing regimen are based on the achievement of therapeutic goals (as measured by spleen and liver volumes, haemoglobin level and platelet count).

4.2.3 Critique of ENCORE (Comparison with imiglucerase in ERT stable patients)

4.2.3.1 Study design

One of the main studies on which the CS evidence is based is the Phase III, open-label RCT, ENCORE. The study design of the trial is summarised below in Table 6: Study design of ENCORE (adapted from Table 9 in CS).

Table 6: Study design of ENCORE

Study details	Description
Location	39 centres in Latin America, US, Canada, Australia, Middle East and Europe
Design	Phase III, randomised, open-label, active comparator study
Duration of study	52 weeks randomised phase then entered a long-term extension period up to a minimum of Week 104 during which all patients received eliglustat..
Method of randomisation	Randomisation was stratified based on the equivalent patients ERT dose prior to any unanticipated treatment interruption, dose reduction, or regimen change. Patients were then randomised in a 2:1 ratio to receive eliglustat or imiglucerase.
Method of blinding	Open-label study. Efficacy and safety evaluations performed by external central outcome assessors blinded to treatment assignment.
Intervention(s)	Eliglustat (n=106): 50mg, 100mg, or 150mg, orally, twice daily (depending on plasma levels)
comparator(s)	Imiglucerase (n=54): infusions every 2 weeks; monthly dose 30–130 U/kg
Duration of follow-up, lost to follow-up information	No patients were lost to follow-up by Week 104.
Primary outcomes	Percentage of patients who remained stable for 52 weeks on the composite endpoint defined as: • Haemoglobin level does not decrease >1.5g/dl from baseline • platelet count does not decrease >25% from baseline • spleen volume does not increase >25% from baseline • liver volume does not increase >20% from baseline
Secondary outcomes	• Total T- and Z-scores for BMD (DXA) of femur and lumbar spine • haemoglobin level • platelet count • spleen volume • liver volume

The randomised open-label trial was conducted at 39 sites across the world including Latin America, US, Canada, Australia, Middle East and Europe. Initially the duration period for the trial was 1 year, extended up to the 2-year period. The ERG identified a published conference abstract that reported data for follow-up to 4 years.[21]

In the randomised phase patients were stratified based on their equivalent ERT dose, and they were randomised on 2:1 basis to either receive eliglustat or imiglucerase respectively. Eliglustat was administered orally at doses 50mg, 100mg, or 150mg, twice daily. Imiglucerase patients received infusions every 2 weeks with a monthly dose of 30–130 U/kg.

The primary outcome measure of efficacy for the trial is the percentage of patients who remained stable for 52 weeks for the following composite endpoints defined as; haemoglobin levels (a decrease of ≤ 1.5g/dl from baseline), platelet counts (a decrease of ≤ 25% from baseline), spleen volume (a decrease of ≤ 25% from baseline) and liver volume (a decrease of ≤ 20% from baseline). These outcomes were assessed for both treatment groups separately along with the difference between two treatment groups and the measurement represented the accepted therapeutic goal in treating Gaucher disease in clinical practice for treatment-stable patients. There were a number of reported secondary outcomes which are listed in Table 9 of the CS, they include Total T and Z-SCORES for BMD of femur and lumber spine, normal haemoglobin levels, platelet counts, spleen volume and liver volume.

The key patient inclusion and exclusion criteria for the trial were adults with confirmed diagnosis of GD1, with documented deficiency of acid beta-glucosidase activity; had received treatment with ERT (including velaglucerase or imiglucerase) for at least 3 years (for at least 6 of the 9 months before randomisation) and the patient had received a total monthly dose of 30 U/kg to 130 U/kg of ERT); and had reached Gaucher disease therapeutic goals prior to randomisation (spleen volume <10 times normal or total splenectomy (if occurred >3 years prior to randomisation), and liver volume <1.5 times normal). The full criteria are found in Table 9 in the CS. The trial inclusion criteria appear to be appropriate and follow SPC special warnings and precautions for eliglustat use. However patients taking strong or moderate CYP2D6 inhibitors concomitantly with a strong or moderate CYP3A inhibitor were not excluded. The ERG notes that the use of eliglustat under these conditions could substantially elevate eliglustat plasma concentrations and these patients should be excluded from trials of eliglustat.

The statistical design of the ENCORE trial was to test non-inferiority, where the difference in the percentage of patients remaining stable in terms of the primary outcome was to be evaluated with 95% CI, computed at 52 weeks for both eliglustat and imiglucerase. If the lower-bound of the 95% CI for the difference was within the pre-specified non-inferiority margin of 25%, then eliglustat treatment was to be declared non-inferior to imiglucerase treatment. This non-inferiority margin was based on a 95% imiglucerase response rate and an 85% eliglustat response rate (as established by the results from the Phase II study).[22] The 95% CI for the primary composite outcome for non-inferiority difference was calculated using the statistical method of Agresti and Caffo's adjusted Wald. This is a common approach used when there are two independent samples with different proportions of responses.

ERG comments on the test for non-inferiority

The underlying assumptions and hypothesis for the non-inferiority margin was specified in the CS as 25%. Non-inferiority margins are often derived based on sound clinical judgement which usually include statistical principles, [23] however this was not clearly explained or visible within the CS. Nor was it reported within the CSR or statistical analysis plan, which the ERG obtained from the company.

The EMA report that prior to the trial commencing, the non-inferiority margin should have been 20% and they suggest that a margin of 25% could be too broad. The statistical properties for using a narrower margin of 20% could affect the power of the trial, which means that to test non-inferiority effectively, a larger sample size would be required.[24] However, as acknowledged by the EMA recruiting more patients within the trial was not considered feasible. The ERG has identified this as a potential obvious limitation.

Furthermore the pharmaceutical benefits advisory committee (PBAC), who are an independent expert body appointed by the Australian government to provide recommendations on new medicines, claimed that the non-inferiority in the trial was not supported.[25] The reasons given are that:

- The non-inferiority margin of 25% assumed that eliglustat could be 10% worse than imiglucerase with no clinically meaningful loss of effect, the additional 15% is for the inherent variability in estimating the difference between these two treatments due to the composite endpoint for stability based on all the four domains (platelet, haemoglobin, spleen and liver). The assumption that a 10% inferiority is a clinically unimportant difference between treatments may not be reasonable for a non-inferiority claim as no justification was provided in either the CS or European public assessment report (EPAR).
- The ERG determined that if eliglustat were administered in ENCORE with 100 mg instead of the maximum dose 150 mg, and this resulted in two fewer stable eliglustat patients (i.e., 82 stable patients out of a total of 99), then the claim of non-inferiority would no longer be supported at the 20% margin suggested by the EMA.

Company's comments on non-inferiority

Based on the uncertainty regarding the acceptability of the non-inferiority margin highlighted by the EMA and the PBAC, the ERG queried the company's assumptions of non-inferiority and asked them to provide justification for why a non-inferiority margin of 25% was selected. The following were asked:

- Do they consider the 25% margin used in the non-inferiority trial to be clinically acceptable?

- Can they specify how the clinical meaningful difference 10% between the two treatments was calculated?
- What would 25% difference in the primary outcome mean for the prognosis of Gaucher disease patients?
- To perform a re-analysis using the non-inferiority margins of 15% and 20% and provide evidence of whether the trial is still efficiently powered at these alternative margins, and whether the conclusion of non-inferiority is met.

The company response was that the EMA approved a licence for eliglustat based upon the acceptance of non-inferiority at 20% from this trial, and on the aggregate data reported in the SPCs on all doses tested in the trial. They did not explain how the clinical meaningful difference of 10% was obtained or what effect this clinical difference may have on GD1 diagnosed patients.

The statistical power of the trial for when the non-inferiority margin was set to 15% and 20% is presented in Table 7. As can be seen, the power to demonstrate non-inferiority using a 15% margin is low (21%) and for 20% margin it was 61%: both are below the usual 80% acceptable level.

Table 7: Power to demonstrate non-inferiority in the ENCORE study per-protocol population for different margins

Non-inferiority margin	Power (%)*
-25%	91
-20%	61
-15%	21
*power using the non-stratified Agresti-Caffo method. Similar results are obtained with the Newcombe test.	

Statistical tests used in Non-inferiority

The Agresti and Caffo's adjusted Wald method was used to calculate the treatment differences. This method computes intervals for single proportions as well as for differences in independent proportions. It is suited when analysing the treatment difference between the two treatment groups. However, the ERG asked the company to consider an alternative approach such as Newcombe's hybrid score interval, to see if there were any differences in stability between both treatments.[26] The company have re-analysed and reported the 95% CIs using a number of alternative methods for testing the difference between two proportions (Table 8). These analyses were performed both on the PPP and intention to treat (ITT) analysis. All methods tested exclude the -20% non-inferiority margin with the exception of the Santner and Snell method (PPP and ITT) and continuity corrected Wald test (PPP), meaning that non-inferiority is only just demonstrated at the 20% margin for all other tests. However the ERG notes that these last two methods should not be used to determine non-inferiority

since the Santner and Snell method is based on an unstandardized test statistic and has an exact type I error rate of 0.06%, which is far too small, and the Wald method with continuity correction is not recommended due to its conservativeness.

Table 8: Lower 97.5% CI of the difference between proportions of patients remaining stable on eliglustat compared to imiglucerase

Analysis Type	Method	PPP	Intention to treat analysis
Exact (non-stratified)	1. Santner and Snell (1980)	-0.2594	-0.2420
	2. Chan and Zhang (1999){Chan, 1999 #2209}[28]	-0.1875	-0.1794
	3. Agresti and Min (2001)	-0.1880	-0.1795
	4. Reiczigel et al. (2008)	-0.1830	-0.1769
	5. Shan and Wang (2013)	-0.1945	-0.1805
Asymptotic (stratified)	6. Agresti-Caffo (MH)+	-0.1756	-0.1706
	7. Wald (MH)	-0.1870	-0.1820
	8. Newcombe-Wilson (MH)	-0.1810	-0.1750
Asymptotic (non-stratified)	9. Agresti-Caffo (2000)	-0.1814	-0.1761
	10. Wald (1940)	-0.1870	-0.1818
	11. Wald (cc)	-0.2027	-0.1959
	12. Newcombe-Wilson (1998)	-0.1811	-0.1739
	13. Newcombe-Wilson (cc)	-0.1795	-0.1724
	14. Hauck-Anderson (1986)	-0.1985	-0.1920
	15. Farrington-Manning (1990)	-0.1854	-0.1774
	16. Miettinen-Nurminen (1985)	-0.1852	-0.1775
cc, continuity-correction; MH, Mantel-Haenszel weights; +, primary efficacy analysis method			

Closed-testing procedure

As the number of patients in the trial was quite large (>80 patients), multiple testing between the treatment effect estimates for each patient would require a closed-testing procedure to control the family wise error rate. However the company suggest that as the trial's main objective was to determine non-inferiority between eliglustat and imiglucerase, that multiplicity was not important. The ERG suggests that to support any statistically significant claims specifically for primary outcomes, the problem of multiple testing should have been addressed.

LOCF

The CS reported that the last observation carried forward method (LOCF) would be used when analysing missing data on all outcomes. The LOCF approach has advantages in that it minimises the number of subjects removed and allows the analysis to examine trends over time rather than focusing

on the endpoint. The ERG will provide a detailed critique in the results section 4.2.3.3 on whether the use of LOCF method was appropriate and detail how many patients were analysed using this approach.

4.2.3.2 Patient Characteristics

The characteristics of the patient population in the trial are summarized in Table 9. There were very few indications of imbalance between the treatment arms. Minor differences were seen in the spleen volumes with 3.17 (SD 1.35) for patients on eliglustat, and 2.74 (1.15) for those on imiglucerase; Lumbar spine BMD T-score was -0.54 (1.38) on eliglustat and -0.34 (1.15) on imiglucerase; and Femur BMD T score -0.15 (1.09) for patients on eliglustat and -0.41 (1.28) for patients on imiglucerase. However, these differences were within the normal expected variation.

Table 9: Patient characteristics of ENCORE

Characteristic	Eliglustat (n=106)	Imiglucerase (n=53)
Mean (SD) age, years	37.6 (14.2)	37.5 (14.9)
Male %	44%	47%
White %	92%	91%
Jewish descent %	27%	26%
Spleen volume, MN, mean (SD) (normal size: ≤5MN)	3.17 (1.35)	2.74 (1.15)
Liver volume, MN, mean (SD) (normal size: ≤2.5MN)	0.94 (0.19)	0.92 (0.16)
Haemoglobin levels, g/L, mean (SD) (normal values: >120g/L for males, >110g/L for females)	136 (13)	139 (13)
Platelet count, 10^9/L, mean (SD) (normal: >120 x 10^9/L)	203 (79)	188 (57)
Splenectomised %	No: 72% Partial: 1% Total: 27%	No: 83% Partial: 2% Total: 15%
Total BMB score, mean (SD)	8.22 (2.66)	8.12 (2.63)
Lumbar spine BMD T score, mean (SD) (normal T-score: ≥-1; osteopenia defined by T-scores <-1 to >-2.5; osteoporosis defined by T-scores ≤-2.5)	-0.54 (1.38)	-0.34 (1.15)
Femur BMD T score, mean (SD) (normal T-score: ≥-1; osteopenia defined by T-scores <-1 to >-2.5; osteoporosis defined by T-scores ≤-2.5)	-0.15 (1.09)	-0.41 (1.28)
CYP2D6 metaboliser status %	Poor: 4% Intermediate: 11% Extensive: 79% Ultra-rapid: 4% Indeterminate: 2%	Poor: 4% Intermediate: 17% Extensive: 74% Ultra-rapid: 2% Indeterminate: 4%
Age at Gaucher disease diagnosis, years, mean (SD)	17.8 (13.6)	20.3 (14.3)
Age at first Gaucher symptom onset, year, mean (SD):	12.7 (12.0)	15.9 (14.2)
Years on imiglucerase, mean (SD)	9.8 (4.0)	10.0 (3.6)
Current ERT %	Imiglucerase: 79% Velaglucerase: 21%	Imiglucerase: 85% Velaglucerase: 15%
BMB, bone marrow burden; BMD, bone mineral density; ERT, enzyme replacement therapy; GD, Gaucher disease; MN, multiples of normal; SD, standard deviation.		

Quality assessment

The quality assessment reported in the CS demonstrated that the trial was appropriately randomised. Patients were stratified to groups at individual sites avoiding any potential imbalance. As this trial was open label due to eliglustat being an oral medication and ERT being administered in hospital by infusion, allocation concealment was not possible. However external assessors were blinded to treatment assignment. The baseline characteristics were relatively well balanced between treatments,

although there were some differences with both age at first symptom and age at Gaucher diagnosis being later in the imiglucerase arm. As external central outcome assessors were blinded to efficacy and safety evaluations and there was no likely impact on risk of bias associated with primary outcomes. The analysis was conducted using the per protocol population (PPP); the criterion for inclusion in the PPP, was that a patient must have observed baseline and Week 52 measurements for the variables composing the stability endpoint. The use of PPP analysis is considered appropriate in non-inferiority studies, as with increasing bias (i.e. flawed randomization) the more likely an ITT analysis will show non-inferiority.[23] ERG conducted its own quality assessment and their results concur with the quality assessment presented by the CS (Table 10).

Table 10: ERGs study quality assessment for ENCORE trial using NICE's template

Entry	ERG's Judgement	Support for judgement
Random sequence generation	Low	Stratified based on patients every 2 weeks equivalent ERT dose, randomised in a 2:1 ratio. Online process used to generate randomisation procedure. Balance across sites and stratum was ensured.
Allocation concealment	N/A	Trial was an open-label study. But selected efficacy and safety evaluations were externally assessed by outcome statisticians who were blinded to treatment assignment.
Balance of prognostic factors between groups at the outset of the study	High	Baseline characteristics were generally well balanced between treatment arms, although key differences were in the age at first symptom onset and age at Gaucher diagnosis was much later in the imiglucerase arm.
Blinding (participant's, caregivers and outcomes assessors)	Low	Outcome statisticians were blinded to treatment assignment for efficacy and safety outcomes. These include organ volume and bone imaging data, ECG and Holter monitor data, and nerve conduction data.
Imbalances due to drop-outs between groups	Low	Overall discontinuations were comparable between groups
Selective reporting	Low	Results for all outcomes presented in the CSRs
Method of analysis, and handling missing data	Low	The primary efficacy analysis in ENCORE was conducted using the PPP, which is common in non-inferiority studies. Efficacy analyses using ITT population were also conducted and the results were similar.

4.2.3.3 Summary of clinical efficacy results from ENCORE trial

An overview of the clinical effectiveness results of ENCORE is provided in Table 11 (PPP analysis set which is recommended in non-inferiority trials). The CS states that both the primary and secondary outcomes were analysed using the PPP and ITT populations and the results were similar.

Table 11: Overview of clinical effectiveness results in ENCORE trial (based on CS Table 17 which give full details)

Outcome	Eliglustat (n=99)	Imiglucerase (n=47)
Composite primary endpoint %	84.8 (76.2, 91.3)%	93.6 (82.5, 98.7)%
Difference in percentage stable for	-8.8% (95% CI: -17.6, 4.2)	

52 weeks, % (95% CI)		
Patients who met stable criteria of primary endpoint % (exact 95% CI)		
Haemoglobin criteria	94.9 (0.89, 0.98)%	100%
Platelet criteria	92.9 (0.86, 0.97)%	100%
Spleen volume criteria	95.8 (0.88, 0.99)%	100%
Liver volume criteria	96 (0.90, 0.99)%	93.6 (0.83, 0.99)%
Percentage stable for 104 weeks % (95% CI)		
	Eliglustat (n=95)	
Composite endpoint	87.4% (0.79, 0.93)%	
Patients who met stable criteria of primary endpoint % (95% CI): Eliglustat (n=99)		
Haemoglobin criteria	96.8 (0.91, 0.99)%	
Platelet criteria	93.7 (0.87, 0.98)%	
Spleen volume criteria	95.8 (0.88, 0.99)%	
Liver volume criteria	96 (0.90, 0.99)%	
Secondary outcomes - absolute and percentage changes in haemoglobin, platelet count and organ volumes at Week 52 and Week 104		
	Haemoglobin levels (g/dL)	**Platelet count (10^9/L)**
	Eliglustat (n=98) / **Imiglucerase (n=47)**	**Eliglustat (n=98)** / **Imiglucerase (n=47)**
Treatment difference: *LS Mean (SEM)* *95% CI* *p-value*	-0.28 (0.12) (-0.52, -0.03) 0.03	1.30 (3.01) (-4.65, 7.24) 0.67
	Liver volume (MN)	**Spleen volume (MN)**
	Eliglustat (n=98) / **Imiglucerase (n=47)**	**Eliglustat (n=70)** / **Imiglucerase (n=39)**
Treatment difference: *LS Mean (SEM)* *95% CI* *p-value*	-1.14 (1.66) (-4.42, 2.15) 0.49	-2.83 (2.68) (-8.14, 2.47) 0.29
Secondary outcomes - changes in bone-related endpoints at Weeks 52 and 104		
	Eliglustat (n=99)	**Imiglucerase (n=47)**
Total spine BMD (g/cm^2)		
Treatment difference: LS Mean (SEM) 95% CI p-value		-0.06 (0.58) (-1.21, 1.09) P=0.9203
Total lumbar spine T-score		
Treatment difference: LS Mean (SEM) 95% CI p-value		0.01 (0.06) (-0.10, 0.13) P=0.8345
Total lumbar spine Z-score		
Treatment difference: LS Mean (SEM) 95% CI p-value		0.0 (0.05) (-0.11, 0.10) P=0.9553
Total femur BMD (g/cm^2)		
Treatment difference LS Mean (SEM) 95% CI p-value		0.19 (0.38) (-0.57, 0.94) P=0.63
Total femur T-score		
Treatment difference LS Mean (SEM) 95% CI p-value		0.03 (0.03) (-0.57, 0.94) P=0.3519
Total femur Z-score		
Treatment difference		

LS Mean (SEM) 95% CI p-value	0.02 (0.03) (-0.04, 0.07) P=0.5847

Eliglustat met the criteria of being non-inferior to imiglucerase in terms of the primary outcome and maintaining stability, as the non-inferiority lower 95% CI was -17.6% which was within the pre-specified threshold of -25%. In both treatment groups, greater than 92% of patients were stable in each component of the composite endpoint. There were no patients analysed using LOCF as it was not necessary to do so.

In the secondary outcome results for absolute and percentage changes in haemoglobin, the difference was statistically significant between treatment groups (95% CI -0.52, -0.03). The bone-related outcomes (Spine BMD, lumber spine T-score and Z-score, femur BMD, T-score and Z-score, spine BMB, femur BMB and total BMB score) showed no statistical significance in treatment difference (eliglustat-imiglucerase)(Full results reported in Table 17 in CS). Following the request by ERG, the company presented subgroup analysis based on metaboliser status for the ENCORE trial. [redacted].

The DS3 scores were reported in Table 17 of the CS. The range of DS3 scoring is from 0 to 19. A score of between 0 and 3 indicates borderline to mild disease; 3 to 6 indicates moderate disease; 6 to 9 indicates marked disease; 9+ indicates severe disease. The DS3 scores in ENCORE showed no clinically important improvements with little change from baseline to week 52. Patient's scores were all below 3 indicating mild disease. These DS3 outcomes will be included in the health economics section.

Post-hoc analysis

The company also performed an unplanned post-hoc analysis which was conducted for the subgroups of patients according to pre-treatment ERT (imiglucerase or velaglucerase). The results showed that:

- Eliglustat has similar efficacy both post-imiglucerase and post-velaglucerase treatment
- Haemoglobin levels showed a similar change from baseline to Week 52 in the eliglustat arms both post-imiglucerase and post-velaglucerase treatment (mean change of [redacted]g/dL and [redacted]g/dL, respectively)

- This was also seen for spleen and liver volume outcomes. Mean change to Week 52 in spleen volume was [redacted] MN compared with [redacted] MN in eliglustat patients pre-treated with imiglucerase and velaglucerase, respectively. Liver volume showed a mean change of [redacted] MN and [redacted] MN, respectively.
- A difference in pre-treated groups was seen in platelet count outcomes with a greater increase seen in patients pre-treated with imiglucerase then those with velaglucerase ([redacted] x 10^9/L vs. [redacted] x 10^9/L)

Long-term follow-up from ENCORE

The ERG identified the 4 year follow-up of the ENCORE trial which has been reported in a conference abstract, the full paper is not yet available. Of the 159 patients treated in the 12 month primary analysis period, 146 (92%) entered the long-term treatment period where all patients received eliglustat.[21] Stability on all 4 composite parameters was maintained in 126/146 (86%) patients treated with eliglustat for 1 year, 115/136 (85%) for 2 years, 93/109 (85%) for 3 years, and 40/44 (91%) for 4 years. Individual primary outcomes (haemoglobin, platelet, spleen and liver) also maintained stability at 2 years and 4 years. Eliglustat proved to be well tolerated over 4 years with only 4 withdrawals due to treatment related AEs of which the severity grading was unknown. However, the reason for a high drop-out rate, particularly that between 3 and 4 years was not explained in the abstract, and the unexplained loss of patients from follow-up raises questions of how to interpret these long-term results.

Patient HRQL outcomes in ENCORE

The ENCORE trial utilised a variety of different measures for the HRQL, these were assessed primarily through questionnaires including the fatigue severity scale (FSS), Brief pain inventory (BPI) (average pain) and the short-form (36) health survey (SF-36) (general health, physical component score and mental component score).

For the BPI, the majority of patients reported minimal or no pain or interference of pain in daily activities at baseline and patients in both treatment groups generally remained stable through week 52 (Table 12). The BPI score showed the largest percentage change difference, between baseline and week 52 for the two treatment groups (-9.12 (SD 103.05)% eliglustat and -32.67% (79.13) imiglucerase) indicating a positive reduction but with large variability, the absolute differences however were not statistically significant in both treatment groups.

Table 12: HRQL reported outcomes in ENCORE

HRQL Measure	Treatment group	Time - Mean (SD)		
		Baseline	**Week 52**	**% change**
FSS	Eliglustat (n=97)	3.06 (1.55)	3.13 (1.63)	14.73 (75.04)
	Imiglucerase (n=45)	3.01 (1.54)	2.92(1.54)	8.78 (57.93)
BPI, Average Pain	Eliglustat (n=95)	1.67 (2.05)	1.55 (1.97)	-9.12 (103.05)
	Imiglucerase (n=46)	1.17 (1.44)	0.85 (1.19)	-32.67 (79.13)
SF-36 – general health	Eliglustat (n=96)	70.5 (19.56)	71.21 (19.03)	4.75 (29.20)
	Imiglucerase (n=46)	75.15 (18.67)	78.91 (15.28)	9.16 (27.14)
SF-36 – physical component score	Eliglustat (n=95)	49·59 (9·16)	51·22 (8·37)	4·78 (16·26)
	Imiglucerase (n=46)	53·38 (7·17)	55·07 (5·20)	4·55 (14·19)
SF-36 – mental component score	Eliglustat (n=95)	51·97 (9·85)	50·97 (10·30)	0·00 (21·39)
	Imiglucerase (n=46)	51·99 (8·87)	51·34 (10·09)	-0·53 (17·88)
BPI, Brief Pain Inventory; FSS, Fatigue Severity Score; HRQL, health-related quality of life; SF-36, Short Form 36.				

The FSS showed considerable variability in the patient's perception of fatigue at baseline, with scores spanning the entirety of the scale (i.e., 1-7). The majority of patients in each treatment group had very little change in FSS score with mean values at baseline of 3.06 and 3.01 for eliglustat and imiglucerase, respectively compared to 3.13 and 2.92 at week 52. For the SF-36, baseline physical component scores and mental component scores were similar for each treatment group and were essentially unchanged at week 52.

Patients, who received eliglustat for 12 months were also questioned regarding their treatment preference. The ERG obtained these questionnaire results from company (Table 13: Summary of treatment preference (Oral vs. infusion)). Ninety-four percent of patients in the eliglustat group and 94% in the imiglucerase group indicated a preference for oral treatment at screening (Table 13). This was not reflected in the SF-36 mental component score. Following 52 weeks of treatment, the proportion of eliglustat patients who confirmed preference for an oral treatment was 94%. The most frequent reasons given for the preference of oral therapy were: more convenient, taken at home, given by tablets, and felt better after treatment.

Table 13: Summary of treatment preference (Oral vs. infusion)

Parameter	Eliglustat (n=99)		Imiglucerase (n=47)	
	Screening, n (%)	Week 52, n (%)	Screening, n (%)	Week 52, n (%)
Preferred treatment				
Oral	93 (94)	93 (94)	44 (94)	0 (0)
IV	3 (3)	0 (0)	2 (40)	0 (0)
Reason for preference				
More convenient	80 (81)	80 (81)	41 (87)	0 (0)
Taken at home	63 (64)	68 (69)	30 (64)	0 (0)
Given in hospital	1 (1)	0 (0)	0 (0)	0 (0)
Given by injection	0 (0)	0 (0)	0 (0)	0 (0)
Given by tablets	48 (48)	58 (59)	22 (47)	0 (0)
May be more effective	32 (32)	0 (0)	8 (17)	0 (0)
May cause fewer side effects	13 (13)	0 (0)	1 (2)	0 (0)
Felt better after treatment	0 (0)	22 (22)	0 (0)	0 (0)
Causes fewer side effects	0 (0)	11 (11)	0 (0)	0 (0)
Other reasons	0 (0)	9 (9)	0 (0)	0 (0)
IV, intravenous				

4.2.3.4 Summary of critique of ENCORE

ENCORE was a well conducted trial with a clinically relevant primary outcome. However, because the comparator imiglucerase is administered by infusion and eliglustat is an oral therapy, the trial was open label. This means that the trial was at high risk of bias for any subjective outcomes. The results demonstrated that patients who are stable on ERT maintain most of that stability after switching to eliglustat. Eliglustat met the criteria of being non-inferior to imiglucerase in terms of the primary outcome and maintaining stability, as the non-inferiority lower 95% CI was -17.6% which was within the pre-specified threshold of -25% (this lower 95% CI for the composite endpoint also confirmed non-inferiority at the 20% acceptance margin). However, these non-inferiority margins are somewhat wider than would normally be accepted: a margin of 15% would have been more robust. Furthermore, the 25% non-inferiority margin assumes that a 10% reduction in efficacy is clinically insignificant, an assumption that was not justified by any clinical argument. The ERG notes the EMA accepted the broader margin due to the rare nature of the disease: the conduct of a larger trial (as would be necessary with a 15% margin) would not be feasible.

Long-term follow-up data from ENCORE demonstrated that for patients who remain on eliglustat stability on all four composite parameters is maintained over 4 years. However, although few patients

withdrew due to adverse events the number of patients in the analysis at 4 years was only 44 out of an original 159 patients: the unexplained loss of patients from follow-up raises a question of how to interpret these long-term results. There is no clear evidence of greater efficacy in terms of bone outcomes with eliglustat compared with ERT, possibly due to limited long term data. As treatment for GD1 is life-long, there is uncertainty regarding the long-term implications of a possible small reduction in efficacy with eliglustat compared with ERT (imiglucerase).

4.2.4 Critique of ENGAGE (Placebo-controlled trial in treatment naïve patients)

4.2.4.1 Study design

The ENGAGE trial is a Phase III, randomised, double-blind, placebo-controlled, multi-centre study of eliglustat in 40 adult treatment naïve patients with GD1 (see Table 14 and Table 10 in CS for full details of the design and methods of ENGAGE). Patients were randomised to either placebo or eliglustat. The dose of eliglustat was 50 mg twice daily with an increase to 100mg twice daily permitted at week 4 for patients whose plasma concentration was <5ng/ml).

The ENGAGE trial maintained randomisation for 39 weeks and then patients entered an open-label extension during which all patients received eliglustat. As in the randomised phase the dose of eliglustat started at 50mg and could be adjusted upwards to 100mg or even 150 mg based on plasma concentrations. The ERG notes that a starting dose of 50 mg twice daily is below the licenced dose of eliglustat: 100 mg once daily is licenced for poor metabolisers only. The dose adjustment used in both phases of the trial was generally in accordance with the SPC for eliglustat except that a second dose adjustment to 150 mg twice daily is not a licensed dose for GD1 patients.

Table 14 Study design of ENGAGE (adapted from CS Table 10)

Study details	Description
Location	26 centres in Latin America, the United States, Canada, Middle East and Northern Africa, India and Europe participated in the study.
Design	A Phase III, randomised, double-blind, placebo-controlled, multi-centre study confirming the efficacy and safety of eliglustat in patients with GD1. A long-term extension study was carried out from Week 39 to a minimum of 78 weeks, with patients being able to receive treatment for a total duration of up to 6 years.
Duration of study	39 weeks then entered a long-term extension period for a minimum of 78 weeks.
Method of randomisation	Randomisation was stratified based on the patient's baseline spleen volume (≤20 MN or >20 MN) and within each stratum patients were randomised in a 1:1 ratio to each treatment group. Randomisation was via an IVRS/IWRS. Patient identification numbers were assigned through this system with each ID number corresponding to an allocated randomisation number.
Method of blinding	Patients, investigators, and sponsors investigational team were blinded to study treatment until all patients completed the double-blind primary analysis period. Blinding was maintained due to both intervention and placebo capsules being identical in appearance.
Intervention(s) and comparator(s)	Eliglustat (n=20): 50mg or 100mg capsule twice daily Placebo (n=20): 50mg or 100mg capsule containing 50% Avicel PH101 and 50% lactose monohydrate USP/Ph-Eur twice daily
Duration of follow-up, lost to follow-up information	No patients were lost to follow-up by Week 78.

Study details	Description
Statistical tests	The primary efficacy endpoint was analysed using an ANCOVA model, normal distribution was confirmed using the Shapiro-Wilk test at a 5% level of significance. Secondary endpoints were analysed using a closed-testing procedure. For within-patient analyses, a paired t-test was used for analysis of endpoints with normally distributed data, and a Wilcoxon signed-ranks test was used for analysis of endpoints with normally distributed data
Primary outcomes	Percentage change in spleen volume from baseline to 39 weeks in MN with eliglustat as compared with placebo.
Secondary outcomes	• Absolute change from baseline in haemoglobin level (in g/dL), • percentage change from baseline in liver volume (in MN) • percentage change from baseline in platelet count (in/mm^3) within patient changes from baseline to 39 weeks of eliglustat treatment for percentage changes in spleen volume, liver volume, and platelet count

Unlike the ENCORE trial the primary outcome was not a composite one but was percentage change in spleen volume (measured in MN) from baseline to 39 weeks in untreatedpatients. Measures of absolute change from baseline in haemoglobin level, percentage change from baseline in liver volume and platelet count were then considered as secondary outcomes in the ENGAGE trial. It should be noted that a number of tertiary outcomes were also evaluated in this trial: bone parameters, biomarkers and health related quality of life. The bone-related outcomes included change in lumbar spine BMD, total spine T-score, total spine Z-score, total femur BMD, total femur T-score, total femur Z-score, and absolute change in spine bone marrow burden (BMB), femur BMB, and total BMB. The biomarker outcomes included changes in normalised chitotriosidase, plasma glucosylceramide, plasma GM3 ganglioside, plasma macrophage inflammatory protein, plasma ceramide and plasma sphingomyelin. The health related quality of life outcomes included fatigue severity score, bone pain inventory and 36-item SF-36 measures. In addition a summary measure of disease activity DS3 (domain and total scores) was assessed and reported in the CS.

The key patient inclusion and exclusion criteria for the ENGAGE trial were $\leq$ 16 years with confirmed diagnosis of GD1, with documented deficiency of acid beta-glucosidase activity. Although the CS refers to the patients in this trial as 'treatment-naïve', this is not strictly correct. At the time of recruitment patients were not on SRT or ERT therapy, but were allowed to have taken these therapies in the past. Specifically, patients receiving SRT within 6 months prior to randomisation or ERT within 9 months prior to randomisation were excluded. In the trial, five patients (out of a total of 40) had received prior ERT with either alglucerase or imiglucerase: two patients in the eliglustat group and three in the placebo group. Four of these five patients had also received prior treatment with miglustat. As consistent with the inclusion and exclusion criteria, all these patients discontinued treatment with ERT and miglustat at least 9 months and 6 months prior to randomization. However, it was unclear whether these patients failed to respond adequately to the ERT or miglustat therapy.

Furthermore, patients who had the following symptoms during the screening period were included: 1) haemoglobin level of 8.0 to 11.0 g/dL for females or 8.0 to 12.0 g/dL for males and/or platelet count of 50,000 to 130,000/mm3 (based on the mean of two measurements obtained at least 24 hours apart). 2) Splenomegaly (defined as a spleen volume of 6 to 30 MN); 3) If hepatomegaly was present, liver volume was less than 2.5 MN. Patients with previous history of splenectomy (either partial or total) were excluded. The full criteria are found in Table 9 in the CS. The ERG notes that the exclusion of splenectomised patients from ENGAGE differs from their inclusion in ENCORE. Also unlike ENCORE, patients taking strong or moderate CYP2D6 inhibitors concomitantly with a strong or moderate CYP3A inhibitor were excluded.

Statistical methods

The primary efficacy endpoint was analysed using an ANCOVA model. Secondary endpoints were analysed using a closed-testing procedure to control the type 1 error rate. However the statistical approach was not explained in the CS so the ERG contacted the company to explain. The following response was provided:

The closed-testing procedure used in the ENGAGE study for the secondary endpoints was the following:

- First, the absolute change in haemoglobin levels (in g/dL) from Baseline to Week 39 was analysed at the 5% level of significance.
- If there was a statistically significant eliglustat treatment effect for the change in haemoglobin levels, then the percentage change in liver volumes (in MN) from Baseline to Week 39 was analysed at the 5% level of significance.
- If there was a statistically significant eliglustat treatment effect for the percentage change in liver volumes (in MN), then the percentage change in platelet counts (in /mm3) from Baseline to Week 39 was analysed at the 5% level of significance.
- Due to the order being pre-specified, no further p-value adjustments were needed for multiple comparisons.

The intention-to-treat analysis was adequately applied in the efficacy analysis. The statistical approaches used were considered appropriate. Similar to the ENCORE trial the last observation carried forward (LOCF) method was used to impute missing values. The submission did not include a justification for this (evidence that treatment effect was maintained and patients did not get worse in their symptoms during the follow-up). However, as only one patient's data were imputed for the analysis at 39 weeks, the ERG considered that this would have minimal impact on the results of the analysis.

4.2.4.2 Patient characteristics

Table 15 presents the patients' characteristics of the ENGAGE trial.

At the end of the protocol-defined titration period, around 85% of patients received eliglustat 100 mg twice daily, which was generally in line with the licenced dose.

Ninety percent of patients in the ENGAGE trial were extensive metabolisers with no poor metabolisers. A small proportion of patients were intermediate metabolisers. Only one ultra-rapid metaboliser was recruited to the trial. However, GD patients who are ultra-rapid metabolisers are excluded currently from the treatment with eliglustat. This is because a higher dosage of eliglustat 150 mg or more is likely to be required as indicated by the observed plasma levels in ultra-rapid metabolisers. The dosing regimen of eliglustat for ultra-rapid metabolisers has not yet been specified by the product license.

Table 15 Baseline characteristics of the ENGAGE trial (Adapted from CS Table 14)

	Eliglustat (n=20)	**Placebo (n=20)**
Age, mean (SD), years	31.6 (11.6)	32.1 (11.3)
Weight, mean (SD), kg	64.8 (11.7)	68.6 (17.2)
Male, n (%)	8 (40)	12 (60)
White, n (%)	19 (95)	20 (100)
Jewish descent, yes, n (%)	3 (15)	8 (40)
Spleen volume, MN, mean (SD) (normal size: ≤5MN)	13.9 (5.9)	12.5 (6.0)
Liver volume, MN, mean (SD) (normal size: ≤2.5MN)	1.4 (0.4)	1.4 (0.3)
Haemoglobin levels, g/dL, mean (SD) (normal values: >12g/dL for males, >11g/dL for females)	12.1 (1.8)	12.8 (1.6)
Platelet count, 10^9/L, mean (SD) (normal: >120 x 10^9/L)	75.1 (14.1)	78.5 (22.6)
CYP2D6 metaboliser status, n (%)	Poor: 0 (0) Intermediate: 1 (5) Extensive: 18 (90) Ultra-rapid: 1 (5)	Poor: 0 (0) Intermediate: 2 (10) Extensive: 18 (90) Ultra-rapid: 0 (0)
cid β-glucosidase activity, nmol/hour/mg, mean (SD)	2.29 (3.38)	2.04 (3.79)
Spine BMB Score, mean (SD)	5.33 (1.503)	5.93 (1.346)
BMD, g/cm^2, mean (SD)	1.04 (0.152)	0.99 (0.162)
Chitotriosoidase genotype, n (%)	Normal: 13 (65) Heterozygous: 6 (30) Homozygous mutation: 1 (5)	Normal: 16 (80) Heterozygous: 4 (20) Homozygous mutation: 0 (0)
Age at Gaucher disease diagnosis, years, mean (SD)	22.3 (9.6)	20.1 (13.2)
Age at first Gaucher symptom onset, year, mean (SD):	16.7 (10.5)	15.2 (12.4)

BMB, bone marrow burden; BMD, bone mineral density; MN, multiples of normal; SD, standard deviation.

The main patients' inclusion criteria for ENGAGE included: patients that did not receive ERT therapy within 9 months and did not receive miglustat within 3 months before randomisation; splenomegaly 6-30 MN; and patients had no indications for splenectomy, thrombocytopenia and/or anaemia. Therefore, the trial population was in line with the licensed indication for eliglustat for use in treatment-naïve GD1 patients.

4.2.4.3 Quality assessment

The CS included a quality assessment of ENGAGE (CS Table 123). This indicated that this was a well conducted trial at low risk of bias. Table 16 presents the ERG's quality assessment for the ENGAGE trial. In this trial, randomisation and concealment of allocation were adequate. Blinding of patients, investigators and outcome assessors was also adequately performed, which minimised the potential bias during the data collection and analysis. There was a low risk of bias in selective reporting. Efficacy outcomes were analysed using an intention-to-treat population. The primary outcome in ENGAGE (a superiority trial) was percentage change in spleen volume from baseline to week 39. This trial was adequately powered to detect a significant difference of this primary outcome between the treatment and placebo groups..

Table 16 ERG's quality assessment for the ENGAGE trial using NICE's template

Quality assessment items	ERG assessment	Evidence to support the assessment
Random sequence generation	Low	Randomised in a 1:1 ratio stratified by spleen volume. Online process was used to generate randomisation procedure. Balance across sites and stratum was ensured.
Allocation concealment	Low	Blinded study medication kits were supplied. All capsules (placebo and active drug) were identical in appearance
Balance of prognostic factors between groups at the outset of the study	Moderate	The placebo group had a higher proportion of male patients and those with Jewish descent. Baseline characteristics in other factors were generally well balanced between treatment arms.
Blinding (participants, investigators and outcomes assessors)	Low	Patients, investigators and sponsor's investigational team were blinded to study treatment until completion of the initial double-blind primary analysis period
Imbalances due to drop-outs between groups	Low	One discontinuation in the eliglustat group (for personal reasons). No dropouts in the placebo arm
Selective reporting	Low	Results for all outcomes presented in the CSRs
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data	Low	All efficacy analyses using an intention-to-treat population were conducted

Low: low risk of bias; moderate: moderate risk of bias

The ERG noted that the placebo group had a higher proportion of patients with Jewish descent than those in the treatment group: 40% in the placebo group versus 15% in the treatment group. Despite this imbalance, our clinical advisor suggests that Jewish patients would not expect to respond to the treatment differently. Therefore, this would have a minimal impact on the treatment response.

There was a general balance in the mean spleen and liver volumes, haemoglobin levels, and platelet counts. Therefore, overall, there was baseline comparability of disease severity between the treatment and placebo groups. There were no unexpected imbalances in drop-outs between the treatment and placebo group in the ENGAGE trial at 39 weeks. One patient had withdrawn from treatment in the treatment group while no patient had withdrawn from treatment in the placebo group.

4.2.4.4 Summary of clinical efficacy results from ENGAGE trial

Efficacy after 39 weeks treatment

The results of the double-blind randomised phase (up to 39 weeks) of the ENGAGE trial are summarised in Table 17.

Table 17 Primary and secondary outcome data randomised phase of ENGAGE trial

Duration	Outcomes	Eliglustat (n=20)	Placebo (n=20)	Treatment difference (95% CI); P value
39 weeks (double-blind phase)	spleen volume Baseline, mean MN (SD)	13.89 (5.93)	12.50 (5.96)	-
	spleen volume Percentage change to Week 39, LS Mean (SEM)	-27.77% (2.37)	2.26% (2.37)	-30.03% (-36.82 to -23.24); P<0.001
	Haemoglobin (g/dL) Baseline, mean (SD)	12.05 (1.82)	12.75 (1.63)	-
	Haemoglobin (g/dL) Absolute change from baseline to Week 39, LS Mean (SEM)	0.69 (0.23)	-0.54 (0.23)	1. 22 (0.57 to 1.88); P=0.0006
	Liver volume (MN) Baseline, mean (SD)	1.44 (0.35)	1.36 (0.28)	-
	Liver volume (MN) % change from baseline to week 39, LS Mean (SEM)	-5.20 (1.64)	1.44 (1.64)	-6.64% ((-11.37 to -1.91); P=0.0072
	Platelet count (10^9/L) Baseline, mean (SD)	75.05 (14.10)	78.48 (22.61)	-
	Platelet count % change from baseline to Week 39, LS Mean (SEM)	32.00 (5.95)	-9.06 (5.95)	41.06% (23.95 to 58.17); P<0.0001
78 weeks (open label phase)	spleen volume Percentage change to Week 78, mean (SD) [95% CI]	-44.6% (10.1) [-49.6, -39.6]	-31.3% (10.1) [-36.0, -26.6]	
	Haemoglobin (g/dL) Change from baseline to Week 78 (SD)	1.02 (0.84)	0.79 (0.82)	

	Liver volume (MN) % change from baseline to Week 78 (SD)	-11.18 (9.35)	-7.31 (9.97)	
	Platelet count (10^9/L) % change from baseline to Week 78 (SD)	58.16 (41.07)	39.82 (37.37)	

The data from the ENGAGE trial demonstrated a significant improvement with eliglustat in adult GD1 treatment-naïve patients for all main efficacy outcomes at 39 weeks. Compared with placebo, eliglustat was associated with a statistically significant decrease in the primary outcome of spleen volume (-30.03%; 95% CI -36.82% to -23.24%). Following the request by ERG, the company presented subgroup analysis based on metaboliser status for the ENGAGE trial. [redacted] However, it should be interpreted with caution as the sizes of these small subgroups were not evenly distributed. For secondary efficacy outcomes, eliglustat also demonstrated statistically significant superior efficacy compared with placebo at 39 weeks: liver volume (-6.64%; 95% -11.37% to -1.91%), haemoglobin level (1. 22 g/dL; 95% CI 0.57 to 1.88), and platelet count (41.06%; 95% CI 23.95% to 58.17%). Moreover, 19 out of 20 patients in the eliglustat treatment group met one (n=8), two (n=9) or three (n=2) of the 1-year therapeutic goals established for Gaucher patients.

The trial reported the results of DS3 at week 39: total score, bone domain, haematological domain and visceral domain. There were small but consistent mean decreases in the total DS3 score (-0.46) and bone domain (-0.23) and visceral domain (-0.24) from baseline to week 39 in the eliglustat treatment group compared with minimal or no changes in these relevant DS3 scores for the placebo group. No change from baseline to week 39 was observed in the haematological domain in either treatment group. It should be noted that none of the mean changes in DS3 scores achieved the minimum clinically significant threshold for improvement (-3.1).[18]

At 39 weeks, eliglustat also demonstrated beneficial effects on a number of bone-related outcomes and this was statistically significant for bone marrow burden (BMB) scores, which decreased significantly with eliglustat therapy compared with placebo: absolute change in spine BMB, femur BMB and total BMB were -0.6 (SEM 0.29) (p=0.002), -0.4 (SEM 0.15) (p=0.026), and -1.1 (SEM) 0.33); p=0.002) respectively. The CS reported that five patients in the eliglustat arm had a clinically significant reduction in total BMB score with at least a 2-point reduction. (CS Table 18).

Eliglustat showed positive effects on health-related quality of life measure. Eliglustat was associated with a significant improvement in disease-specific quality of life outcome (fatigue severity score 0.7; 95% CI 0.02 to 1.33) compared with placebo at week 39. However, there was no statistically significant difference in brief pain inventory (BPI)(average pain) (-0.2; 95% CI -0.81 to 0.36) between the treatment and placebo groups. In terms of the SF-36 measures, no statistically significant differences between the two groups were observed for general health score (-2.4; 95% CI -9.84 to 4.94), physical component score (3.3; 95% CI -0.67 to 7.29) and mental component score (-2.2; 95% CI -7.01 to 2.59) at week 39.

A statistically significant reduction was observed for eliglustat in chitotriosidase (-39.0%; 95% CI -53.0% to -25.0%; p<0.001 vs. placebo), plasma glucosylceramide for eliglustat at week 39 (-71.7%; 95% CI -79.5% to -64.0%; p<0.001 vs. placebo, plasma GM3 ganglioside for eliglustat at week 39 (-54.0%; 95% CI -64.4% to -43.7%; p<0.001 vs. placebo plasma macrophage inflammatory protein for eliglustat at week 39 (-51.6%; 95% CI -60.3% to -42.9%; p<0.001 vs. placebo, and a statistically significant increase in plasma sphingomyelin for eliglustat was also observed (21%; 95% CI 12.5% to 29.4%; p<0.001 vs. placebo),

However, there was no statistically significant difference in the biomarker level of plasma ceramide (-4.7%; 95% CI -16.9% to 7.5%; p=0.86 vs. placebo) between the eliglustat and placebo groups at week 39. This biomarker is an indicator of a potentially undesirable effect of inhibition of glucosylceramide synthesis (i.e. accumulation of the substrate precursor for glucosylceramide synthesis or other glycosphingolipids synthesised from this substrate).

Long-term follow-up (uncontrolled open label phase up to 78 weeks treatment)

As stated earlier, the ENGAGE trial maintained randomisation for 39 weeks followed by an open-label extension during which all patients received eliglustat.

As seen in Table 17, by week 78 patients who commenced eliglustat at week 39 showed a similar response to that achieved at week 39 by those randomised to eliglustat at week 0. For those patients who received 78 weeks of eliglustat the results for all primary and secondary efficacy measures at week 78 extension demonstrated a maintenance and possibly an improvement on those observed at the 39 week follow-up. There were no drop outs and therefore the results strongly suggest that the benefits of eliglustat were at least maintained up to 78 weeks of treatment. The results for DS3 scores, biomarker measures and health-related quality of life outcomes at 78 weeks were not reported. The ERG did not find any explanation in the CS why this was unreported.

There was an indication of continued small improvements in absolute changes of lumber spine BMD, total spine T-score and total spine Z-score at follow-up of 78 weeks. However, this trend was not seen

for the other bone outcomes. The duration of follow-up may be too short to properly evaluate the impact of eliglustat on bone.

4.2.4.5 Summary of critique of ENGAGE

ENGAGE was a well conducted placebo-controlled RCT in patients not being treated with ERT. However the sample size was small (40 patients), the primary outcome was only spleen volume, other clinically important outcomes (haemoglobin, platelet and liver) were secondary outcomes. The randomised phase was only 39 weeks which the ERG consider to be too short a time period to measure improvements in GD1 patients.

At 39 weeks, eliglustat was associated with a statistically significant mean difference of -30.03%. Eliglustat was also associated with statistically significant beneficial effects on liver volume, haemoglobin level (1.22 g/dL; 95% CI 0.57 to 1.88) and platelet. The effect sizes of point estimates for spleen and liver volumes were moderate to large with -27.77% and -5.20 MN respectively, implying that these treatment effects could be clinically significant. Nineteen out of the 20 patients in the eliglustat treatment group met at least one of the 1-year therapeutic goals established for Gaucher patients (9 met 2 goals, and 2 met 3 goals). Small improvements were also seen in DS3 scores, bone-related outcomes and some health-related quality of life measures, though most were not statistically significant.

The open-label extension data indicated that the beneficial effects on organ volumes, haemoglobin level and platelet count were sustained at 78 weeks, with continued small improvements in some though not all bone parameters; the trial reported that there were no drop outs.

4.2.5 Critique of the Non-Randomised Phase II trial

4.2.5.1 Study design

The study design of the Phase II, single arm, eliglustat trial is provided in Table 18 (adapted from CS Table 12).

Table 18: Study design of Phase II trial

Study details	Description
Location	7 sites in 5 countries (Russia, Argentina, the United States, Israel and Mexico)
Design	A Phase II, open-label, non-randomised single-arm trial
Duration of study	52-week primary analysis period, and additional 3-year extension period
Intervention	Eliglustat supplied as 50mg and 100mg hard capsules. Eliglustat was administered at 50mg twice daily from Day 1 to Day 20 after which the dose could be increased to 100 mg if plasma levels were <5ng/ml.

Primary outcomes	• A composite endpoint requiring improvement from baseline to Week 52 in at least 2 of the 3 main efficacy parameters: - Spleen volume - Haemoglobin level - Platelet count
Secondary outcomes	• Changes over time in the main efficacy parameters (Hb, platelets, spleen) • Liver volume in MN • Disease-related plasma biomarkers - Chitotriosidase - CCL18 - Angiotensin-converting enzyme - Tartrate-resistant acid phosphatase • Exploratory biomarkers - Plasma glucosylceramide - Ganglioside GM3 • Bone-related outcomes - Bone pain - Bone crises - Mobility - Skeletal changes - Bone mineral density • HRQL - SF-36 - Fatigue Severity Scale • Safety outcomes • Pharmacokinetic outcomes

The phase II, single-arm, open-label trial was conducted at 7 sites across five countries Russia, Argentina, the United States, Israel and Mexico. A 52-week primary analysis period, with an additional 3-year extension period (total duration 4 years) was planned. Eliglustat was administered to patients with confirmed GD1. The dose of eliglustat was 50 mg twice daily with an increase to 100mg twice daily permitted at day 20 for patients whose plasma concentration was <5ng/ml. The ERG notes that a starting dose of 50 mg twice daily is below the licenced dose of eliglustat: 100 mg once daily is licenced for poor metabolisers only. However, the dose adjustment used in both phases of the trial was generally in accordance with the SPC for eliglustat.

The primary outcome measure of efficacy in the trial was a composite outcome requiring improvements from baseline to week 52 in at least two of the three main efficacy parameters (spleen volume, haemoglobin level and platelet count). There was also a range of secondary outcomes. They include changes of the main parameters over time, liver volume, biomarkers, bone related outcomes, HRQL and safety outcomes.

The ITT population was used for analyses of the primary outcome. The statistical analysis plan was not reported in the CSR; the ERG requested this from the company which they were unable to provide. Therefore certain trial details on the parameters analysed, as well as a description of the primary and secondary analyses, handling drop-outs or missing data and analytical methods was not clear in the CS. A subgroup analysis was not performed in this trial.

Patients with a diagnosis of GD1 and documented deficiency of acid β-glucosidase activity were included in the trial. Patients with partial or total splenectomy were excluded. Further inclusion and exclusion criteria are given the Table 12 of the CS. The ERG noticed that there did not appear to be an age restriction in this trial. Also, unusually, patients with a negative pregnancy test were not a pre-specified inclusion criterion: pregnant patients were excluded from all the other trials, and the SPC clearly states that these patients should not be included. In general the inclusion criteria appeared to be less restrictive than ENCORE and ENGAGE.

4.2.5.2 Patient characteristics

The characteristics of the 26 patients in the trial are summarised in Table 19. Thirty eight percent of the patients were male, with a total of 7% of the total population relating to the Ashkenazi Jew ethnic group. The average age of the 26 patients was 34 years, which was very similar to the other three trials.

Table 19: Patient characteristics of Phase II trial

Characteristic	**Population (n=26)**
Male %	38%
Ashkenazi Jew %	27%
Mean age years (SD)	34 (13)
Primary outcomes:	
Haemoglobin level, g/dL, mean (SD) (normal values: >12g/dL for males, >11g/dL for females)	11.1 (1.7)
Platelet count, n/mm^3, mean (SD) (normal: >120,000/mm^3)	66,442 (20,118)
Spleen volume, MN, mean (SD) (normal size: ≤5MN)	20.0 (12.8)
Secondary outcomes:	
Liver volume, MN, mean (SD) (normal size: ≤2.5MN)	1.8 (0.6)
Chitotriosidase, nmol/h per mL (n=24), mean (SD) (normal: <15 to 181 nmol/h per mL)	9,168 (5,395)
MN, multiples of normal	

4.2.5.3 Quality Assessment

A quality assessment was carried out using the Downs and Blacks checklist for non-randomised trials. The checklist produced by the company includes 24 of the 29 original items that were possible to assess (See CS, Table 125). The ERG performed their own assessment on these 24 items using the Downs and Blacks and identified only four discrepancies as indicated in Table 20.

Table 20: Study quality assessment for Phase II trial using Downs and Black criteria

Description of criteria	CS assessment	ERGs assessment	ERGs Comment
Have the characteristics of patients lost to follow-up been described?	Yes	No	Patients lost to follow-up were not reported in the CSR
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Unclear	No	30 day follow-up period following completion or patient withdrawal
Were losses of patients to follow-up taken into account?	Yes	No	Not clearly reported in the CSR
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance?	Yes	No	CSR reports that the trial was too small and that the lack of a control comparator (single-arm) limits the power

The characteristics of patients lost at follow-up were not clearly reported in the CS, CSR or journal publication. There were no adjustments for variable follow-up time lengths for patients, this was just specified as 30-days or when patients withdrew. Losses of patients due to follow-up were not reported in the CSR. Most importantly the ERG discovered from the CSR that the trial did not have sufficient power due to the limited sample size, the reasons for this were not explained in the CS.

4.2.5.4 Summary of efficacy results from Phase II trial

The clinical effectiveness results of the Phase II trial are provided in Table 21. Of the 26 patients who entered the trial, 22 completed the primary 52 week period and 20 patients completed year 2 and 19 completed Year 4 (The full CONSORT diagram is given in the CS Figure 13). Year 3 results were not included in the submission but provided on request to the ERG.

Table 21: Overview of clinical effectiveness results in Phase II trial (based on CS Table 19 which gives full details)

Primary outcome		**Eliglustat (n=26)**
Improvement to Year 1, %, [95% CI]	ITT patients (n=26)	77 [58 – 89] %
	Completer patients (n=22)	91 [72 - 98] %
Improvement to Year 2, %	patients (n=20)	85%
Secondary outcome – changes over time in the main efficacy parameters		
Change in haemoglobin levels (g/dL)	Year 1 (n=26)	+1.62 (p<0.001)
	Year 2 (n=20)	+2.1
	Year 3 (n=18)	+2.5 (p<0.0001)
	Year 4 (n=19)	+2.3 (p<0.0001)
Percentage change in platelet count (n/mm^3)	Year 1 (n=26)	+40.3 (p<0.001)
	Year 2 (n=20)	+81
	Year 3 (n=18)	+41.0 (p<0.0001)
	Year 4 (n=19)	+95 (p<0.0003)
Percentage change in spleen volume (MN)	Year 1 (n=26)	-38.5 (p<0.001)
	Year 2 (n=20)	-52
	Year 3 (n=19)	-59.6% (p<0.0001)
	Year 4 (n=19)	-63 (p<0.0001)
Percentage change in liver volume (MN)	Year 1 (n=26)	-17.0 (p<0.001)
	Year 2 (n=20)	-24
	Year 3 (n=19)	-21% (p<0.0001)
	Year 4 (n=19)	-28 (p<0.0001)
Secondary outcome – changes in bone-related outcomes		
	Bone Mineral Density, mean (SD)	
Lumbar spine (n=19)		
Z-score	Year 1	0.31 (0.46), P=0.01
	Year 2	0.6 (0.7), p=0.003
	Year 3	-35.2 (p=0.0038)
	Year 4	
T-score	Year 1	0.33 (0.50), P=0.01
	Year 2	0.6 (0.8), p=0.012 7.8% change from baseline
	Year 3	
	Year 4	0.8, p=0.014 9.9% change from baseline

At year 1, 77% of the 26 patients achieved the primary outcome (a composite outcome requiring improvements from baseline to week 52 in at least two of the three main efficacy parameters (spleen volume, haemoglobin level and platelet count)). At year 2, the figure was 85% for 20 patients. The results for the primary outcome were not reported for year 4. The CS stated that at 4 years all 19 patients included at this point met their therapeutic goals for spleen volume and haemoglobin level, 94% met the goal for liver volume and 47% met the goal for platelet count.

The changes over time in the main efficacy parameters haemoglobin, platelet count, spleen volume and liver volume all showed an improvement at years 1, 2 and 4 with an indication for greater improvement with longer follow-up (though this was not tested formally). It should be noted that patient's measurements were missing for 6 patients at year 2 and for seven at year 4, and this was not explained. Thus the apparent mean improvement over time may merely reflect patient selection.

For changes in bone related outcomes, lumber spline data were collected from 19 patients. The lumber spine Z-score showed a statistically significant change at 2 years and 3 years follow up with p=0.003, however the 4 year follow up was not reported. The T-score showed a statistically significant change at the 3 year and 4 year follow-up, with 31% and 9.9% change from baseline respectively (p=0.0285 and p=0.014). Femur Z-score and T-score were followed up at years 1, 3 and 3, and there were very small changes from baseline -0.1 and 0 respectively. The outcomes bone crisis, bone lesions and bone infarctions showed no change from baseline (Table 19 in CS).

[redacted]

Year 3 data provided in the Company's response to the ERG reported a median DS3 of 5 (range 1.4, 8.6) with a median reduction of 1.5 at 3 years (range -5.0 to 2.0).

Patient HRQL outcomes in Phase II

HRQL data was collected in the Phase II trial using version 2 of the SF-36 instrument. These results were reported in the CSR and not the CS.

[redacted]

4.2.5.5 Summary of critique of the Phase II trial

The Phase II trial was single-arm phase II study including 26 patients who were not being treated with ERT. The trial provides supporting data for one, two and 4 years of treatment with eliglustat, although not all patients remained in the analysis beyond one year and, not all outcomes were reported at 4 years. At year 1, 77% of the 26 patients achieved a composite outcome requiring improvements from baseline in at least two of spleen volume, haemoglobin level and platelet count. At year 2, this was 85% of 20 patients remaining in the analysis. At 4 years all 19 patients included at this point met their therapeutic goals for spleen volume and haemoglobin level, 94% met the goal for liver volume and 47% met the goal for platelet count. Bone parameter and HRQL data suggested some small improvements by 2 years, but were not reported at 4 years. Due to the lack of control group in this

study, the small sample size and the unexplained loss of patients from the later time points; the treatment effects observed over the four year follow-up are uncertain.

4.2.4 Critique of the EDGE trial (comparison of once versus twice-daily dosing with eliglustat)

4.2.5.6 Study design (Details summarised in CS Table 11)

The EDGE trial is a multicentre, randomised, double-blind study to evaluate maintenance of therapeutic goals with once-daily versus twice-daily dosing of eliglustat. The trial started with a lead-in period of up to 18 months during which patients received eliglustat 50mg or 100mg twice daily for at least four months until therapeutic goals were achieved. The patients entering the lead-in period were patients with confirmed GD1 (documented deficiency of acid Beta-glucosidase activity by enzyme assay), both treatment naïve and treatment experienced. Full inclusion and exclusion criteria are given in the CS Table 11. Patients who, during the lead-in period, demonstrated clinical efficacy stability through achievement of all five pre-specified therapeutic goals and a peak (two-hour) plasma eliglustat level of <50 ng/ml would then be randomised to eliglustat 100 or 200mg once daily versus eliglustat 50 or 100mg twice daily.

The submission presented the interim analysis for the lead-in period only.

The primary composite outcome of the lead-in period was the proportion of patients who maintained or achieved therapeutic goals. The composite endpoint was based on five measures relating to bone crisis, haemoglobin level, platelet counts, and spleen and liver volumes for the lead-in period (see results below for details).

4.2.5.7 Patient characteristics

The characteristics of the 170 patients included in the lead-in period are given in CS Table 15.

At the time of the CS 131 patients had completed the lead-in period, 12 had withdrawn, and 27 patients were ongoing (CS figure 12).The results presented included all patients including the 27 patients ongoing in the lead in period.

4.2.5.8 Results for lead in period

The proportions of patients achieving individual therapeutic goals were:

- ≤1 bone crisis and no symptomatic bone disease during previous 6 months of the lead-in period – 100%
- Haemoglobin ≥11 g/dL for females and ≥12 g/dL for males – 94%;
- Platelet count ≥100,000/mm3 - 94%;

- Spleen volume ≤10 MN (if applicable) – 99%;
- Liver volume ≤1.5 MN – 95%

A total of 137 (83%) patients achieved all five therapeutic goals during the lead-in period. The mean haemoglobin levels of patients remained stable or showed minimal, transient changes around baseline levels. The mean platelet counts and spleen volume of patients remained within ±20% of baseline levels. The mean liver volume of patients remained within approximately ±5% of baseline values.

The company provided a summary of baseline characteristics for the randomised part of the study on the per protocol population and the intent-to-treat population (see Table 1 and Table 2 in company's response to ERG's clarification questions). Baseline demographic characteristics of patients between the two treatment arms were generally well balanced. However, the company did not provide baseline characteristics of disease severity relating to spleen and liver volumes, haemoglobin levels, and platelet counts. Therefore, it was unclear whether there was a general balance in disease severity at baseline between the two treatment arms.

The company did not present the analysis of the 12-month, double-blind randomised part of the study in the submission as it had not been completed. In their response to a request from the ERG the company confirmed that the CSR for the EDGE study is not yet finalised.

Overall, the data from the lead-in period from this trial provide supporting evidence for the efficacy of eliglustat in GD1.

4.3 Generalisability of the study populations presented in the CS

In addition to the clinical trials, the CS presented data from some 'real-life' cohorts. The CS made comparisons with these types of data in order to examine the generalisability of the trial data.

Across all the sources of data presented the proportion of males and age at which patients presented with GD1 have been summarised by the ERG (Table 22).

Table 22 Comparison of basic demographic details across all sources of evidence presented in the CS (ERG constructed)

Study	Treatment status	N	Age	% Male
ENCORE	ERT stable	159 (randomised)	Mean 37.6	45%
ENGAGE	Treatment naive	40 (randomised)	Mean 32	50%
Phase II	No ERT for 12 months prior to study	26	Mean 34	38%
Edge (lead in Phase)	Mixed patient group	170	Median 33.5	52%
Royal Free Hospital Cohort	1st presentation at Royal free clinic (mixed patient group)	86	Median 26	57%
Wyatt study	Mixed patient group	150	Mean 46.4	
Gaucher international registry	Patients treated with ERT	757	Unknown	45%

The submission presented a comparison of baseline characteristics of treatment-naïve patients between the ENGAGE trial and those patients at diagnosis of GD1 at the Royal Free Hospital, London (n=45). As seen in Table 23, there was a substantially higher rate of patients who experienced bone pain in the ENGAGE trial than those in the Royal Free Hospital (67% vs. 36%). A higher rate of hepatomegaly was also seen in the ENGAGE trial: 63% with moderate or severe disease vs. 44% (without indication of disease severity in the data from the Royal Free Hospital). Thus, the trial participants in the ENGAGE trial were likely to have more severe disease of GD1 compared to patients at first diagnosis. The clinical advisor to the ERG confirmed that in England there is unlikely to be a delay between diagnosis and the start of ERT therapy. Therefore the patients in the ENGAGE trial are not exactly generalisable to clinical practice in England and it remains unclear that the beneficial effects observed in the ENGAGE trial participants would be reflected in routine clinical practice.

Table 23 Patient characteristics in ENGAGE compared with Royal Free Hospital newly diagnosed cohort (adapted from CS Table 30)

	Royal Free Hospital London – Cohort at time of diagnosis	ENGAGE
Number of patients	45	40
Splenomegaly	87%	100%
Hepatomegaly	44%	63% moderate or severe
Bone pain	36%	67%
Avascular necrosis	11%	Not reported (note: prior bone crisis was an exclusion criterion, and only 1 patient had severe bone disease)

Anaemia	20% had anaemia as an indication for ERT	20%
Thrombocytopenia	82%	100%
Skeletal disease	75% severe enough to be an indication for ERT	53%
ERT, Enzyme replacement therapy.		

The ERG identified relevant data from the International Collaborative Gaucher Group (ICGG) Gaucher patient registry.[27] This publication reported summary patient characteristics at the start of ERT therapy and after 10 years' therapy. The former data are summarised by the ERG in Table 24 below (the latter were included in the CS to support the generalisability of the ENCORE trial and are discussed later in this section). The comparison suggests that patients in the ENGAGE trial are approximately similar to pre-ERT, non-splenectomised patients from the registry as are the cohort in the supportive Phase II trial.

Table 24 Patient characteristics in ENGAGE, the Phase II trial and the ICGG Gaucher Registry[27] and study of DS3[18]

	Eliglustat (ENGAGE)	Placebo (ENGAGE)	Eliglustat (Phase II)	Weinreb 2013[27] Non-splenectomised patients only)
Number of patients	20	20	26	557
Spleen volume, MN, mean	13.9	12.5	20	(n=107) 19.4
Liver volume, MN, mean	1.4	1.4	1.8	(n= 105) 1.8
Haemoglobin levels, g/dL, mean	12.1	12.8	11.1	(n= 376) 11.2
Platelet count, 10^9/L, mean	75	79	Reported on different scale	(n= 379) 95

A published UK cohort of adult patients with GDI, 87% of whom were receiving ERT, was identified in the CS.[28] The reported information (Table 25(Table 31 in the submission) suggest that the ENCORE patients are similar. However, details of clinical parameters of disease severity in were not reported. Thus, the CS compared the baseline characteristics of patients in ENCORE with those in the ICGG Gaucher registry who had been on ERT (imiglucerase only) for 10 years (Table 25 (adapted from CS Tables 31 and 32)). The data show that for most characteristics the populations were not very different. The CS states that lower mean spleen volume in the ENCORE study can be explained by the inclusion criterion for that trial that excluded patients with spleen volume greater than 9. This indicates that the ENCORE trial patients do not encompass the most severely affected ERT stable patients that might be treated with eliglustat in routine practice.

Table 25 Patient characteristics in ENCORE, a UK observational study, and the ICCG Goucher registry

	Eliglustat (ENCORE)	Imiglucerase (ENCORE)	UK observational study [28]	Weinreb 2013 [27]
Number of patients	99	47	150	757
Age, mean years	37.2	38.6	46.4	
Male %	43%	21%	43%	
Splenectomised %	29%	19%	32%	26%
Age at Gaucher disease diagnosis, years, mean	17.1	20.8	24.8	
Years on imiglucerase, mean	9.8	10.2	10.8	
Spleen volume, MN, mean	3.2	2.6	NR	5.2
Liver volume, MN, mean	0.9	0.9	NR	1.0 (both non-splenectomised and splenectomised)
Haemoglobin levels, g/dL, mean	13.6	13.8	NR	13.6 (non-splenectomised) and 13.4 (splenectomised)
Platelet count, 109/L, mean	206.8	192.3	NR	167 (non-splenectomised) and 311 (splenectomised)

The ERG notes that because the ICG Gaucher registry is international, it may not be fully representative of those ERT treatment-stable patients in England. The ERG also notes the lack of information regarding bone manifestations in the non-trials data, precluding any comparison on this parameter.

Patients recruited into the ENCORE trial had to be stable on ERT at a total monthly dose between 30 U/kg and 130 U/kg. At the start of the trial on average, study participants had been on ERT for about 10 years, with nearly 60% receiving doses of at least 35 U/kg every two weeks. Details of the most common upper limit were not reported. As will be discussed in Section 4.6 later , the dose of ERT used in clinical practice, especially once patients are stable varies between patients but are generally lower than the 60 U/kg recommended by the product licence. The SOP for Gaucher disease recommends that 15 to 30 U/kg every two weeks is appropriate for most patients, and this is reflected in the clinical expert advice given to the ERG, though practitioner submissions to NICE suggest 20-40 U/kg. This would suggest that the patients in the ENCORE trial may have been on higher than the typical doses used in UK practice. The implications of this for the generalisability of the results of the ENCORE trial are unclear: patients in the trial may be somewhat over-treated with ERT or maybe a less responsive cohort than seen in practice, and hence in clinical practice eliglustat would look relatively more effective.

The patient characteristics for the trials in the CS reported summary baseline DS3 scores did not include the DS3 categorisation; this has been added by the ERG based on the mean score (Table 26).

Table 26 DS3 Scores in ENCORE, Engage, and IICG registry data

	ENCORE	IICG registry based study Weinreb 2015[18]	ENGAGE	IICG registry based study Weinreb 2015[18]
DS3 score*		5 years ERT scores (n=133)		Baseline scores
Total	2.2	3.1	4.5	5.6 (2.6)
Category	Mild		Moderate	Moderate

Approximate average for whole trial population

Overall, as far as can be determined from limited data sets, the generalisability of findings from the two main Phase III trials (ENGAGE and ENCORE) to routine practice in England is adequate. There is nothing to suggest that the beneficial effects observed in these trials would not be reflected in practice except for a lack of information on the treatment of ERT stable patients with very large spleens and some question over the ERT dosing.

4.4 Critique of indirect comparison and/or multiple treatment comparison

In the absence of head-to-head trials of the three therapies, the relative efficacy evidence for each therapy was investigated in the CS by means of an indirect treatment comparison analysis. The indirect treatment comparison analyses used RCTs: one trial comparing eliglustat with imiglucerase (ENCORE) and one trial comparing imiglucerase with velaglucerase (Ben-Turkia 2013) [29].

The outcomes synthesised were mean differences in haemoglobin level, platelet count, spleen volume and liver volume using the available endpoint at 6-month follow-up for all these efficacy outcomes and at 9-month follow-up for two outcomes of haemoglobin level and platelet count.

The key difference in population characteristics between the two trials was that the ENCORE trial recruited ERT-stable patients while Ben-Turkia (2013) recruited ERT-naïve patients, making disease severity at baseline not comparable between these two trials.

Whilst the ERG notes that in theory a Bayesian indirect comparison analysis incorporating the available data of direct and indirect evidence is a useful approach to estimate the relative efficacy between alternative treatments that have not been compared directly in RCTs but where separate trials have used a common comparator. In the present case both eliglustat and velaglucerase have been compared in the included trials with imiglucerase, allowing the network between eliglustat and velaglucerase to be established. However, it is important to note that the validity of the indirect treatment comparison of meta-analysis is built on the assumption that no important differences exist between trials in terms of baseline characteristics such as disease severity.[30] This assumption is

essential to ensure the results of indirect comparisons are valid. Given the significant heterogeneity of population characteristics at baseline between the included trials, i.e. ENCORE in ERT stable patients and Ben Turkia in treatment naive patients, the ERG considered the exchangeability of outcomes across the included trials in the indirect comparison analysis to be unacceptable. The complete lack of validity of this indirect comparison was recognised by the company in the CS.

Given the limitations mentioned above, it was not possible to use a network meta-analysis to determine the relative effectiveness of eliglustat and velaglucerase.

For the current appraisal it is important to understand the relative effectiveness of imiglucerase and veleglucerase. Generally, imiglucerase and velaglucerase are presently considered equivalent in clinical efficacy; this is the position currently adopted by the SOP for treating adult Gaucher disease in England.[12]

In the CS the direct clinical evidence of comparing velaglucerase with imiglucerase was derived from Ben Turkia trial 2013.[29] This trial was a nine-month, global, double-blind, non-inferiority study comparing velaglucerase alfa with imiglucerase in 35 treatment-naıve patients. The primary efficacy outcome was the difference in the mean change from, baseline to month 9 in hemoglobin concentration between the two groups, where velaglucerase was considered non-inferior to imiglucerase if the lower bound of the 95% CI exceeded the pre-specified non-inferiority margin of -1 g/dl. This non-inferiority assessment differs from the ENCORE trial as only one primary outcome was considered and not a composite endpoint consisting of four parameters.

The trial reports that after 9 months the mean treatment difference for velaglucerase alfa against imiglucerase was 0.14 g/dL and 0.16 g/dL in the intention to treat and per-protocol populations, respectively. Each population statistic estimates a lower bound of the 97.5% one-sided CI of -0.6 g/dL, which was within the pre-defined non-inferiority margin of -1.0 g/dL. The trial therefore indicates that velaglucerase alfa was non-inferior to imiglucerase with or without adjustments for baseline hemoglobin concentration. No statistically significant differences were observed in the secondary endpoints (including platelet counts, spleen volume and liver volume). As was seen in the ENCORE trial, the clinical justifications made regarding the non-inferiority margin were not explained.

The CS included a quality of assessment of the Ben Turkia trial (CS Table 124). Table 27 presents the ERG's quality assessment for the Ben Turkia trial, which due to limited reporting rates the trial as being of unclear risk of bias. This non-inferiority trial was powered to at least 80% using a 0.025 significance level (one sided test). Although the primary efficacy analysis for this trial was conducted

using ITT, the per-protocol population analysis, which is more robust in non-inferiority trials, gave the same result.

Table 27: ERG's quality assessment for the Ben Turkia 2013 trial using NICE's template

Quality assessment items	ERG assessment	Evidence to support the assessment
Random sequence generation	Unclear	Details on the randomisation method was not reported
Allocation concealment	Low	This trial was a double blind trial. Patients were randomised 1:1 to receive imiglucerase or velaglucerase drug as a continuous 60-min intravenous infusion every other week
Balance of prognostic factors between groups at the outset of the study	Low	Patients' characteristics at baseline were generally well balanced between the two groups, but the paediatric population in the imiglucerase arm was skewed toward very young children (<5 years old). There was also a difference in median haemoglobin level between the imiglucerase and velaglucerase groups at baseline (10.6 g/dL vs. 11.4 g/dL, with a difference of 0.8 g/dL). However, this difference was not clinically relevant in terms of potential response to treatment.
Blinding (participants, investigators and outcomes assessors)	Unclear	The study is reported as a double-blind trial. However, the trial did not report detailed information on blinding. It was unclear whether blinding of outcome assessor was used.
Imbalances due to drop-outs between groups	Low	Overall discontinuations were comparable between groups
Selective reporting	Low	Results for all outcomes presented.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data	Low	The primary efficacy analysis for this trial was conducted using the per-protocol population, which is common in non-inferiority trials. The efficacy analysis using the intention to treat population was also performed and the results were similar.

Low: low risk of bias

The ERG identified a descriptive analysis on the treatment effects of switching from imiglucerase to velaglucerase in patients with GD1.[31] Thirty-two patients, who had previously had their dose of imiglucerase reduced due to the worldwide imiglucerase shortage (1 to 8.5 months of dose reduction), switched to treatment with velaglucerase alfa after imiglucerase. Patients started velaglucerase essentially at dosages equal to their original imiglucerase dose, with the exception of one patient in whom the dose was doubled. The outcomes of interest in GD1 patients that were assessed in the study include; hemoglobin concentration, platelet count, plasma chitotriosidase activity in all patients, and spleen and liver volumes in ten patients.

The study results showed that switching to velglucerase at a dose that is equivalent to imiglucerase dose before the shortage, is effective in most adult patients with GD1. Reductions in platelet count were generally quickly restored and five out of ten patients had an increase in liver volume of at least 10% after receiving velaglucerase treatment for six months. In summary, the trial concludes that veleglucerase appears to be as safe and effective as imuglucerase based on the non-inferior result, and that the cost-effectiveness ratio may become the only factor in the choice of treatment which will be explored further in the cost effectiveness section.

4.5 Adverse effects

The data on adverse events presented in the CS were derived from three Phase III trials (ENCORE, ENGAGE and EDGE) and the long-term Phase II trial. In particular, the ENCORE trial was a large-scale trial with 160 patients randomised over a relatively long period of 52 weeks, then followed by an extension period of a minimum of a further 52 weeks. It also provides a comparison of the adverse effects patients experience when switching from ERT to eliglustat with those of remaining on imiglucerase (or velaglucease).

In the three trials (ENCORE, ENGAGE and EDGE) and the long-term Phase II trial, safety was specified as a secondary outcome. In each of the four trials the MedDRA coding dictionary for AEs was used, however the version of the dictionary was not specified, which could lead to heterogeneity in coding when pooling the safety data.

The pooled safety data were presented in the CS and these are outlined below

4.5.1 Descriptive pooled analysis of adverse effect data

A descriptive pooled safety analysis was presented in the CS, where the AEs data from ENCORE, ENGAGE, EDGE and the phase II trial have been grouped together. As the trial populations and designs were regarded too heterogeneous, a pooled meta-analysis was not possible. However the ERG has assessed the risk differences for the AEs reported in the placebo-controlled trial ENGAGE, where only two AEs (Arthralgia at 32 weeks and Nasopharyngitis at 109 weeks) were found to be statistically significant. A sensitivity analysis was performed on these events and they were classified as mild and not treatment related (Table 28).

Table 28: Risk differences for adverse events in ENGAGE trial

MedDRA terms	39 Weeks		109 weeks	
System Organ classification Preferred term	RD	95% CI	RD	95% CI
Infections and infestations	0	(-0.3083; 0.3083)	0	(-0.3083; 0.3083)
Nasopharyngitis	0.15	(-0.0222; 0.3222)	0.2	(0.0128; 0.3872)
Musculoskeletal and connective tissue disorders	0.15	(-0.1464; 0.4464)	0.15	(-0.1528; 0.4528)
Arthralgia	0.35	(0.0954; 0.6046)	0.25	(-0.0298; 0.5298)

In total across all four of these trials there were 393 patients with GD1 who received eliglustat, the vast majority for over 6 months 349 (%), but only 19 (%) for 4 years or more (Table 29). Table 17 displays the pooled results for the AEs and SAEs with a breakdown for the severity grading and treatment relatedness. Of the 334 AEs reported across all four trials, the majority were mild or moderate with only 11% classified as severe. In total 40% of the reported AEs were treatment related, and 12 patients (3%) experienced AEs leading to study drug discontinuation, with 10 of the AEs

considered possibly or probably related to eliglustat. These include ventricular tachycardia; lethargy and exfoliative rash in the same patient; upper abdominal pain; palpitations; and nausea, headache, and anaemia in the same patient.

Table 29: Summary of adverse effects data in eliglustat trials

Safety category	All n (%)
Treated patients	393
Any AE	334 (85)
Mild AEs	308 (78)
Moderate AEs	171 (44)
Severe AEs	45 (11)
Treatment-Related AEs	159 (40)
Discontinuations due to AEs	12 (3)
SAEs	35 (9)
Mild SAEs	6 (2)
Moderate SAEs	11 (3)
Severe SAEs	19 (5)
Treatment related SAEs	5 (1)
Deaths*	0 (0)
Discontinuations due to SAEs	4 (0)
Estimate eliglustat exposure	Number of patients
< 6 months	44
≥ 6 months	349
≥ 1 years	204
≥ 2 years	62
≥ 4 years	19

A total of 35 patients (9%) experienced 42 SAEs, most of which were due to hospitalisations for inter-current illnesses (e.g. appendicitis) and underlying diseases for which GD patients are at increased risk (e.g. femur fracture, joint dislocation, hepatocellular carcinoma, and cholecystitis). The most frequently reported SAE was syncope, reported in five patients. These syncopal SAEs were severe in four patients, and were considered at least possibly related to eliglustat in three patients. Other SAEs occurring in more than one patient included myocardial infarction in four patients. In each case, the investigator assessed these events as not related or as remote/unlikely related to eliglustat. No deaths were reported across the four trials. The majority of patients were exposed to eliglustat use between the time periods of 6 months and less than two years.

The most common AEs occurring in ≥5% of patients across the four trials are presented in Table 30.

Table 30: Most common TEAEs occurring in ≥ 5% of patients

MedDRA SOC Preferred term	Patients (n=393) %
Patients with events	85%
Infections & Infestations	47%
Nasopharyngitis	13%
Upper respiratory tract infection	11%
Influenza	6%
Sinusitis	6%
Urinary tract infection	6%
Gastrointestinal disorders	41%
Diarrhoea	10%
Abdominal pain upper	8%
Nausea	8%
Dyspepsia	7%
Abdominal pain	6%
Constipation	6%
Gastroesophageal reflux disease	5%
Nervous system disorders	32%
Headache	17%
Dizziness	10%
Musculoskeletal and connective tissue disorders	32%
Arthralgia	14%
Back pain	9%
Pain in extremity	8%
Bone pain	5%
General disorders and administration site conditions	22%
Fatigue	7%
Respiratory, thoracic and mediastinal disorders	21%
Cough	6%
Investigations	19%
Blood creatine phosphokinase increased	5%
Skin and subcutaneous tissue disorders	16%
Injury, poisoning, and procedural complications	15%
Cardiac disorders	10%
Palpitations	5%
Reproductive system and breast disorders	8%
Blood and lymphatic system disorders	6%
Psychiatric disorders	6%
Vascular disorders	5%
Renal and urinary disorders	5%

4.5.2 Adverse events from ENCORE (eliglustat compared with imiglucerase) (CS Table 20)

In the ENCORE trial TEAEs were only reported for those occurring in ≥10% of patients. Up to week 52 a TEAE was experienced by 92% of patients on eliglustat and 79% on imiglucerase. Serious adverse event was reported in 10% on eliglustat compared to no patients on imiglucerse and 12% eliglustat patients and 8% of imiglucerase patients experienced severe TEAEs. Adverse events leading to discontinuation were rare in both treatment groups (2%).

By 104 weeks 5 patients had discontinued eliglustat dues to AEs. Specifically, in the eliglustat group at week 108, 21 patients experienced 18 serious adverse events (SAEs). As these events were not

reported in the CS, the ERG requested further detail from the company. The company stated that thirteen of the SAEs were graded as severe events with three possibly related to eliglustat (Table 31). These preferred term AEs include hepatic neoplasm malignant, neuropathy peripheral and intestinal obstruction where they received eliglustat doses of 50 mg, 150mg and 150 mg respectively. There were no deaths in either treatment arm during the whole study.

Table 31: Summary of patients with treatment-emergent SAEs in ENCORE

Patient number	System Organ Class (S) Preferred term (P)	Severity	Relation to study drug/G. disease	Eliglustat dose
9	S: Neoplasm benign, malignant and unspecified (including cysts and polyps) P: Hepatic neoplasm malignant	Severe	Possible	50mg BID
17	S: Nervous system disorders P: Neuropathy peripheral	Moderate	Possible	150mg BID
18	S: Gastrointestinal disorders P: Intestinal obstruction	Severe	Possible	150mg BID

4.5.3 Summary

The adverse effects profile from the four trials suggests that eliglustat is well tolerated. There were no deaths reported, very few discontinuations (3%) and minimal SAEs (9%) and eliglustat related SAEs (1%) reported across the trials. Most AEs were reported as mild (78%) or moderate (44%), with 79% of AEs considered not related. The most common AEs were headache, arthralgia, nasopharyngitis, diarrhoea, most were of mild severity.

In the ENCORE trial adverse events, including serious and severe ones were more common on eliglustat than on imiglucerase. However, this difference in tolerability may be due to the fact that patients were stable on ERT at recruitment into the trial.

In the economic model, a subgroup of AEs was included in the cost-consequence analysis in section 12.2.6 of the CS (See table 52 of CS). These include the AEs that occurred in at least 15\5 of patients on eliglustat, imiglucerase or velaglucerase: back pain, abdominal pain and joint pain, fever, weakness, infusion reaction, URTI, dizziness and headache. Potentially more severe AEs or those more relevant to eliglustat were not considered. The event rate per year for all of these events included in the economic model was highest in the patients receiving velaglucerase. This is discussed further in the health economics Section 5.

4.6 Doses of eliglustat, imiglucerase or velaglucerase in clinical practice

The ERG present the recommended doses of eliglustat, imiglucerase or velaglucerase from the trials in the CS, the SPCs, the European public assessment report (EPAR), the UK standard operating procedure (SOP) for Gaucher disease, registry data (ICGG Gaucher registry) and expert advice (clinical advise to ERG and professional submissions to NICE). As there is limited information about the dosing of eliglustat and uncertainty for the dosing of ERT in clinical practice, other relevant studies including 'real life' cohorts will be identified.

Eliglustat

For the four trials (ENCORE, ENGAGE, EDGE and phase II) included in the CS, the doses of eliglustat administered are presented in Table 32. In all four trials of eliglustat patients were initially administered 50 mg twice daily, but dose adjustments to 100 mg and 150 mg at later time intervals were possible. The EMA approved recommended dose of eliglustat is 100 mg twice daily in CYP2D6 intermediate metabolisers (IMs) and extensive metabolisers (EMs) and 100mg once daily in CYP2D6 poor metabolisers (PMs).[19] It should be noted that eliglustat capsules contain 84.4 mg eliglustat free base, which is equivalent to 100 mg eliglustat tartrate. Before initiation of treatment with eliglustat, patients should be genotyped for CYP2D6 to determine the CYP2D6 metaboliser status. Eliglustat is not indicated in patients who are CYP2D6 ultra-rapid metabolisers (URMs) or indeterminate.[19]

Table 32 Eliglustat doses used in the trials included within the company submission

Trial	Study treatment
ENCORE	Eliglustat 50 mg BID (initial dose) or imiglucerase Potential eliglustat dose adjustment up to 100 mg at 4 weeks and up to 150 mg at 8 weeks
ENGAGE	Eliglustat or placebo 50 mg BID (initial dose) Potential eliglustat dose adjustment up to 100 mg BID at 4 weeks and up to 150 mg after 47 weeks
EDGE	Eliglustat 50 mg or 100 mg at lead in period (up to 18 months) Eliglustat 50 mg or 100 mg extended treatment period
Phase II	Eliglustat (open label) 50 mg BID (initial dose) Potential dose adjustment up to 100 mg BID at Day 20 and up to 150 mg after at least 18 to 24 months of treatment

In the ENCORE study, ERT-stable patients randomised to oral eliglustat received 50mg oral eliglustat capsules BID from Day 1 to Week 4. If patients had a plasma trough concentration of <5ng/mL at Week 2, dosage was increased to 100mg BID at Week 4. Patients with a trough concentration of ≥5ng/mL continued to receive 50mg BID. At Week 8, dosage was increased again if patients had trough concentration of <5ng/mL. For patients on 50mg, dosage was increased to 100mg, and for patients on 100mg dosage was increased to 150mg. Patients randomised to the control arm received imiglucerase until Week 52, at their usual doses (i.e., the doses received and stabilised upon before enrolment in the trial). During randomisation, patients were stratified by ERT dose level (<35U/kg/Q2W or ≥35U/kg/Q2W).

At the end of the protocol-defined titration period, the percentage of patients receiving the three possible eliglustat doses was: 20% (21/106) receiving 50mg BID, 32% (34/106) receiving 100mg BID and 48% (51/106) receiving 150mg BID. The EPAR states that "Based on an analysis [using a population pharmacokinetic/pharmacodynamics model], the loss of efficacy is clinically negligible in most patients switching from 150mg BID to 100mg BID. This conclusion is justified by the actual data that do not show a difference in response between EM patients treated with 100 or 150 mg/ BID. [32, 33]

Typical dosing of eliglustat during long-term follow-up

In the Phase II patients initially received a single 50 mg dose of eliglustat, then beginning day 20 the dose was adjusted to 100 mg twice daily for 18 patients. At week 52, patients could opt to continue in the study extension period (an additional 3 years). This study was the only long term assessment of eliglustat reported in the CS. The doses used were reported in the published paper (Lukina 2010).[22]In this study most of the 19 patients who completed 4 years follow-up were taking a dose of 100 mg twice daily: 15 patients received eliglustat 100 mg twice daily, 3 patients received 50 mg twice daily, and one patient received 50 mg twice daily for 3 years then increased to 100 mg twice daily for the fourth year.[22]

The ERG identified 4 year follow-up data from the ENCORE trial, but unfortunately the doses used during this follow-up period were not reported.[21]

None of the practitioner submissions to NICE suggested individualisation of the dose of eliglustat (other than according to the metaboliser status specified in the SPC). In summary, the doses recommended in the SPC are likely to be used in clinical practice.

ERT

Both imiglucerase and velaglucerase are approved for the treatment of Gaucher disease. For both imiglucerase and velaglucerase the SPC recommends individualisation of the dose with a suggested initial dose of 60 U/Kg of body weight once every two weeks. [34, 35] The SPC for imiglucerase also states that administration of doses as low as 15 U/kg of body weight once every 2 weeks has been shown to improve haematological parameters and organomegaly, but not bone parameters .

Standard operating procedures (SOPs) were prepared in 2012 (to assist commissioning of services for adult Gaucher disease in England) by a group of prescribing physicians, commissioners and patient group representatives working in the Lysosomal Storage Disorder Expert Advisory Group (Ref on shared drive).[12] At the time of developing the SOP in 2012, eliglustat was still at the early phase of development so no dosing recommendations for eliglustat were made. The SOP recommends velaglucerase as the first choice for initiation of therapy, based on cost, but imiglucerase is also

recommended as it is considered of equivalent efficacy. Specifically, the SOP reports that a maintenance dose of 15-30 Units (U)/kg very two weeks is appropriate for most patients on either imiglucerase or velaglucerase, though this may be increased to 60 U/kg.

Additional to the SOPs and SPCs, the clinical advisor for the ERG advises that a typical dose of ERT is 25 U/kg (range: 15-28 U/kg) which is considerably lower than the 60 U/kg suggested in the SOP and SPCs. This dosage is based on patients achieving their therapeutic goals in spleen and liver volumes and haematological parameters. The one practitioner submission to NICE for this appraisal of eliglustat that stated a typical dose of ERT, reported doses of 20-40 U/kg.

In ENCORE, 58% of the patients received a dose ≥35 U/kg every two weeks and the remaining 42% received a dose <35 U/kg; the mean dose was not reported.

Long term doses of ERT

Patients recruited into the ENCORE trial had to be stable on ERT at a total monthly dose between 30 U/kg and 130 U/kg. At the start of the trial on average, study participants had been on ERT for about 10 years, with nearly 60% receiving doses of at least 35 U/kg every two weeks. Details of the most common upper limit were not reported.

The CS reported that in clinical practice in England adult imiglucerase patients receive [redacted] units per month based on the prescribing data (n=[redacted]). Although the weight of these patients is not known, this equates for patients with a weight of 67.5kg to [redacted]U/kg. Data for the UK from the International Gaucher Register suggests imiglucerase dosing of [redacted]/kg (n=[redacted]) with patients weighing a mean of [redacted]U/kg. This would suggest that dosing of patients on imiglucerase in ENCORE is [redacted] than in UK clinical practice.

To investigate further what can be considered a typical dose of ERT in clinical practice for patients stable on ERT, the ERG carried out a search in MEDLINE to identify studies which followed adult patients with GD1 over a longer period of time. The search identified twenty three studies which were then screened at abstract level for relevance. Online searches were also conducted and references from the CS report were checked. Six of these studies clearly specified the dosing of either imiglucerase or velagulcerase and are detailed in**Error! Reference source not found.**.

Table 33: Studies identified from ERG search on dosing of ERT

Study	Country	Follow up duration	ERT	Description of dosing over time
Weinreb et al 2008 (ICCG Gaucher registry) [36]	International	4 years	Imiglucerase	The average dose of imiglucerase over 4 years was 67.5 +/- 31.7 U/kg every 4 weeks. Individual patient dosing not explained
Weinreb 2013 (ICCG Gaucher registry) [27]	International	10 years	imiglucerase	At initiation of treatment most patients were dosed in the middle range at either >15 to ≤45 U/kg every 2 weeks (n=244 patients, 43.8 %) or >45 to ≤90 U/kg every 2 weeks (n=198, 35.5 %). After 10 years of imiglucerase, 58 %) were receiving imiglucerase doses in the range >15 to ≤45 and 25% >45 to ≤90 U/kg every 2 weeks, reflecting shifts away from lower and higher dose groups.
Tukan et al 2013 [37]	Israel	4 years	Imiglucerase	Achievement of therapeutic goals after 4 years in the current cohort on low-dose : most adults on 15 U/kg /2 weeks (mean=34.2 U/kg/ 4 weeks). The individual patient doses were not reported.
Elstein et al 2011 [38]	Israel	69 months (3 years 5 months)	Velaglucerase	(n=10 treatment naïve) Initial dose of 60 u/kg then in the extension study between 15 and 18 months of cumulative treatment, patients were eligible for a step-wise dose reduction to 30 U/kg every 2 weeks. Actual dose used not reported
Zimran et al 2015 [39]	Israel	7 years	Velaglucerase	12 GD1 patients received doses of 60 U/kg of velaglucerase every two weeks. They then continued into the extension study where they were eligible to receive a stepwise dose reduction of 30 U/kg after the cumulative treatment period of 15 to 18 months
Van Dussen 2012 [31]	UK /The Netherlands	Unclear	Imiglucerase and velaglucerase	Monthly Dose of imiglucerase ranged from 15 to 120 Mean 53.5 (SD 29.3) U/kg; median 46.5 U/kg (UK patients only range 20 to 120; mean 55.1 (SD 28.3) U/Kg; median 48 U/Kg), Monthly Dose of velaglucerase ranged from 20 to 120, Mean 54.2 (SD 28.2) U/kg; median 46.5 U/kg (UK patients only 20 to 120; mean 55.2 (SD 27.6) U/Kg; median 48 U/Kg),

The available observational study data indicate that the approved doses of imiglucerase and velaglucerase are much higher than those used in practice to maintain therapeutic goals. Across the studies mean doses reported ranged from 34.2 U/kg/4 weeks to 67.5 U/kg/ 4 weeks, approximating to 17 U/kg every 2 weeks to 34 U/Kg every two weeks. From the largest cohort (ICCG Gaucher registry) at 10 years follow-up 58 % were receiving imiglucerase doses in the range >15 to ⩽45 and 25% >45 to ⩽90 U/kg every 2 weeks. Specifically in one UK cohort (other than that reported in the CS) a median monthly dose of 48 U/kg was reported, approximating to 24 U/kg every two weeks; it should be noted it is unclear how long these patients had been established on ERT and also the data were collected during a shortage of imiglucerase. One small study of velaglucerase illustrates the possibility of maintaining therapeutic benefit with a reduced dose of ERT.[39]Ten patients received

doses of 60 U/kg of velaglucerase every two weeks for 9 months, then continued into an extension study where they were eligible to receive a stepwise dose reduction of 30 U/kg after the cumulative treatment period of 15 to 18 months. At the lower dose (30 U/kg) velaglucerase appeared to induce good responses in platelet counts, even among patients who were slower to initiate responsiveness.

Summary

SPCs for imiglucerase and velaglucerase recommend higher starting dose of 60U/kg every two weeks however the SOP, developed by expert consensus in England reports that a maintenance dose of 15-30 U/kg is appropriate for most patients on either imiglucerase or velaglucerase, though this may be increased to 60 U/kg. Expert opinion suggests typical doses of 25 U/kg (range: 15-28 U/kg) or 20-40 U/kg (practitioner submission to NICE). Across the observational studies mean doses of ERT reported ranged from 34.2 U/kg/4 weeks to 67.5 U/kg/ 4 weeks. Patients recruited into the ENCORE trial had to be stable on ERT at a total monthly dose between 30 U/kg and 130 U/kg; at the start of the trial on average, study participants had been on ERT for about 10 years, with nearly 60% receiving doses of at least 35 U/kg every two weeks. Although information is limited about timing of dose reduction, the available information makes it clear that whilst patients may initiate ERT on 60 U/kg, in the long term lower doses are used. The ability of patients to maintain their therapeutic goals with lower doses of eliglustat and particularly ERT will affect the long-term costs. The impact of the ERT dose on the cost-effectiveness of eliglustat will be discussed in the health economics section.

4.7 Additional work conducted by the ERG

The ERG identified one additional relevant article [20] which was published after the company's literature search in their review. This study was a case series summary of 6 adult patients from the Netherlands diagnosed with GD1 and receiving eliglustat: four treatment naïve and two after switching from ERT. We provide a brief summary of the findings below.

Results

Eliglustat treated patients naïve to treatment were mildly affected by GD1 at initiation of therapy. Treatment with eliglustat decreased the biomarkers chitotriosidase, CCL18 ans GlcSph , though none completely normalised after two years' therapy. The study demonstrates good clinical response to eliglustat treatment with liver and spleen volumes decreased, platelet counts increased and no bone marrow fat fraction levels improved. Haemoglobin levels improved in those with anaemia at baseline. Of the two patients that switched from ERT to eliglustat one was a severely affected GD1 patient when starting ERT and stopped eliglustat after 17 weeks due to an AE. In this patient biomarkers improved whilst on eliglustat. The other switch patient, who was mildly affected when starting ERT, remained stable on eliglustat with normal/improved biomarkers.

4.8 Clinical effectiveness conclusions

The clinical effectiveness evidence in the company's submission was based on a systematic review of eliglustat for the treatment of adult patients with GD1. The ERG is confident that all relevant trials (including trial extensions) were included in the submission. The company's submission on the clinical direct efficacy of eliglustat was primarily based on two phase III trials (ENCORE and ENGAGE) and a single arm Phase II study. Supporting evidence was provided by an ongoing RCT (EDGE).

The ENCORE trial, conducted in 159 ERT stable patients demonstrated that when patients switched from ERT therapy, eliglustat maintained haematological and organ volume stability. Eliglustat met the criteria of being non-inferior to imiglucerase in terms of the primary outcome and maintaining stability, as the non-inferiority lower 95% CI was -17.6% which was within the pre-specified threshold of -25% (lower 95% CI for the composite endpoint confirmed non-inferiority at the 20% acceptance margin). However, this non-inferiority margin is somewhat wider than would normally be accepted: a margin of 15% would have been more robust. Furthermore, the 25% non-inferiority margin assumes that a 10% reduction in efficacy is clinically insignificant, an assumption that was not justified by any clinical argument. The ERG notes the EMA accepted the broader margin due to the rare nature of the disease: the conduct of a larger trial (as would be necessary with a 15% margin) would not be feasible.

The results for individual outcomes of spleen and liver volume, haemoglobin levels and platelet counts indicate small reduction in efficacy with eliglustat, although this reached statistical significance only for haemoglobin levels (-0.28 (95% CI (-0.52, -0.03))). There were no significant changes in DS3 scores and measures of bone health. Eliglustat was not associated with any improvement in quality of life despite patients expressing a marked preference for an oral therapy. A post hoc analysis showed that eliglustat efficacy was similar both post-imiglucerase and post-velaglucerase treatment.

Long-term follow-up data from ENCORE demonstrate that for patients who remain on eliglustat, stability on all four composite parameters is maintained over 4 years. However, although few patients withdrew due to adverse events, the number of patient in the analysis at 4 years was only 44 out of an original 159 patients: the unexplained loss of patients from follow-up raises a question of how to interpret these long-term results. As treatment for GD1 is life-long, there is uncertainty regarding the long-term implications of a possible small reduction in efficacy with eliglustat compared with ERT.

ENGAGE was a well conducted placebo-controlled RCT in patients not being treated with ERT. However the sample size was small (40 patients), the primary outcome was a single measure of spleen

volume, rather than a more clinically relevant composite outcome, and the randomised phase was only 39 weeks. At 39 weeks, eliglustat was associated with a reduction in spleen volume of 27.8% compared with an increase of 2.3% on placebo (statistically significant mean difference of -30.03%; 95% CI -36.82% to -23.24%). Eliglustat was also associated with a reduction in liver volume of 55.2% compared with an increase of 1.4% on placebo (statistically significant mean reduction of 66.64% (95% -11.37% to -1.91%). The effect sizes of point estimates for spleen and liver volumes were moderate to large, implying that these treatment effects could be clinically significant. Compared with placebo eliglustat achieved a statistically significant increase in haemoglobin level (1.22 g/dL; 95% CI 0.57 to 1.88) and platelet count (41.06%; 95% CI 23.95% to 58.17%). Nineteen out of the 20 patients in the eliglustat treatment group met at least one of the 1-year therapeutic goals established for Gaucher patients (9 met 2 goals, and 2 met 3 goals). Improvements were also seen in DS3 scores, though none achieved the minimum clinically significant threshold for improvement. At 39 weeks, eliglustat also demonstrated beneficial effects on a number of bone-related outcomes and some reached statistical significance. Eliglustat showed some positive effects on health-related quality of life measures, being associated with a significant improvement in disease-specific quality of life outcome (fatigue severity score 0.7; 95% CI 0.02 to 1.33) compared with placebo but there was no statistically significant difference in BPI (average pain) (-0.2; 95% CI -0.81 to 0.36) between the treatment and placebo groups nor for the SF-36 general health score (-2.4; 95% CI -9.84 to 4.94), physical component score (3.3; 95% CI -0.67 to 7.29) or mental component score (-2.2; 95% CI -7.01 to 2.59) at week 39.

The open-label extension data indicated that the beneficial effects on organ volumes, haemoglobin level and platelet count were sustained at 78 weeks; there were no drop outs. There was also an indication of continued small improvements in some but not all bone parameters. Results for DS3 scores, biomarker measures and health-related quality of life outcomes at 78 weeks were not reported.

The results of the two RCTs are supported by the single-arm phase II study in 26 patients. At year 1, 77% of the 26 patients achieved a composite outcome requiring improvements from baseline in at least two of spleen volume, haemoglobin level and platelet count. At year 2, this was 85% of 20 patients remaining in the analysis. At 4 years all 19 patients included at this point met their therapeutic goals for spleen volume and haemoglobin level, 94% met the goal for liver volume and 47% met the goal for platelet count. Bone parameter and HRQL data suggested some small improvements by 2 years, but were not reported at 4 years. Due to the lack of control group in this study, the small sample size and the unexplained loss of patients from the later time points, the treatment effects observed over the four year follow-up were uncertain.

Supportive evidence also came from the single-arm open label lead-in period of the EDGE trial in which 83% of the 170 patients achieved all five therapeutic goals during the lead-in period.

As far as can be determined from limited data sets, the generalisability of findings from the two main Phase III trials (ENGAGE and ENCORE) to routine practice in England is adequate. There is nothing to suggest that the beneficial effects observed in these trials would not be reflected in practice except for a lack of information on the treatment of ERT stable patients with very large spleens and some question over the ERT dosing.

No data comparing eliglustat with imiglucerase or veleglucerase in treatment naive or untreated patients was presented, nor any making a direct comparison of eliglustat with velaglucerase in ERT stable patients. There are no pertinent data to enable an indirect comparison analysis to be performed. It is generally accepted that imiglucerase and velaglucerase are equivalent, though the trial data to support this are limited to one small non-inferiority trial with haemoglobin levels as the primary outcome.

The adverse effects of eliglustat were based on the limited available evidence from ENCORE, ENGAGE and the Phase II trial. The adverse effects profile from the trials suggests that eliglustat is well tolerated. There were no deaths reported, very few discontinuations and few eliglustat related SAEs. Most AEs were reported as mild (78%) or moderate (44%). The most common AEs were headache, arthralgia, nasopharyngitis, diarrhoea; most were of mild severity. The evidence from ENCORE shows a higher number of patients experiencing treatment related AEs and severe TEAEs. However, this apparent difference in tolerability may be due to the fact that patients were stable on ERT at recruitment into the trial. The evidence was mostly limited to the short-term data although some longer-term data up to 4 years demonstrate that eliglustat is generally well tolerated.

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the company and the additional information provided to the ERG following points for clarification. The submission was subject to a critical review on the basis of the company's report and direct examination of the electronic version of the economic model. The critical appraisal was conducted with the aid of a checklist to assess the quality of economic evaluations and a narrative review to highlight key assumptions and possible limitations. Section 6 presents additional work undertaken by the ERG to assess uncertainty surrounding a number of assumptions made in the company's model.

The company's initial economic submission included:

- A description of the search strategy and databases used in the literature review of cost-effectiveness studies (CS, pg. 166 to 177), quality-of-life studies (CS, pg. 154 to 162) and resource use studies (CS, pg. 197 to 200);
- A report on the *de novo* economic evaluation conducted by the company which included a cost consequence model and budget impact analysis. The report outlined the intervention; comparators and patient population; the modelling methodology; the resource components and unit costs; data input sources and assumptions; the base-case results; and sensitivity analysis (CS, pg.178 to 266);
- The company's electronic Excel-based *de novo* model.

Following the points of clarification raised by the ERG, a number of addenda were submitted by the company. These included:

- A revised electronic model, which corrected a number of minor calculation errors and included a number of additional scenarios requested by the ERG;
- Individual patient data on the weight and height of patients enrolled in the ENGAGE and ENCORE studies;
- The SAP for the ENCORE clinical trial;
- A full report on the utility associated with mode of treatment administration.

Further to the above, at the request of the ERG, NICE has supplied the confidential prices of velaglucerase and imiglucerase used in the NHS along with agreed prices relating the administration of velaglucerase in the NHS.

5.1 ERG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review to identify relevant economic evaluations for the treatment of GD1. The ERG's critique of the systematic review presented by company is given below.

5.1.1 Searches

The CS described the search strategies used to identify cost-effectiveness analyses of interventions for GD1. The search strategies were briefly described in the main body of the submission in Section 11.1.1 and full details were provided in Appendix 3 of the CS.

The electronic databases MEDLINE, MEDLINE In process, EMBASE, NHS EED, HTA database and EconLit were searched during May/June 2014. Update searches were performed on the same set of databases during July/August 2015. The searches were limited by date from 1990 onwards.

To supplement the electronic database searches, hand searching of poster and podium presentation abstracts from the following 2 conferences was carried out: European Working Group on Gaucher Disease (EWGGD) and American Society of Human Genetics (ASHG).

The search strategies presented are appropriate to capture cost-effectiveness studies of interventions for Type1 Gaucher disease. The searches are well reported with enough details to allow the searches to be reproduced.

The structure of the search strategies was appropriate with terms for the population combined with terms to capture economic studies. A comprehensive set of subject heading and text word search terms for Gaucher disease and economics were included in the strategy. All search lines have been combined correctly using Boolean operators, the correct fields have been searched and truncation and wildcards have been used appropriately. Animal only studies have been excluded correctly from the search strategy.

HRQL studies

The CS described the search strategies used to identify relevant HRQL data for people with type 1 Gaucher disease. The search strategies were briefly described in the main body of the submission in Section 10.1.5 and full details were provided in Appendix 4.

The electronic databases MEDLINE, MEDLINE In process, EMBASE, NHS EED, HTA database and EconLit were searched. There is some slight confusion as to the date of the search, with the CS appendix reporting the date of the search as October 2015 (section 17.4.2) but in the main body of the report the date of the search is given as July/August 2015 (section 10.1.5). The searches were limited by date from 1990 onwards.

To supplement the electronic database searches, hand searching of recent records from the following two conferences was carried out: European Working Group on Gaucher Disease (EWGGD) and American Society of Human Genetics (ASHG). This was reported in CS Section 10.1.5, however further details of these searches do not appear in the CS Appendix 4.

The searches of MEDLINE and EMBASE are reported as being carried out via the Ovid interface, however the strategies presented would not run correctly on the Ovid versions of these databases. The search syntax used in the strategies presented is incorrect for Ovid. Therefore it is not possible to be certain that a thorough search of MEDLINE and EMBASE has been carried out to identify HRQoL data.

The searches of NHS EED, HTA database and EconLit are correct and are appropriate for the retrieval of HRQL data for type 1 Gaucher disease. However a search of MEDLINE and EMBASE would be necessary to ensure comprehensive retrieval of all possible studies.

5.1.2 Inclusion/exclusion criteria used for study selection

The cost-effectiveness review presented in the CS sought to identify previous economic analyses evaluating treatments for GD1. Details of the inclusion and exclusion criteria used for the selection of cost-effectiveness studies can be found on page pg. 167 of the CS, but in brief were as follows:

- **Population:** Patients with GD1;
- **Intervention/comparators:** Any medical treatment, best supportive care, placebo or no treatment;
- **Outcomes:** Costs, life years, QALY or any other measure of effectiveness;
- **Study designs:** Economic evaluations of the following type: cost-consequence, cost-minimisation, cost utility, cost-benefit;
- **Publication type:** all study types except for letter, comments and systematic and non-systematic reviews/narrative reviews;
- **Other restrictions:** Studies published in English

The ERG considers that the inclusion/exclusion criterion used were largely reasonable. Only English language articles were selected for the review, creating the potential for language bias. However, it is unlikely that any relevant economic evaluations were excluded from the review on the basis of language of publication.

5.1.3 Studies included and excluded in the cost effectiveness review

The CS's search identified three relevant studies Connock et al,[7] Van Dussen[40] and All Wales Medical Strategy Group (AWMSG) assessment place.[41]

The first study Connock et al.[7] reported the results of a cost–utility study carried out as part of the NHS HTA programme. The study compared ERT with standard supportive care from UK NHS perspective. The model used a Markov model structure. No comparative clinical evidence was used in the model, transitions were therefore based on natural history studies and a number of assumptions about the clinical effectiveness of ERT. The outcomes of the Markov model included costs over a lifetime time horizon, life-years, quality-adjusted life-years (QALYs). The results of the analysis showed an incremental cost-effectiveness ratio (ICER) of £397,275 per QALY.

The second study Van Dussen et al[40] reported the results of Markov model comparing ERT with standard supportive care from Dutch societal perspective. Clinical data were sourced from a Dutch Gaucher disease registry. The outcomes of the model included costs, QALYs and life years over a lifetime time horizon. The results of the analysis showed an ICER of EUR432,540 per QALY.

The final cost-effectiveness study identified was a cost minimisation study submitted to the AWMSG in support of velaglucerase.[41] The submission compared imiglucerase with velaglucerase and assessed differences in drug acquisition costs (other costs were assumed the same) between the two treatments. The model reported that lifetime costs associated with velaglucerase were £5,120,956 and £3,903,338 for imiglucerase. The report states that drug acquisition costs accounted for 99% of total costs (note, this excludes a discount currently available for velaglucerase).

5.1.4 Conclusions of the cost effectiveness review

Currently there is a lack of evidence on the cost-effectiveness of eliglustat. The company's search did not identify any relevant economic assessments of eliglustat for the treatment of GD1 in the UK setting. A number of studies evaluating the cost-effective of ERT in the UK and non-UK settings were identified comparing ERT with standard supportive care. These studies demonstrated that ERT had an ICER that far exceeds current established thresholds and that drug acquisition costs are the primary driver of costs. Given the above the ERG therefore considers the cost-consequence and budget impact analysis reported in the current submission to be the most relevant source of economic evidence to inform the decision problem.

5.2 ERG's summary and critique of company's submitted economic evaluation

A summary of the company's approach and signposts to the relevant sections in the company's submission are reported in Table 34 below:

Table 34 Summary of the company's economic evaluation (and signposts to CS)

	Approach	Source / Justification	Signpost (location in CS)
Model	A cost consequence analysis using a 10 health state Semi-Markov model	No justification of model structure given.	Section 12.1.3 Pg. 179 to 182
States and events	The model contains 9 health states plus death. The 9 living health states were based on the GD DS3 severity scoring system.	The model health states were designed to represent the heterogeneity of the Gaucher disease population.	Section 12.1.3 and 12.1.4 Pg. 179 to Pg. 182
Comparators	Eliglustat is compared with the ERT therapies imiglucerase and velaglucerase.	The choice of comparators is based on the Standard Operating Procedures (SOP) for Gaucher disease in England.	Section12.1.2 Pg. 179
Subgroups	IM and EM Gaucher disease patients were analysed separately from patients with PM Gaucher disease. Stable and treatment naïve patients.	These subgroups were presented separately due to differential drug acquisition costs for IM/EM patients compared with PM patients.	Section 12.1.4 Pg. 182
Treatment effectiveness	For stable patients transition probabilities in the first year were based on the ENCORE trial and therefore after based on data from the DS3 score study. For treatment naïve patient's treatment effectiveness was assumed equal and based on the eliglustat arm of the ENGAGE study. In both patient groups clinical effectiveness was based on the GD-DS3 score and mapped directly to the respective health state. The effectiveness of the two ERT therapies imiglucerase and velaglucerase was assumed to be equal in all analyses.	The ENGAGE study is the only RCT comparing eliglustat with ERT therapy in stable Gaucher disease patients. There have been no comparisons of eliglustat with ERT therapies in treatment naïve patients.	Section 12.1 Pg. 186 to pg. 188.
Adverse events	Adverse events were included if they occurred in 15% of patients or greater. Patients were only at risk of AE during the first 36 months of the model and thereafter were assumed to experience no further AEs.	Adverse event rates were taken from a pooled analysis of a number of studies including the ENGAGE and ENCORE trials. No adverse events were assumed after 36 months on the basis that that patients are stable on treatment after this time and will not discontinue due to AEs.	Section 12.2.4 Pg. 188 to 189
Health related quality of life	Utility values were assigned to each of the 9 health states based on SF 36 QoL data collected in the DS3 Score study and mapped to EQ-5D.	Utility values for each health state were sourced from a regression analysis of QoL data collected in the DS3 scoring studies.	Section 10 Pg. 146 to 164

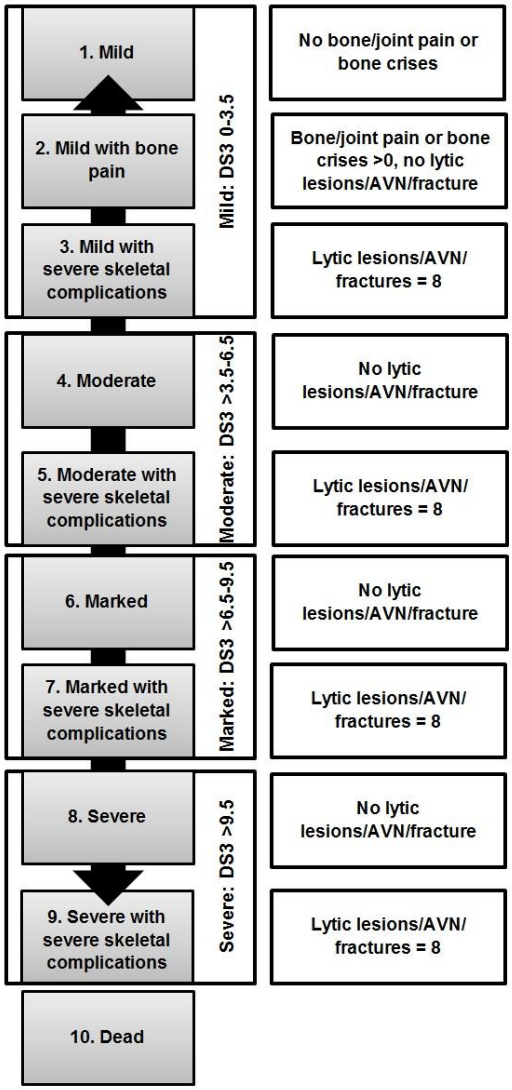
	A QoL of life increment was assumed for eliglustat patients to represent the benefits of oral therapy this was based on a TTO study of 100 members of the UK general public Disutilites were applied for a number of AEs.	A QoL increment assigned to eliglustat patients to represent the benefits of oral therapy was sourced from Mapi (2015) a company sponsored study. Disutilises associated with AE were sourced from a number of published studies.	
Resource utilisation and costs	Cost categories were as follows: drug acquisition, administration and monitoring/disease management.	Drug acquisition costs for eliglustat were sourced form the company. For imiglucerase costs were sourced from the BNF and for velaglucerase from MIMS. Drug administration costs were sourced from data on file and NHS reference costs (2014 to 2015). Unit costs for monitoring were taken from NHS reference costs (2014 to 2015). Resource use items were obtained mainly based on expert opinion, but also based on previous economic analyses.	Section 12.3 Pg. 195 to 217
Discount rates	Costs and benefits were discounted at 3.5% per annum	In accordance with the NICE reference case.	Section 12.4.4 Pg. 222
Sensitivity analysis	Probabilistic sensitivity analysis was performed. Deterministic univariate probabilistic analysis was performed on a series of model parameters. A series of scenario analyses was also performed.	In accordance with the NICE reference case.	Section 12.5.11 to 12.5.13. Pg. 246 to 259

5.2.1 Model structure

The *de novo* cost consequence analysis presented by the company considers two different patient groups: those who are treatment-naïve and those who were taking ERT and are considered clinically stable. Within these groups, further sub-groups are analysed based on metaboliser status, with intermediate and extensive metabolisers (IM and EM) receiving 100mg of eliglustat tartrate twice daily, and poor metabolisers (PM) receive 100mg once daily. The structure of the model is presented in Figure 3. The analysis uses a ten-health state semi-Markov model structure. The model is a semi-Markov structure because, unlike a normal Markov model which is memoryless, the transition probabilities used in the model depend on a patient's initial health state. The health states used in the model are defined by a patients score on the GD-DS3, a validated measure used to score the severity of GD1 in clinical practice (described briefly in Section 2.2.2 of this report). Patients are grouped by: mild (DS3 = 0-3.5), moderate (DS3 = 3.5-6.5), marked (DS3 = 6.5-9.5), and severe (DS3 >9.5) disease. Within these categories, patients are also divided by the presence of bone symptoms, based

on individual assessment of the bone domain. The model also includes a death state, with all health states having an equal mortality risk of death.

Figure 3 Model schematic with description of health states [CS, Figure 23, pg. 181]



The initial health state distributions are based on the baseline distributions in the ENCORE and ENGAGE trials. Over each annual cycle patients can transition to any health state in the model except death, which is an absorbing state. The model therefore implicitly assumes that disease severity can both increase and decrease. Transition probabilities in the first year of the model are based on the results of the ENGAGE trial for the treatment naive patients and on the ENCORE trial for treatment stable patients. Longer term transitions are sourced from the DS3 score study[18] a registry validating the DS3 scoring system (see section 5.2.7 for further details).The same long-term transition probabilities were used for both treatment arms and therefore equal effectiveness of eliglustat and ERT is assumed in the long-term. Quality of life was quantified by applying utility weights to each

model state in order to estimate quality-adjusted life years. Utility decrements were applied to patients on treatment to reflect the impact of adverse events. Costs for drug acquisition, administration, and monitoring and management were included in the model. Differential monitoring and management costs were applied to each health state, broadly increasing with severity of disease. No costs associated with adverse events were included in the model.

The ERG has significant concerns about the structure of the model developed by the company. These concerns focus on the long-term transitions used in the model and the use of GD-DS3 score system to define health states.

With regards to the long-term transitions, the ERG is concerned about the approach taken by the company to generate the long-term transition probabilities. The CS outlines that the transition probabilities were derived using logistic regression analysis which included terms for past DS3 score. The transition probabilities used in the model therefore depend on the baseline distribution of patients across the health states. This introduces an element of memory in to the model as a patient's prognosis depends on the patient's history. The ERG does not understand the justification for such a complicated model structure given that the same transition probabilities are applied to both treatment and comparator groups; CS includes minimal justification for the use of this structure. The ERG also highlight that no reference was made to the use of this structure in the main body of the CS, with details confined to an appendix, which itself was not referenced in the main body text. The ERG considers the approach taken by the company to generally be overly complicated adding minimal added value to the predictions of the model. Further, the ERG considers that this complexity significantly reduces the transparency of the model making validation of the company's model very difficult.

With respect to the use of the GD-DS3 score system, the ERG acknowledges that the GD-DS3 scoring system is a validated measure of disease severity and is widely used in practice. However, the use of this scoring system in the model structure has a number of important detrimental implications. Firstly, the GD-DS3 score appears to be somewhat insensitive to changes in disease status, and as a consequence, does not reflect differences between the treatments that are observed in the ENCORE trial. This means that differences between the treatment and comparators are not accounted for in the model, effectively biasing the model towards equivalence in clinical benefits. This and further issues regarding assumptions made about clinical effectiveness are discussed further in Section 5.2.7.

Secondly, the GD-DS3 score has a many levels (11 in total) and as a consequence, the model includes a total of 9 alive health states to represent the different levels of disease severity. The ERG questions whether the inclusion of so many heath states is desirable or necessary. The principal advantage of

more health states is one of increasing precision within the model: increased precision is particularly important where there are non-linear relationships between disease severity and both QoL and costs because the increase precision provided by more health states improves the accuracy of the model. It is, however, not clear in the present context that non-linearity in costs and benefits associated with each health state are extensive, particularly in relation to costs which are dominated by drug acquisition costs that are independent of a patient's health state. The limited advantage must be set against the disadvantage of increased model complexity and associated reduced transparency, as well increased demands on available data. The latter issue is particularly important in the present context because data on GD1patients is limited.

5.2.2 The company's economic evaluation compared with the NICE reference case checklist

Table 35 summarises the economic submission and the ERG's assessment of whether the *de novo* evaluation meets NICE's reference case and other methodological recommendations.

Table 35 Features of de novo analysis

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de-novo evaluation meets requirements of NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Partly	The model compares eliglustat with two ERT therapies imiglucerase and velaglucerase, which are the primary treatments for Gaucher disease in UK practice. However, a small number of patients receive milglustat ~ 2%. No comparison of eliglustat with milglustat was presented in the economic analysis.
Type of economic evaluation	Cost-effectiveness analysis	Yes	The submission presents a cost-consequence analysis
Perspective on costs	NHS and PSS	Yes	NHS and PSS costs have been taken into account.
Perspective on outcomes	All health effects on individuals	Yes	QALY benefits to treated individuals were considered.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	The economic model follows a time horizon of 70 years representing lifetime time horizon. No patients are expected to live beyond this period.
Synthesis of evidence on outcomes	Systematic review and mixed treatment comparison of relative effects.	Partly	No evidence synthesis was used to obtain health benefits estimates, as there were no other relevant studies conducted in Gaucher patients.
Measure of health effects	QALYs	Yes	Health state utilities were drawn from a regression analysis of SF 36 data from the DS3 score study.
Source of data for measurement of HRQL	Reported directly by patients and/or caregivers	Partly	Health state utilities were drawn from Gaucher disease patients. A QALY increment was assigned to eliglustat patients to represent the benefit of oral therapy and was derived from the general public.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes	
Discount rate	Annual rate of 3.5% on both costs and health effects	Yes	Costs and benefits have been discounted at 3.5% per annum.

Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	No special weighting undertaken.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was undertaken.

5.2.3 Model inputs

The following section describes and critiques the key inputs and assumptions that influence a patient's transit through the model and how costs and benefits are accumulated.

5.2.3.1 Discontinuation

The model assumes that patients can discontinue treatment for up to three years following of initiation of therapy. After three years it is assumed that patients will become stable on the selected treatment. For the treatment naïve population initiating eliglustat or ERT, a discontinuation rate of 1.9% is applied. This was based on the discontinuation rate of eliglustat in the ENCORE trial which enrolled ERT stable patients; this source was selected because no discontinuation was observed in the ENGAGE study which enrolled un-treated patients. For treatment stable patients a discontinuation rate of 1.9% from ENCORE was applied to eliglustat patients only. For treatment stable patients on ERT, a 0% discontinuation rate was assumed; this was justified on the grounds that ERT stable patients have been treated with ERT for an extensive period of time and as such are unlikely to discontinue therapy. The assumption of stability after three years is based on the cumulative discontinuation of approximately 6% for ERT patients, being roughly equivalent to the proportion of patients who were not on stable treatment in UK cohort study. [28]

Discontinuation rates for imiglucerase and velaglucerase were assumed to be equal based on the fact that they have been shown to be equal in efficacy. If patients discontinue imiglucerase then they are assumed to switch to velaglucerase and vice versa. Patients who discontinue on eliglustat are assumed to be treated with the main ERT comparator selected. It is assumed that discontinuation does not have an impact on the efficacy. It is also assumed that no patients would be untreated, with the CS citing clinical expert opinion and data from Wyatt et al. (2012) to support this.

The ERG acknowledge that there is a lack of evidence regarding discontinuation available and therefore do not consider the simplifying assumptions made by the company to be unreasonable. However, the ERG also note that the results of the costs-consequence analysis are highly sensitive to the discontinuation rates used and the duration over which they are applied has a significant impact on life-time drug acquisition costs. This is because patients incur the costs of follow-on treatment following discontinuation, which can be substantially different to the drug the patient initiated on.

In addition to ENCORE and ENGAGE, the ERG has identified a number of alternative sources of discontinuation data. With respect to eliglustat, further evidence on discontinuation rates is available from the extension periods of the ENCORE and ENGAGE studies. In the extension period of 1 year in the ENCORE a further 3% of patients on eliglustat discontinued therapy, and 8% of patients who switched from imiglucerase to eliglustat also discontinued. This contrasts with no discontinuations in the ENGAGE study during the primary analysis or extension periods which totalled 78 weeks. From a pooled safety analysis of GD1 patients from the ENGAGE and ENCORE Phase III trials and a Phase II study, with a total of 535 patient years of data collected, a combined 3% of patients were reported to have discontinued eliglustat.

With respect to the two ERT treatments evidence on discontinuation is similarly conflicting. Evidence from the longitudinal study of a cohort of patients with lysosomal storage disorders[28] reported that 24 patients of 175 (13.7%) patients discontinued treatment in the prospective follow up period suggesting the discontinuation rate maybe higher than the1.9% used in the model. However, a significant proportion of the discontinuations reported in this study were due to pregnancy or breast feeding and as such likely temporary. Uneven follow up also means that calculation of an exact discontinuation rate is not possible. A randomised trial comparing imiglucerase with velaglucerase in 35 ERT-naïve patients, reports no discontinuations after nine months from the velaglucerase group and 1 patient (5.5%) discontinuing treatment in the imiglucerase group.[29] Given the uncertainty the ERG also asked the clinical advisor to the ERG for their experience on discontinuation of ERT treatments. Their reply suggested that the rate of discontinuations amongst patients on ERT was very low (almost zero).

Given the uncertainty regarding the discontinuation of treatment and sensitivity of the model to this input the ERG presents additional scenario in Section 6 where 0% discontinuation is assumed, and a further scenario in which a higher rate of 3% discontinuation is used for eliglustat patients in the second and third year of treatment.

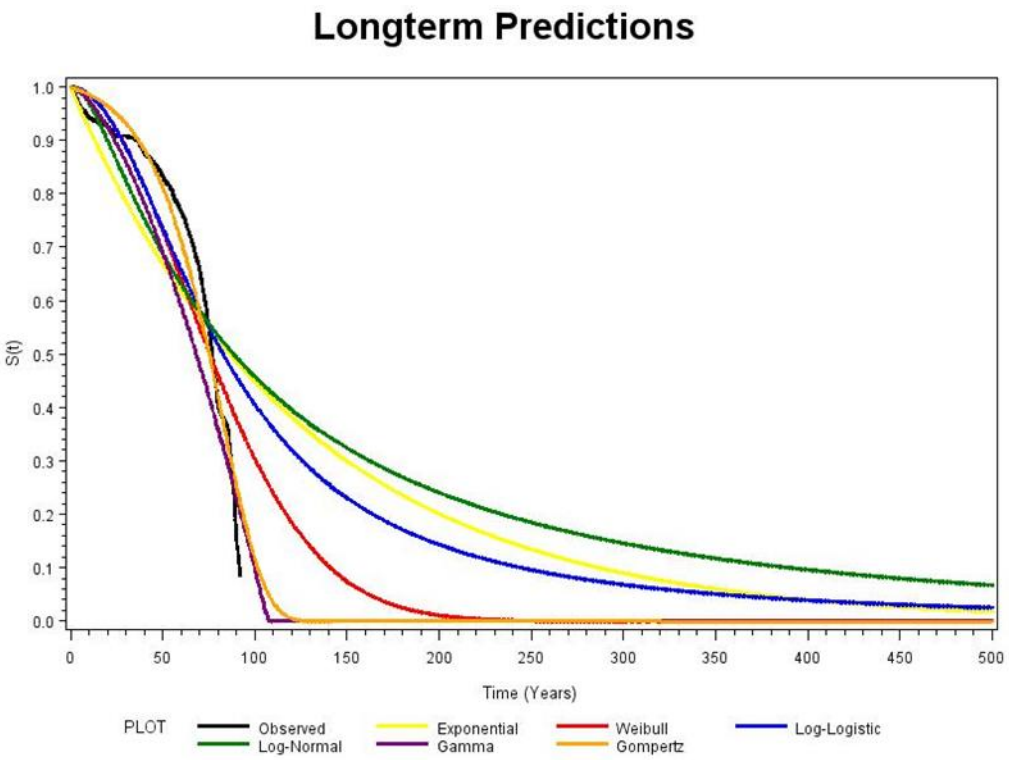
5.2.3.2 Mortality

Mortality in the model was assumed to be the same across both treatment and comparator and across all health states. Therefore the mortality rate does not increase with disease severity. Morality rates used in the model were based on a combination of data from the ICGG registry on Gaucher (Type 1) mortality[11] and general population mortality sourced from the office for national statistics[42].

To construct the mortality rate used in the model, simulated patient level data was generated from the Gaucher mortality data and from this a Kaplan Meier plot was derived (see Figure 4 below). A number of parametric curves were then fitted to this Kaplan Meier plot: exponential, Weibull, Generalised gamma, Gompertz, log-logistic and log-normal. The Company selected the best fitting

curve on the basis of statistical fit (AIC and BIC), plausibility of median survival estimate, and visual match to the Kaplan Meier plot. While noting the better statistical fit of the generalised gamma the company to select the Gompertz curve, considering it to have better visual fit despite it having and to provide a more plausible estimate of median survival. The CS did not include a fitted curve for the generalised gamma function, but this was provided following a request by the ERG at the points for clarification stage. The fitted curves for all fitted functions are presented in Figure 4 below.

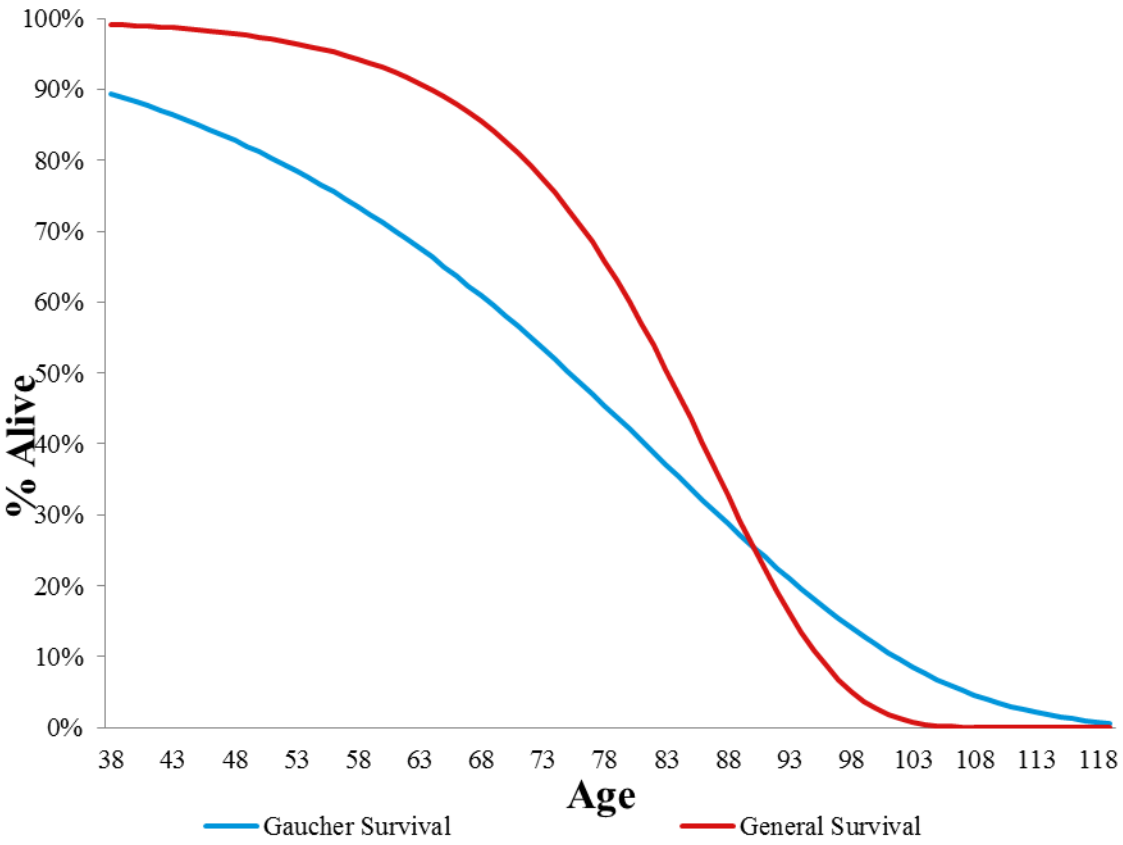
Figure 4 Fitted parametric curves to Gaucher mortality data



As can be clearly seen from Figure 4, neither the Generalised Gamma curve (purple) or the Gompertz fit well to the tail of the distribution, but the Gompertz curve (orange) has better visual fit to the earlier portion of the Kaplan Meier plot when compared with the Gamma curve (purple).The ERG therefore agree that the Gompertz curve selected by the company is likely the most appropriate. Due to the long tail in the predicted survival curves including the Gompertz curve, the mortality rate of patients estimated using these parametric curves is significantly underestimated at older ages. This can be seen Figure 5 in which survival curves for the Gaucher and general population are plotted. This inconsistency is most obvious after 90 years of age when the curves cross, but is also evident at earlier ages when looking at the slope of the curves as after the age of 77 the mortality rate in the general population exceeds that of the of Gaucher patients. The company acknowledge this inconsistency in the data and therefore make the assumption that mortality in the model is equal to the highest predicted mortality rate from either the general population or the predicted Gaucher mortality. To

implement this a Gompertz parametric survival curve was fitted to the general population mortality data (note this is based on the ERG understanding of the executable model as this was not stated in the CS) and then highest mortality rate based on the two predicted survival curves used in the model. This was justified in the CS on the basis that this ensured that the mortality rate used in the model was always higher or equal to that of the general population.

Figure 5 General population and Gaucher survival curves



While the ERG acknowledges the paucity of data on mortality in GD1 patients, it has some concerns regarding the company's approach to integrating mortality in the model. Firstly, the ERG does not understand why the company has chosen to fit a parametric function to the general mortality data given that this is complete data set and requires no extrapolation. The ERG pointed this out to the company at the points for clarification stage. The company's response indicated that they considered their approach the most appropriate commenting and that is was their desire to describe as accurately as possible mortality within the GD1 patients and that the model has the ability to run mortality based on both parametric curve fitting and lifetables. The ERG, however, does not fully understand this response, as the lifetables included in the model appear to be generated based on the fitted values as

predicted by the parametric curve and do not exactly match the raw lifetable data cited as the source of general population mortality. There also is lack of transparency in the company submission regarding which curve was fitted to the generalised population mortality data and why this curve was chosen: this is not mentioned in the CS or in the response to the points for clarification question. The use of a fitted curve to model general population mortality, is however, unlikely to have a significant impact on model results due to the low mortality of GD1 patients; the fact the same mortality rate is applied across all health states; and the fact that mortality rates are applied equally to both treatment and comparator.

Secondly, the ERG considers that the approach taken by the company to modelling mortality is inconsistent and makes somewhat implausible assumptions about the impact of GD1 on mortality. Specifically, the model makes the assumption that GD1 mortality is equal to general population mortality at older ages. This assumption is not supported by any data and would seem optimistic given that patients are likely to have lived with progressive chronic disease for much of their life. The ERG considers that a simpler approach would be to have assumed constant proportional hazard such that the mortality rate in the GD1 population is assumed to be a fixed proportion of mortality in the general population. The ERG acknowledge that this assumption may not hold reality, but given the paucity of data consider it reasonable and far more plausible than the company's assumption that the mortality of GD1 patient's is the same as that of the general population after 77 years of age.

In addition to the above issues the ERG is also concerned about the assumption that mortality risk for GD1 patients is equal for all health states and therefore that mortality risks are independent of disease severity. The consequence of this important assumption is that treatment has no impact on the life-expectancy. The ERG considers this a strong assumption particularly given the evidence presented in Section 6.3 of the CS on life expectancy in untreated patients; instead the ERG considers it more likely that mortality risk would increase with severity of disease. This assertion was also confirmed by the clinical advisor to the ERG. While the current data available on mortality does not consider severity of disease, the ERG considers that it would have been plausible to explore scenarios where mortality increased with severity of disease. The ERG therefore considers a number of alternative assumptions based on the available mortality in which a constant hazard is assumed and in which the mortality rate increases with severity of disease. These analyses are presented in Section 6.

5.2.3.3 Adverse events

Adverse events were included in the model if they occurred in 15% of patients or greater on either eliglustat, imiglucerase or velaglucerase, based on safety data from ENGAGE, ENCORE and published studies and FDA reviews of the adverse effects of imiglucerase and velaglucerase. A total

of 6 adverse events met this criterion: back pain; abdominal pain; joint pain; infusion reaction; URTI; and dizziness.

The ERG noted that these 6 AEs were always more common on velaglucerase than on imiglucerase or eliglustat. However, these are only the common, and possibly mild AEs associated with treatment. Less common, but potentially more significant AEs have not been included.

It is unclear to the ERG how the rates of adverse events presented in CS (CS Table 50) were complied. The sources cited in the CS are imprecise and examination of relevant FDA documents did not identify corresponding numbers. The ERG found that the EPAR report for velaglucerase does indicate that common adverse events are more frequent with velaglucerase than with imiglucerase. The most significant of these being infusion reactions, but these were generally mild and rarely prevented continuation of, or compliance with, the IV therapy. The EMA EPAR report for eliglustat found eliglustat to be well tolerated but stated, "The AEs currently identified were mostly mild and reversible. Most remarkable AEs were cardiovascular disorders including syncope and palpitations, infections predominately of the upper respiratory tract, gastrointestinal disorders including diarrhoea, nervous system disorders, fatigue and asthenia." None of these are considered as AEs of eliglustat in the economic model.

How adverse effects are included in the model as utilities or costs is discussed in Sections 5.2.7.2 and 5.2.8.6

5.2.4 Population

The base-case economic analysis focussed on four different sub-groups of adults with GD1 which are as follows:

- IM and EM patients initiated on treatment for the first time
- PM patients initiated on treatment for the first time
- IM and EM patients stable on ERT
- PM patients stable on ERT

Patients were also divided by metaboliser status as those who are IM or EM are licensed to take 100mg of eliglustat tartrate twice daily, while those who are PM are assumed to take 100mg once daily. It is however assumed that those treated with ERT receive the same dose regardless of their metaboliser status (42.4 U/kg). This issue is discussed further in Section 5.2.9. The population is in line with the NICE scope, with ultra-rapid and indeterminate metabolisers excluded as these groups are outside of eliglustat's licence. In the ENCORE trial 3.1% of patients were ultra-rapid metabolisers, and 2.5% were indeterminate, while in the ENGAGE study 2.5% were ultra-rapid

metabolisers and 7.5% were indeterminate. Therefore, eliglustat is licensed for the vast majority of the GD1 population, and the impact on the trial results of including these patients is likely to be small.

The starting age of patients in the treatment-naïve population was assumed to be 32 years based on the mean age of the ENGAGE trial, while the starting age of patients in the ERT stable population who switch to eliglustat was assumed to be 38 years. Starting age impact on the model results as it influences survival rates within the time horizon of the model, and therefore affects number of QALYs and costs that patients accrue. Underestimating the starting age therefore has the effect of overestimating lifetime differences and vice versa.

The ERG notes that there is significant variability in the age of patients enrolled in different studies and predicted age at initiating treatment. Table 36 presents an overview of data on the age of patients from the ENGAGE and ENCORE trials as well as other published studies. The Wyatt et al[28] study is particularly noteworthy as this was UK based cohort of 150 patients and likely to be the most representative of the UK GD1 patients. This suggests that the age values used in the model potentially underestimate the mean age at which treatment is initiated and the mean age of stable patients. The ERG considers that this patient group is likely to have more representative of the age of patients in the UK than the trial data and as such presents additional scenario analysis using these alternative values in Section 6.

Table 36Age of patient in published studies

Study	Treatment naïve	Treatment stable
ENGAGE	32	NA
ENCORE	27.9	37.6
Phase II	38.0	NA
Wyatt (UK cohort)	35.2	46.4
DS3 score study	44.5	57.8

The initial distribution of patients across health states is summarised in Table 37. These are based on the baseline DS3 score patients enrolled in the ENGAGE and ENCORE studies respectively for treatment naïve and treatment stable patients. The base-line distribution of patients in the model is particular important as it determines the transition probabilities that are used in the model and therefore the impacts both on total QALYs and total costs.

Table 37 Summary of base-line disease severity

Health state	Treatment naïve	Treatment stable
Mild	17.50%	77.12%
Mild with bone/joint pain	0.00%	12.71%
Mild with severe skeletal comp	0.00%	0.00%
Moderate	77.50%	10.17%
Moderate with severe skeletal comp	0.00%	0.00%
Marked	0.00%	0.00%
Marked with severe skeletal comp	5.00%	0.00%
Severe	0.00%	0.00%
Severe with severe skeletal comp	0.00%	0.00%

The ERG note that the populations in the two trials are quite different in terms of the severity of disease, treatment naive patients being predominantly patients with moderate severity disease and treatment stable patients being predominantly patients with mild disease. Further, as noted in Section 4.3 the patient enrolled in the ENGAGE study appeared to have more severe disease than indicated in UK cohort of GD1 patients (Royal Free Hospital).

5.2.5 Interventions and comparators

The economic model presented in the CS compares eliglustat with two ERT's; imiglucerase and velaglucerase.

Patients are assumed to receive their respective treatments over their lifetimes, unless they discontinue and go on to receive another therapy. As described in Section 5.2.3.4, patients are permitted to discontinue therapy in the first three years and then are assumed to remain on therapy until death. In the eliglustat arm, when patients discontinue they are assumed to receive the main comparator treatment which can be either imiglucerase or velaglucerase. Patients discontinuing ERT therapy are assumed to switch to the other ERT comparator.

The comparators used in the model are broadly in line with the NICE scope and clinical practice, however, the model excludes a comparison with milglustat, an alternative SRT, which is licensed for patients with GD1 in whom ERT is unsuitable. Miglustat was included in the final scope issued by NICE but was not incorporated into the analysis as the Company did not deem it to be a relevant comparator. The reason for this stated in the CS is that miglustat is only used in fewer than 2% of adult GD1 patients in England in 2015, and that miglustat is not a replacement for ERT given

concerns over its efficacy and high discontinuation rates, which come as a result of tolerability issues. In their points for clarification the company state that eliglustat would not be expected to be used in place of miglustat. The ERG does not believe that it is reasonable to omit miglustat from the analysis and believe that it is likely that eliglustat would be a direct replacement for miglustat in practice due to them both being oral therapies. The clinical advisor to the ERG concurred that that they would envisage eliglustat replacing miglustat in those for whom ERT is not an option, as they perceive it to be more effective and better tolerated by patients.

5.2.6 Perspective, time horizon and discounting

The economic perspective is the National Health Service (NHS) and the Personal Social Services (PSS) in accordance with the NICE reference case. The reference case indicates that the time horizon used for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs and benefits between the technologies being compared. The time horizon used was 70 years to represent a lifetime time horizon. The ERG considered the time horizon to be sufficiently long as no patients in the model were expected to remain alive after 70 years. Costs and benefits in the model were discounted at an annual 3.5% rate as per the NICE reference case.

5.2.7 Treatment effectiveness and extrapolation

The clinical inputs used in the first year of the model were dependent on whether a treatment naïve population or treatment stable population was under consideration. Where a treatment naïve population was assumed, first year transitions were sourced from the ENGAGE trial and were based on observed changes in changes in DS3 score in the eliglustat arm of the trial. These changes were based on the 39 week follow period of the trial and therefore the model assumed that the changes at 9 months would be equivalent to those at 12 months. Both treatment and comparator arms used the same transition probabilities and therefore the model assumes equal effectiveness in the treatment naive population. For treatment stable patients transition probabilities were sourced from the ENCORE trial which compared eliglustat with imiglucerase. Differential effectiveness was therefore assumed in the stable population based on the results of the ENCORE trial. In both populations the relative effectiveness of the ERT therapies imiglucerase and velaglucerase were assumed to be equivalent.

In both treatment naïve and stable patients, after the first year transition probabilities were based on data from the DS3 score study. The DS3 score study was a cohort study based on data from International Gaucher disease registry. The study enrolled a total of 275 patients who were followed up for up mean period of 10 years. Patients enrolled in the study included patients from a number of countries including the UK and were made up primarily of stable Gaucher disease patients. To model long-transitions the company carried out logistic regression analysis on the data from the DS3 score

study to calculate the odds of transition to different health state. As described in Section 5.2.1 this regression analysis included terms for previous health status and therefore the transition probabilities used in the model depend on the base-line health status of the patients in the model. Both treatment and comparator arms used the same transition probabilities after the first year and therefore equal efficacy is assumed in both treatment naïve and treatment stable patients after the first year.

The ERG has very significant concerns regarding the company's modelling of the clinical data and the assumptions made regarding effectiveness. As outlined in Section 5.2.1, the ERG considers that the use of the DS3 score system as basis for the structure of the model to be problematic. The principal problem being that this scoring system is largely insensitive to change. As a consequence of this the transition probabilities estimated from the ENCORE and ENGAGE trials are often based on the movement of very small numbers of patients experiencing a change in DS3 score. Furthermore, the insensitivity of this disease measure means that the differences in the effectiveness of eliglustat and ERT apparent in the primary outcome of the ENCORE trial are not translated to the transition probabilities used in the model. This is clearly demonstrated by the fact there is almost no difference in the transition probabilities used in the eliglustat and ERT arms of the model. This lack of sensitivity has the effect of biasing the model towards equivalence and therefore underestimates the differences between the eliglustat and imiglucerase observed in the ENCORE study.

The economic model also makes a number of simplifying assumptions regarding relative effectiveness of eliglustat and ERT which are not justified by the relatively limited clinical effectiveness data and are not explored adequately in the presented sensitivity analysis. These assumptions concern both the short-term and long-term effectiveness of eliglustat. With respect to the short-term effectiveness of eliglustat the company's model assumes that eliglustat and ERT are equivalent in treatment naïve patients. The company justify this assumption on the basis that there is a lack of evidence on comparative effectiveness in this population group. However, given the evidence available from the ENCORE trial it seems much more reasonable to use this data to model comparative effectiveness in treatment naïve patients than assume equivalence, particularly as ENCORE did not demonstrate equivalence of the therapies and indeed as discussed in Section 4.X, the claim of a lack of inferiority is itself weak given the large inferiority margin assumed.

With respect to the long-term transitions in the model, the ERG considers the company's approach to be overly complicated and poorly justified. As described above, the company's approach makes use of dynamic transition probabilities to model long-term effectiveness. The CS does not include any justification for the approach and details in the CS are limited to a short appendix which is not referenced in the main body text. Furthermore, because the same transition probabilities are applied to both treatment and comparator arms the actual values used do not fundamentally impact on estimated

incremental differences. The net effect of this approach is likely to be limited due the fact the same transition probabilities are applied to both to the both treatment and comparator arm, however, lack transparency means the ERG has been unable to fully validate this part of the model and has not be able to carry some explanatory due to the clarity regarding which transition probabilities are used in the model.

The application of the same transition probabilities to both treatment and comparator arm is, however, a more important and problematic issue, as it implies the long-term equivalence of eliglustat and ERT. This assumption is crucial to the calculation of long-term benefits and has a considerable impact on estimated incremental QALYs. Specifically, the assumption of long-term equivalence acts to constrain any difference in incremental QALYs regardless of assumptions made about clinical effectiveness in the first cycle of the model. Available evidence on the long-term effectiveness of eliglustat is very limited and comparative evidence is limited to the 12 month follow period in the ENCORE trial: the reported non-inferiority of eliglustat in the ENCORE study. Interpretation of the ENCORE trial results of the non-inferiority of eliglustat to the long-term is problematic for a number of reasons. Firstly, non-inferiority is not equivalence and as discussed in Section 4 the results of the ENCORE do demonstrate that there are differences in the effectiveness of eliglustat and imiglucerase even in the short term. Secondly, non-inferiority in the short-term does not imply non-inferiority in the long term, as small difference in disease control may have a cumulative effect resulting in significant differences in long-term prognosis. Thirdly, attempting to extrapolate results over such a long-term period is inherently uncertain. The assumptions made in the company base-case of long-term equivalence are therefore subject to considerable uncertainty. Furthermore, regardless of the base-case assumptions made, the ERG considers that the lack of any exploration of the impact of alternative assumptions about the relative long-term effectiveness of eliglustat unjustifiable and a significant weakness of the company model. The ERG had hope to carryout additional scenario analysis exploring different assumptions regarding the long-term effectiveness of eliglustat, but in the time available could not fully establish which transition probabilities are being used in the company's base-case analysis.

5.2.7.1 Health state utilities

In order to assign appropriate utility values to each of the many health states in the model the company considered a variety of different sources of utility data, an overview of which is provided below.

The primary source of quality of life data considered by the company was the ENGAGE and ENCORE phase III trials, the Phase II study and Gaucher DS3 multi –site study. In all four studies quality of life data was collected using the SF-36 tool. In the Phase III and II studies utility data was

collected using version 2 of the SF-36 at baseline and then at 39 weeks in ENGAGE, 52 weeks in ENCORE, and at 52, 104, 156 and 208 weeks in the Phase II study. The DS3 score study made use of version 1 of the SF-36, but did not collect data at regular time intervals, so instead the company matched the DS3 measures, and therefore the health state, to the closest responses within a 90 day period around the dates that DS3 scores were measured. Because of this, there is some potential for the estimates to be slightly biased as the utility value might not have been accurately matched to the patients' health states, but the impact of this bias is likely to be minimal. In addition, in order to compare the utility scores across studies, the DS3 study scores were converted to SF-36 version 2 scores, by coding 'yes' responses in version 1 as a 1 for version 2, and the 'no' responses in version 1 as a 5 in version 2. This is a simplified assumption and may again lead to some inaccuracies in the utility scores.

The SF-36 scores for each study were to EQ-5D using the published algorithm by Brazier and Roberts (2004)[43] in order follow the NICE methods guide. Although the approach is appropriate, it should be noted that these methods are imperfect, which may result in some inaccuracies in the EQ-5D results.

To calculate the health state utilities a regression model for utility was fitted separately for each study using generalised estimating equation (GEE) regression model, with a Gaussian error term and the identity link, to account for multiple observations per patient. The company justified the choice not to pool the data from the clinical studies on the grounds that this avoided confounding study design and patient characteristic with health state utility relationships. The utilities for each health state were then calculated by estimating the average predicted utility values for each health state based on the estimated coefficients. Because no patients in the ENCORE and ENGAGE study had marked or severe disease, utilities for these health states were not estimable from the analysis based on these studies. Similarly the Phase II did not include any patients with severe disease and therefore no predicted values were estimable for patients in this health state. The DS3 data, however, included patients with mild, moderate, marked and severe disease and therefore was selected by the company as the most appropriate source of health state utilities. The results of the regression analysis carried out by the company on the DS3 data are presented in Table 38. Utilities were also estimated using dummy variables to represent each health state, but this method resulted in inconsistent results and therefore utilities based on the regression analysis were considered superior.

Table 38: GEE regression results for health state utility based on severity, bone pain, and severe skeletal complications

	Coefficient	**Standard error**	**95% CI**
DS3 Severity (vs. Mild)			
Moderate	−0.078**	0.035	−0.15 – -0.01
Marked	−0.122***	0.046	−0.21 – -0.03
Severe	−0.168**	0.079	−0.32 – -0.01
Bone Pain	−0.098***	0.036	−0.17 – -0.03
Severe Skeletal Complications	0.018	0.040	−0.06 – 0.10
Female	−0.049	0.031	−0.11 – 0.01
Age at Treatment Initiation	−0.002*	0.001	0.00 – 0.00
Constant	0.880***	0.057	0.77 – 0.99
Number of observations	97		
Number of patients	50		

Key: CI, confidence interval; GEE, generalised estimating equation; DS3, disease severity scoring system.
Notes: *** p<0.01, ** p<0.05, * p<0.10.
Source: Ganz et al. 2015[44]

In addition to quality of life measures collected in the clinical trials the company also conducted a systematic review in order to identify any additional HRQL data that was available in the literature. This review identified five studies a summary of which is present in Table 39 below.

Table 39: Summary of included utility studies

Publication	Utilities	Number of participants	Elicitation technique
Clarke et al., 1997[45]	Three Gaucher disease health states valued: Patient 1: 0.87 (0.83-0.91) Patient 2: 0.86 (0.81-0.91) Patient 3: 0.82 (0.78-0.86)	39 healthy participants	Time trade-off
Connock et al., 2006[7]	Mild: 0.82 Moderate: 0.66 Severe: 0.54	n/a	n/a Based on Clarke et al.
Deegan et al., 2011[8]	Patients with a history of osteonecrosis: 0.679 (median) Patients with no history of osteonecrosis: 0.796 (median) Those who had suffered a fragility fracture: 0.626 (median) Those who had not suffered a fragility fracture: 0.796 (median)	100	EQ-5D, Time trade-off
van Dussen et al., 2014[40]	Symptoms/recovery 0.8716 (0.8177-0.9225) Splenectomy 0.7532 (0.6768-0.8215) Bone complication 0.8614 (0.7530-0.9685) Multiple complications 0.7323 (0.6601-0.8202) Malignancy 0.15 (no CI, n=1)	Symptoms/recovery: 17 Splenectomy: 4 Bone complication: 6 Multiple complications : 13 Malignancy: 1	EQ-5D, Time trade-off
Wyatt et al., 2012[28]	Gender Male: 0.00 Female: -0.02 (-0.11, 0.06) Age Linear effect/year: -0.003 (-0.006, -0.0005) Time on ERT Not on ERT: 0.00 <12 months: -0.02 (-0.26, 0.23) 12-36 months: 0.02 (-0.19, 0.23) >36 months: -0.02 (-0.23, 0.18)	214 EQ-5D observations	EQ-5D, Time trade-off

Key: EQ-5D, EuroQoL 5 dimensions; ERT, enzyme replacement therapy.

The company did not consider any of the utilities identified in the systematic review to be superior in terms of relevance to the HRQL data from the DS3 study registry. The main difference between the values reported in the registry and the values found from the systematic review was that the utility's reported in the review tended to generally be higher. The health state utilities used in the cost-

effectiveness model were therefore based on regression analysis of the DS3 study as described above and are summarized in Table 40.

Table 40: Predicted utilities used in cost-effectiveness analysis

Health state	Predicted utility	Standard error	Confidence interval
Mild	0.764	0.028	0.709–0.820
Mild + Bone Pain	0.666	0.022	0.623–0.708
Mild + SSC	0.683	0.046	0.593–0.774
Moderate	0.686	0.020	0.648–0.725
Moderate + SSC	0.606	0.061	0.487–0.724
Marked	0.642	0.038	0.567–0.717
Marked + SSC	0.561	0.058	0.448–0.674
Severe	0.596	0.078	0.443–0.749
Severe + SSC	0.515	0.074	0.371–0.659

Key: SSC, severe skeletal complications.
Note: Error bars depict 95% confidence intervals.
Source: Ganz et al. 2015[44]

The ERG considers the DS3 score study to be an appropriate source of QoL given the health states included in the model, as it provides the most complete set of utility values when compared to the other studies available. However, there are issues with the registry data and the analysis carried out by the company. The first of these relates to the number of observations included in the analysis. The regression analysis presented by the company includes a total 97 observations from 50 patients. Table 33 in the CS however, suggests that there are a total of 275 observations from 101 patients were recorded; there appears to be significant attrition of patients in the analysis presented by the company and the extent to which this attrition is non-random this may impact on the results of the regression analysis due to selection bias. The second issue relates to the decision to analyse the QoL data available to the company separately. The company justify not pooling the four studies available on the grounds that they wish to avoid issues of confounding as a result of differences in patient characteristics and study design. The ERG, however, do not see the relevance of study design to the decision to pool the data, and do not understand how analysing the studies separately will mitigate the impact of confounding: any such effect will occur at the individual patient level. The decision not to combine the data from all four studies serves to reduce the available sample size considerably and as a consequence, increase uncertainty around estimated utilities.

The final issue relates to the estimated impact of severe skeletal complications (SSCs). Only 9% of the 275 observations from the DS3 Score Study were of patients across the mild, moderate, marked and severe states who had SCCs, and it is unclear how many of these were included in the regression

analysis. As a result, the estimates of the impact SCCs in the regression analysis have wide confidence intervals and, and the regression coefficient for SSCs (shown in Table 38: GEE regression results for health state utility based on severity, bone pain, and severe skeletal complications) is positive, which appears clinically implausible given that the occurrence of SSCs is like to represent a more severe health state. Additionally, six of the health states only contain a combined 12% of the DS3 study's 275 observations, meaning that the predicted utility values are estimated from a small number of observations, particularly as only 97 observations were used in the regression analysis. This is particularly an issue for the severe health states, with there being zero observations in the 'severe' state, and two in the 'severe + SSC' state. With such small samples it is difficult to ascertain the accuracy of the values, which brings into question the choice of model structure adopted in the CS. With so few observations per health state available the ERG believe it may have been more appropriate to reduce the number of health states in the model, in order to increase the number of observations for each state. However, it is unlikely that this would have a significant impact on the outcomes of the analysis, due to the assumption of non-inferiority and due to the relatively small differences in the utility values between each state.

5.2.7.2 Adverse Event Disutility

As stated earlier adverse events were included in the model if they occurred in 15% of patients or greater based on safety data from ENGAGE, ENCORE and other published studies. A total of 6 adverse events met this criteria: back pain; abdominal pain; joint pain; infusion reaction; URTI; and dizziness.

The ENGAGE and ENCORE trials did not report HRQL measurements as a results of AEs, so a systematic review was conducted to find data on the impact of the 6 most common AEs. An overview of the searches carried out and the critique are reported in Appendix 2 of the CS. The systematic review of HRQoL carried out by the company identified no studies; the company therefore used published literature to derive to derive utilities. It was not detailed how this "published literature" was identified.

In the absence of reported disutility values, data from the ENCORE trial on the duration of some AEs experienced by trial participants were used to annualise the utility decrement as a result of an AE. If the duration of an event was unavailable then additional published literature and assumptions were used. The adverse event decrements used in the cost-effectiveness model are summarised in Table 40 in the CS.

As the decrements are calculated using such limited data the reliability of the values is unclear. There is also a lack of clarity in the CS relating to the method used to estimate the AE event decrements in the absence of data on the duration of the event.

As noted in Section 5.2.3.3 the model also excludes a number of serious , but less common adverse events. These serious adverse events include a number of serious adverse events experienced primarily by eliglustat patients including

However, the ERG believes that due to the lack of data available that making use of additional published literature is reasonable, and is likely to have minimal impact on the results due to the adverse event profile being comparable between the intervention and comparator arms.

5.2.7.3 Oral Therapy Increment

The cost-effectiveness model also formally incorporates patients' reported preference for oral therapy over infusion therapy in the base-case analysis via a utility increment of 0.12, which is applied in every cycle. This value was taken from a vignette study which was commissioned by the company [46]. The study included 100 patients from the general population who were enrolled based on their socio-demographic characteristics to approximate the UK general public. The mean age of participants was 35 years, and 66% were female. The authors developed five different health state descriptions which were validated by a clinician and piloted on six members of the general public. The first state described a scenario were an individual had GD1 but whose disease was under control through treatment, without making any reference to the type of treatment received. The second and third states posed the same scenario, however one stated that treatment would be administered orally, and another intravenously.

The study used EQ-5D, and elicited utility values from participants using the time trade off method. The CS supports these findings by referring to the ENCORE trial, where 92% of patients on eliglustat responded to a survey that found that 100% of these patients preferred oral treatment over the infusion therapy they had previously received. The utility increment is applied in every cycle of the analysis regardless of treatment duration. The ERG has several issues with incorporating this value into the base case analysis.

It is likely that there will be improvements in quality of life attributed to patients taking an oral treatment instead of receiving an IV therapy. These improvements will stem from increased convenience attributed to not having to receive an IV infusion at home or in hospital every two weeks. However, it is not clear whether these benefits would yield quality of life gains due to improved health, or whether the differing method of administration would result in an improvement in general quality of life instead. Any benefits directly related to health have already been incorporated using data on the efficacy of the treatments, and by including an adverse event decrement associated with infusion related issues which may come as a result of ERT.

The NICE methods guide states that in the reference-case, benefits should be valued in terms of health related quality of life, measured using QALYs. It also states that there may be reasons to apply non-reference-case methods but that these should be clearly stated and justified. This therefore raises the question as to whether this increment should be formally implemented in the base-case analysis as presented in the CS, or whether these benefits should be considered separately. A judgement needs to be made about whether this increment is capturing benefits related to health, or whether non-health related quality of life should be considered in the base-case analysis: incorporating this increment in the base-case analysis would set a precedent for future technology appraisals.

The ERG were originally only supplied with the results of the study and not the methods, however, the fully study report was later provided after a request from the ERG. Examination by the ERG of the methods of this study identified that the wording of the questions posed to participants to elicit their utility valuations potentially captured aspects unrelated to the mode of administration.

The health state description for IV therapy states,

> 'You also need to consider your access to treatment when travelling as the infusion must be administered by, or under, the supervision of a healthcare professional.'

This contradicts the company's analysis which assumes that 48% of GD1 patients receive ERT therapy at home with no supervision from a healthcare professional. As patients do not need supervision this health state description over-states the inconvenience caused by receiving IV therapy, and therefore may result in the oral therapy utility increment being over-valued.

Also, the health states presented to participants for oral therapy and for IV therapy do not just differ in terms of the route of administration. The IV health state says that patients may experience, 'a reaction to the drug resulting dizziness or a rash', whereas the oral therapy health state says that patients may experience, 'a minor side-effect such as temporary diarrhoea'. This difference in adverse event profile removes parity between the two states, meaning that the utility increment calculated may not reflect the benefits of the route of administration, but also differences in the adverse event profile.

In addition, the IV health state describes that 'there is a small chance you may experience an infusion-related reaction (discomfort, burning, swelling)'. However, the model already includes an adverse event utility for infusion reaction of '-0.011', meaning that the analysis will be double counting this disutility.

Finally, if the benefits of treatment administration are incorporated into the base-case analysis, then there are potential issues relating to the 0.12 utility value that is implemented as the benefit of oral

therapy. This increment is relatively large, when compared, for example, to the adverse event disutilities incorporated into the analysis. Back pain was assumed to have a disutility of -0.0187, joint pain -0.0012, abdominal pain -0.0006, URTI -0.0001, and dizziness -0.0004. Use of the 0.12 value means that patients over the time horizon of the cost-effectiveness model are willing to exchange 2.29 years of full health in order to have the increased convenience of taking an oral therapy over an equally efficacious ERT. If an extreme scenario is assumed in which patients experience '0' utility for the two hours they spend each fortnight receiving ERT and a utility of '1' otherwise, then the decrement each fortnight would be equal to '-0.005'. In this scenario you would have to experience a utility of '0' for 1.68 days as a result of ERT in order for the oral therapy increment to equal '0.12'. This value is implausibly large given that patients receive ERT for approximately two hours once every two weeks, and that 96% of these patients receive therapy at home.

Estimates presented in the literature and utilised in other NICE technology appraisal's which have been identified by the ERG cast further doubt on this value of 0.12. There is evidence to demonstrate that patients have a clear preference for oral over IV treatments when they are of a similar efficacy (Liu et al. 1997, [47] Twelves et al., 2005)[48] and that periods of stable disease on oral therapy are valued more highly than those on IV treatment [49]. However, a study by Liu et al. 1997 in patients with cancer found that although 92 of the 103 assessed patients stated a preference for oral therapy over IV, 70% were not willing to accept a lower response rate, and 74% were not willing to accept a shorter duration of response to maintain this preference.[47]

TA162 investigated erlotinib, an oral therapy for the treatment of non-small-cell lung cancer, versus chemotherapy[50]. This appraisal incorporated a utility decrement of '0.025' which was taken from a study conducted by Tabberer et al. 2006[49]. This study explored the impact of non-small-cell lung cancer on quality of life by eliciting utilities from a community sample of 154 people across the UK. Health states were valued using the EQ-5D, with the decrement calculated by taking the difference between the utility of patients with stable disease receiving IV therapy, and the utility of patients receiving an equally efficacious oral therapy. Hux et al. 2015[51] conducted a utility study in Canada on women suffering from symptomatic uterine fibroids. The study calculated a utility decrement of 0.02 when comparing treatment by injection to oral therapy. The study commissioned by the company which generated an increment of '0.12' stated that this 'level of burden is on par with that suggested of the use of subcutaneous insulin in diabetes'. The study that is referenced is one by Ericsson et al. 2013,[52] which evaluates the cost-utility of two types of insulin. The treatments differ both in terms of their treatment effectiveness, but also in the flexibility with which doses can be taken. The study therefore makes use of a disutility for inflexible dose timing of '0.015' which is taken from a time trade-off survey conducted by Evans et al. 2013.[53] Therefore, it is unclear why the study

commissioned by the company claimed that the value of '0.12' was comparable to the value reported in Ericsson et al. 2013.[52] Although all of these studies are not completely generalizable to the decision problem as they investigate different diseases and different therapies, they highlight the large difference in the findings presented in the CS and values found in the literature, which raise doubts around the validity of the estimate produced.

In summary, The ERG suggest that the inclusion of a utility for oral therapy is not within NICE standard methods. Furthermore the methods used to derive the utility value used by the company are not robust and involve some double counting and the value generated is implausibly high.

5.2.8 Resources and costs

5.2.8.1 Treatment costs for patients treated with eliglustat

In line with the licence for eliglustat, patients in the model were assumed to take either two 100mg capsules daily or one 100mg capsule daily according to their metaboliser status: patients with IM or EM status were assumed to receive two capsules per day; patients with PM status were assumed to receiving one capsule per day. The anticipated price per capsule for eliglustat is £282.34. Assuming an annual dose of 730.5 capsules for IM and EM patients and 365.25 capsules per year for PM patients the annual drug acquisition costs per annum for eliglustat by metaboliser status are respectively £206,249.37 and £103,124.69.

The ERG considers the dose of eliglustat used in the model is in line with what is likely to be used in practice, however, notes an inconsistency between the dose used in the model and that used in the ENCORE trial. In the ENCORE study a significant number of patients (48%) received a higher dose of eliglustat of 150mg BID for the majority of the trial period. As noted, in Section 5.2.7 this inconsistency may mean that that the effectiveness observed in practice may not be the same as that observed in the ENCORE trial. Increasing the dose used in the model such that it matches the ENCORE trial increases the drug acquisition costs of eliglustat and as a consequence significantly increases total costs; this scenario is presented in Section 6. It should be noted that the ERG does not consider this to reflective of how eliglustat will be used in practice, however, this scenario means that both the dose of eliglustat and ERT reflect doses used in the ENCORE trial and therefore costs align with the effectiveness data used in the model.

5.2.8.2 Administration and delivery for patients treated with eliglustat

No administration costs were included the model for eliglustat, the ERG assumes that this is due to the fact that eliglustat is an oral therapy and therefore self-administered (this was not stated in the CS). However, a delivery cost of £40 per month (£480 per year) for eliglustat was included in the model to represent the cost of delivering the drug to the patient's home.

The ERG sought further clarification on how delivery of the drug to the patients would operate at the points for clarification stage. The company response was as follows:

"Healthcare professional (HCP) writes prescription for patient for eliglustat and sends to Homecare Company that the patient is already receiving current therapy under. Homecare Company (HCC) arranges delivery to patient at either home address or nominated patient address. This delivery could be 1, 2 or 3 months' worth of eliglustat but this would be determined by the HCP/ treating centre/ prescription..."

The ERG is satisfied that the costs of the process seem reasonable though note that costs of the healthcare profession writing the prescription are not accounted for in the model. The ERG also notes that in previous assessments by NICE of oral therapy the committee have noted that administration costs are not likely to be zero.[54, 55] In line with the recent appraisal of Ceritinib the ERG therefore considers at a minimum pharmacy dispensary costs should be included to represent the cost of administering eliglustat. Scenario analyses including this additional cost are presented in Section 6.

5.2.8.3 Treatment costs for patients treated with ERT

Patients receiving either of the ERT therapies imiglucerase or velaglucerase were assumed to receive a bi-weekly IV treatment and therefore a total of 26.09 treatments per annum. The dose of ERT was based on the dose of imiglucerase received in the ENCORE trials of 42.4 U/kg with patients assumed to have mean body weight of 67.5 kg based on the mean weight of patients in the imiglucerase arm of the ENCORE study. The unit and annual costs of are each ERT therapies are summarized in Table 41.

Table 41: ERT unit costs

Drug	Tablet dose (pack size) /vial dose	Cost per vial/pack/capsule	Source
Imiglucerase	200U	£535.65	BNF 2014[56]
	400U	£1,071.29	
Velaglucerase	400U	£1,410	MIMS 2015[57]
Key: BNF, British National Formulary; MIMS, Monthly Index of Medical Specialities.			

These list prices, however, do not represent the prices faced by the NHS for the two drugs. The ERG was however, given access to confidential data on the prices paid by the NHS for imiglucerase and velaglucerase. These revised prices include a discount currently in place for velaglucerase. These revised prices are described in a confidential appendix to this document along with a complete set of analyses including the company's base and all analysis carried out by the ERG.

With respect to the dosing of ERT treatment the ERG has identified a number of issues regarding the values used in the model. The first of these issues relates to the calculation of drug costs. The model

currently assumes patients receive a total of 2862 units every two weeks; this was based on data from the ENCORE study in which patients' mean weight of 67.5 kg was multiplied by the mean dose per kilo of 42.4 U/kg. The cost per annum is then calculated by calculating the cost per unit of imiglucerase and velaglucerase, which is respectively £2.68 and £3.53 and multiplying the number of units per treatment by the cost per unit and treatments per year. The ERG has three concerns with this approach. Firstly that it does not account for any vial wastage, secondly that the assumed dose may be incorrect; and thirdly it assumes treatment naïve patients and ERT stable patients use the same dose of ERT.

Both ERT therapies are sold in specific vial sizes and as such there is the potential for wastage resulting from the partial use of vials. The ERG raised this issue with the company who suggested that where doses did not allow for a complete vial to be used, this is likely to be wasted as there are limited opportunities for vial sharing, and that partially used vials have a short shelf life and hence could not be stored until the next treatment. This issue was also raised with the clinical advisor to the ERG, who agreed that where incomplete were used opportunities to avoid wastage would be limited. The clinical advisor, however, also stated that clinicians would seek to avoid wastage wherever possible due to the high costs of ERT treatments. To the extent that this is the case the approach taken by the company of omitting drug wastage is reasonable and likely to reflect mean drug acquisition costs. The ERG, however, considers that there is at least the possibility of some wastage, particularly for velaglucerase which is only available in the larger 400U vial size, and therefore additional scenarios are explored in Section 6 which assess the impact drug wastage has on total costs.

Regarding the dose of ERT used in the model of 42.4 U/kg every 2 weeks this figure is based on the mean dose of imiglucerase received in the ENCORE study. As discussed in Section 4.6 the considerable evidence to suggest that substantially lower doses are used in practice. The SOP, (developed to assist commissioning of services for adult Gaucher disease in England) reports that a maintenance dose of 15-30 Units (U)/kg every two weeks is appropriate for most patients. Further, the clinical advisor to the ERG advises that a typical dose of ERT is 25 U/kg (range: 15-28 U/kg) and a practitioner submission to NICE for this appraisal also stated that a typical dose of ERT reported doses of 20-40 U/kg. A review of six studies carried by the ERG, into typical prescribed dose of ERT treatments presented in Section 4.6 suggests a plausible range of doses to between 17.1 U/kg and 33.75 U/kg every two weeks. Further, based on UK prescribing data for of 100 GD1 patients in England the mean dose of ERT used in clinical practice is 25 U/kg.

The ERG is therefore concerned that the dose of ERT treatment assumed in the model substantially overestimates the typical dose used in practice and as a consequence, dramatically overestimates the drug acquisition cost associated with ERT. The ERG raised this issue with the company at the points

for clarification stage and in particular asked the company to comment on the external validity of the ENCORE study. The company response raised a number of points which are explored below.

The company noted that the ERT dosing in the ENCORE study is based on international real life clinical dosing and that the dose used in the trial is that on which patients had been stabilised prior to commencement of the trial. The ERG note that while the ENCORE trial may be reflective of international practice this does not imply that it is reflective of practice in the UK, particular as many of the centres in the ENCORE trial were based in the United States where attitudes to dosing and cost may be quite different.

The company then go on to note that lower doses of ERT seen in clinical practice in the UK compared to the dosing seen in the ENCORE trial may be associated with reduced effectiveness. As noted in Section 4.6, there is some evidence of dose response relationship with the use of ERT therapies and as such the use of lower dose in clinical practice may mean that effectiveness is reduced relative to that observed in the ENCORE study. This may mean that the effectiveness observed in the ENCORE would not be observed in practice in England. However, as the company also note in their response to the ERG clarification question, the recommended dosing for ERTs in the UK Gaucher Disease SOP is related to symptoms, with higher doses recommended where therapeutic goals have not been met. In so far as clinical practice reflects the UK Gaucher Disease SOP, clinicians are already dosing patients in such a way to maintain stability and dependent on clinical need. Furthermore, as discussed in Section 4.6 there evidence that substantial evidence to suggest that lower doses of ERT can be used to maintain stability. Higher doses may therefore not necessarily lead to significantly improved outcomes as clinicians are already dosing to maintain disease control.

The ERG also note the apparent inconsistency between how eliglustat and ERT dosing are used in the model, as in the ENCORE study patients on eliglustat also received a higher dose than is likely to be used in clinical practice, yet for cost purposes it was assumed by the company that the lower dose would be used. The ERG considers the impact of alternative doses of ERT on costs in Section 6, though no allowance is made for any reductions in effectiveness due to the difficulty in adjusting the effectiveness data appropriately.

A further issue relating to the dose of ERT used in the model is that treatment naive patients are assumed to receive the same dose of ERT as stable patients. Evidence on practice regarding dosing of ERT in treatment naïve patients is limited, and is likely to vary. The SPC and SOP suggests initial dosing of 60U/kg, and the evidence suggest that initial doses of ERT will be higher in treatment naïve patients than among stable patients to bring haematological and visceral factors under control and then subsequently adjusted and reduced on an individual patient basis until an appropriate stable dose

can be established. A review article describing the use of the ERT in the treatment of Gaucher disease described the process as follows:

> "The treatment phases are: *initiation*, followed within 6-12 months by an *adaptation* phase in which dose adjustments are made to reach optimal symptom relief, therapeutic progress and surrogate parameter control. After *stabilization* of the disease process, which usually takes a couple of years, the enzyme dosage can be decreased (*tapering*), to reach a stable dose that the patient receives for the rest of his or her life (*maintenance*)." p.g.149

However, there is also evidence to suggest that initial doses can actually be lower dependent on the approach of treating clinician; with doses increased as needed rather than reduced.[58] Advice from the ERG's clinical advisor also highlighted that newly diagnosed adults are typically less severely affected than patients who initiate treatment in childhood and as such typically do not require such intensive dosing. The company's approach to assume a fixed dosing regimen based on the dose received in already stabilised patients may therefore not be appropriate. Given that there is some uncertainty regarding the approach used in the UK with regard to the dosing of treatment naive patients, the ERG presents two additional scenario analyses in Section 6: one in which higher a higher initial dose is assumed in the first two years of treatment; and a second in which a lower doses of ERT is assumed in the first two years of treatment. Further details of this analysis are included in Section 6.

5.2.8.4 Administration and Delivery for patients treated with ERT

Patients receiving ERT treatment are assumed to do so in one of three ways:

- Self-administration at home;
- Nurse supported administration at home;
- Day unit hospital attendance.

The proportion of patients receiving ERT by each administration strategy is presented in Table 42. Derivation of the proportions was based on the following assumptions:

- That 96% of patients would receive ERT in a home setting either with or without nurse support;
- That 50% of administrations at home would require nurse support.

These figures were derived from practice at the UK treatment centres, responsible for the management of approximately 80% of GD1 patients in the UK (Addenbrooke's Hospital, Cambridge and the Royal Free Hospital, London).[59]

The unit costs and proportions of patients assumed to receive IV treatment in each setting are presented in Table 42.

Table 42: Cost and setting of administration of intravenous (IV) ERT

Administration Setting	Proportion	Annual cost	Source
Cost of nursing support	NA	£114*26.09=£2,974	PSSRU 2015. 10.1: Community nurse. Unit cost per hour of patient-related work, including qualifications. Assumed 2 hour infusion time (2 x £58)[60]
Home: independent administration	48%	£11,624=£199,976*0.073-£2,974	Assumption that homecare costs are 7.3% of list price of imiglucerase[61] minus cost of nursing support
Home: with nurse support	48%	£14,598 =£199,976*0.073	Assumption that homecare costs are 7.3% of list price of imiglucerase[61]
Day unit (haematology)	4%	£309.45* 26.09=	NHS Reference costs 2014-2015: Other haematological or Splenic Disorders with CC score 0-2 – Day Case
Key: PSSRU**,** Personal Social Services Research Unit.			

The cost of home administration of ERT was assumed to be 7.3% of the list price of imiglucerase.[61] This was assumed to cover the cost of providing delivery of the drug to the home, nursing costs and the provision of a refrigerator and administration pump: this cost was £559.52 per treatment. For patients not requiring nursing support the cost of administering ERT was assumed to be this figure minus the cost of nursing care: £445.53 per treatment. The cost of nursing care was based on the cost of a community nurse, with a 2 hour infusion time (data taken from the PSSRU). Costs of a hospital infusion was taken from NHS Reference costs "Other haematological or Splenic Disorders with CC score 0-2 – Day Case" and assumed to be £309.45 per hospital attendance.

The ERG considers the administrative costs for ERT delivered at home assumed by the company to be excessive and not reflective of actual costs likely to be incurred. The ERG does not consider it plausible that the costs of home administration are greater than the costs of administration in hospital. A number of studies have compared the cost-effectiveness of in home administration of IV therapies with in hospital administration of IV therapies and have consistently found the cost of in home administration of IV therapies to be lower than that of in hospital administration.[62-64]However, there is a paucity of publicly available data specifically to Gaucher disease patients in the UK regarding the relative costs of IV infusion at home compared with in hospital administration. NICE, were, however, able to supply the ERG with confidential data from the CMU on the rates charged by the by the 3 different homecare companies on the framework. This data suggest the costs of administration for home based ERT treatment are substantially less than those used in the company's base case model. This data, however, is present in a format that could be meaningfully incorporated into the company's model in the time available and therefore could note carry out analysis using this data. Instead the ERG present scenario analysis in which administration costs for home IV is assumed to be equal to

the cost of hospital IV. Given the confidential data this scenario is likely to still overestimate the administrative costs of home IV, but is more realistic than the company's base-case assumptions.

5.2.8.5 Monitoring and management costs

The CS incorporated monitoring and management costs associated with the care of patients with GD1. These costs were assumed to vary with severity of disease with greater resources required by patients with more severe disease. The level of resources required in each health state was based on figures published in the literature and clinical expert opinion from a clinician caring for patients with GD1 at a specialist centre in the UK. The costs incurred in the monitoring and management of GD1 patients was assumed to be divided into five categories:

- Medical services - which were assumed to reflect costs associated with visits to the general practitioner (GP) and therapist (counsellor, psychologist, physiotherapist and occupational therapist).
- Specialist centre based care - this was assumed to include visits with specialists nurses, support from a nurse at the centre and monitoring tests (i.e. haematological, organ volume, bone marrow burden, and bone density), and face-to face consultations with a specialist/consultant.
- Hospital based care - this assumed to include all hospital visits such as visits for orthopaedic-related procedures for joint replacement, fracture avascular necrosis, lytic lesions, and accident and emergency attendances
- Social services - this includes provision of home help, housing worker and social worker. This is assumed to be used by all patients with severe skeletal complications.
- Bisphosphonates - drug costs associated with the provision of bisphosphonates for the management of osteoporosis. It was assumed that patients would receive treatment for an average of six years and that the proportion of patients effected would increase with severity of disease.

The frequency of resources used by health state are presented in Table 43, unit costs are lists in Table 44 and annual resource use costs by health state are presented in Table 45. The ERG has consulted with advisor with the clinical advisor to the ERG regarding the assumed levels of resource use and consider them broadly reasonable and reflective of current practice in the UK. Assessment of the costs assigned to each resource is also considered reasonable by the ERG and as such the health stated costs assumed in the model are considered to be broadly reflective of what would be incurred by the NHS.

Table 43 Frequency of healthcare resources used by health state

	DS3 Health State																	
	1		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**	
Resource use	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**
Medical services																		
GP visits	100	1	100	4	100	4	100	1	100	4	100	4	100	4	100	4	100	4
Counsellor	1	3	1	3	1	3	1	3	1	3	1	3	1	3	1	3	1	3
Other therapist	4	2	4	2	4	2	4	2	4	2	4	2	4	2	4	2	4	2
Psychologist	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
Occupational therapist	0	0	0	0	100	1	0	0	100	1	0	0	100	1	0	0	100	1
Physical therapist	0	0	0	0	100	3	0	0	100	3	0	0	100	3	0	0	100	3
Specialist centre based care																		
Nurse clinic visit	100	2	100	2	100	2	100	2	100	2	100	2	100	2	100	2	100	2
Nurse management calls	100	26	100	26	100	52	100	26	100	52	100	52	100	52	100	52	100	52
Consultant clinic visit	100	2	100	2	100	2	100	2	100	2	100	2	100	2	100	2	100	2
Blood counts and CHITO	100	2	100	2	100	2	100	2	100	2	100	2	100	2	100	2	100	2
Bone marrow burden MRI	100	0.2	100	0.2	100	0.2	100	0.2	100	0.2	100	0.2	100	0.2	100	0.2	100	0.2
Dexa scan	100	0.2	100	0.23	100	0.23	100	0.23	100	0.335	100	0.335	100	0.335	100	0.335	100	0.335
Abdominal imaging	0	0	0	0	100	1	100	1	100	1	100	2	100	2	100	2	100	2
Hospital based acute care																		
Liver/lung disease inpatient stay	0	0	0	0	0	0	0	0	0	0	100	0.5	100	0.5	100	0.5	100	0.5
Orthopaedic inpatient	0	0	0	0	10	1	0	0	10	1	0	0	10	1	0	0	10	1

	DS3 Health State																	
	1		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**	
Resource use	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**	**% use**	**#/ year**
stay (with hip/joint replacement)																		
Orthopaedic inpatient stay (without joint replacement)	0	0	0	0	90	1	0	0	90	1	0	0	90	1	0	0	90	1
A&E visits	0	0	0	0	5	2	0	0	5	2	0	0	5	2	0	0	5	2
Social services																		
Social worker	0	0	0	0	2	1	0	0	2	1	2	1	2	1	2	1	2	1
Home help/care worker	0	0	0	0	3	145	0	0	3	145	3	145	3	145	3	145	3	145
Housing worker	0	0	0	0	1	5	0	0	1	5	1	5	1	5	1	5	1	5
Treatment of osteoporosis(proportion of patient requiring annual care)																		
Bisphosphonates		0		10		10		10		45		45		45		45		45

Table 44: Unit costs of healthcare resources and data sources

Resource use	Unit cost (2013 GBP [£])	Source of cost estimate	Source of frequency estimate
Medical services			
GP visits (per hour)	£37.00	PSSRU 2015.[65] 10.8b: General practitioner – unit costs. Per patient contact lasting 11.7 minutes, including direct care staff costs, without qualification costs	KOL[66]
Counsellor (per consultation)	£50.00	PSSRU 2014.[67] 2.8: Counselling services in primary medical care. Unit cost per consultation	Wyatt et al.[28]
Other therapist (per hour)	£44.00	Assumed to be equal to occupational	Wyatt et al.[28]
Psychologist (per hour)	£74.00	PSSRU 2015. [65] 9: Cost per working hour Band 8b. Chapter 18: Clinical Psychologist (Band 8a-b) Face to face cost not reported.	Wyatt et al.[28]
Occupational therapist (per hour)	£44.00	PSSRU 2015. [65] 9.2: 11.5: Cost per working hour Face to face cost not reported.	KOL[66]
Physical therapist (per hour)	£36.00	PSSRU 2015. [65] 9: Cost per working hour Band 5. Chapter 18: Physiotherapist (Band 5). Face to face cost not reported.	KOL[66]
Specialist centre based care			
Nurse clinic visit (1+ hour)	£416.71	NHS Reference costs 2014/15[68] WF01A: Non-consultant led face to face outpatient attendance, follow-up - Clinical Genetics (311)	KOL[66], Deegan 2005[16]
Nurse management calls	£31.01	NHS Reference costs 2014/15 [68] N29AN: Community Health Services - Nursing: Other Specialist Nursing, Adult, Non face to face	KOL[66]
Consultant clinic visit	£433.18	NHS Reference costs 2014/15 [68] WF01A: Consultant led face to face outpatient attendance, follow-up - Clinical Genetics (311)	Deegan 2005[16]
Blood counts and CHITO	£4.20	NHS Reference costs 2014/15[68] Sum of: DAPS04: Clinical Biochemistry. Total. DAPS05: Haematology. Total.	Deegan 2005[16]
Bone marrow burden MRI	£111.90	NHS Reference costs 2014/15[68] Average of IMAGOTH - RA01A: MRI scan, 1 area, no contrast, 19+ years RA04Z: MRI scan, 2-3 areas, no contrast RA07Z: MRI scan, extensive repositioning and /or >1 contrast	KOL[66], Assumption: one received every 5 years

Resource use	Unit cost (2013 GBP [£])	Source of cost estimate	Source of frequency estimate
		agent.	
Dexa scan	£59.44	NHS Reference costs 2014/15[68] DIAGIMOP - RD50Z: Dexa Scan	KOL[66], For disease state 1, 5 yearly. For disease state 2 - 4, 10% every other year; 90% 5 yearly. For disease state 5 - 9, 45% every other year, 55% 5 yearly.
Abdominal imaging	£92.03	NHS Reference costs 2014/15[68] Sum of: DIAGIMOP – RD40Z: Ultrasound Scan, < 20 minutes Consultant led outpatient attendance: WF01B: Non-admitted face to face attendance, first – Diagnostic imaging	KOL[66]
Hospital based acute care			
Liver/lung disease inpatient stay	£1,652.02	NHS Reference costs 2014/15[68]. Liver enlargement and pulmonary arterial hypertension. Weighted average of non-elective long and short stays by number of FCEs:	Patients in more severe health states assumed to be admitted every other year, KOL input[66]
Orthopaedic inpatient stay (with hip/joint replacement)	£3,855.58	NHS Reference costs 2014/15[68]. Sum of: Elective inpatient stay: Weighted average of HN13A-F, HN23A-C, HN53A-C, by number of FCEs – Trauma and Orthopaedics REHABL2 - VC18Z: Rehabilitation for joint replacement	KOL[66], 10% of patients with skeletal complications assumed
Orthopaedic inpatient stay (without joint replacement)	£1,351.78	NHS Reference costs 2014/15[68]. Weighted average of Elective inpatient stays by number of FCEs: WH08A-B Unspecified Pain with CC Score 0-1+, HD23H HD23J	KOL[66], this assumes anyone with a fracture, AVN or lytic lesion is admitted to hospital.
A&E visits	£113.55	NHS Reference costs 2014/15[68]. Accident and emergency services. Weighted average of TA01NA-TA04NA by number of FCEs. All A&E visits not leading to admission.	KOL[66], assumed 5% of patients with skeletal complications
Social services			
Social worker	£179	PSSRU 2013[65, 69]. 11.2: Social worker (adult services) unit costs per hour £79 (including qualifications)	KOL[66]
Home help/care worker	£24	PSSRU 2015[65 67] 11.6: Home care worker. Per hour of weekday face to face contact	KOL[66]
Housing worker	£24	PSSRU 2015[65 67] 11.6: Home care worker. Per hour of weekday face to face contact. Assumed same as home help	KOL[66]

Resource use	**Unit cost (2013 GBP [£])**	**Source of cost estimate**	**Source of frequency estimate**
Treatment of osteoporosis			
Bisphosphonates	£107.22	MIMS 2015 and eMIT 2015	See table below
Key: AVN, avascular necrosis; A&E, Accident and Emergency; eMIT electronic market information tool, GP, general practitioner; KOL, key opinion leader; MIMS, Monthly Index of Medical Specialists; MRI, magnetic resonance imaging; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.			

Table 45: Annual healthcare resource costs by health state

Disease state	Annual direct medical service costs	Annual social services costs	Total costs per health state per year
1. Mild with no clinical symptoms of bone disease	£2,583.05	£0.00	£2,583.05
2. Mild with bone pain	£2,707.01	£0.00	£2,707.01
3. Mild with SSC	£5,371.82	£108.02	£5,479.84
4. Moderate with no SSC	£2,688.03	£0.00	£2,688.03
5. Moderate with SSC	£5,385.57	£108.02	£5,493.59
6. Marked with no SSC	£4,536.95	£108.02	£4,644.97
7. Marked with SSC	£6,303.61	£108.02	£6,411.63
8. Severe with no SSC	£4,536.95	£108.02	£4,644.97
9. Severe with SSC	£6,303.61	£108.02	£6,411.63
Key: SSC, severe skeletal complications.			

5.2.8.6 Adverse event cost

To populate the costs of adverse events a systematic literature review was carried out to identify relevant costs in patients with Gaucher disease. A critique of the search for this review is presented in Appendix A. The inclusion and exclusion criteria of this review are presented in Table 46 below.

Table 46: Inclusion and exclusion criteria for cost and resource use search of relevant adverse events

Inclusion criteria		
Category	**Criteria**	**Rationale**
Study type	Primary studies, economic evaluations reporting cost and/or resource use outcomes, costing studies of trial patients	Both these study types may report relevant values.
Population	Studies will include adult patients with Gaucher disease	The aim was to restrict the search to the relevant population.
Interventions/comparators	No restriction by treatment.	Any costs were to be included if they were relevant adverse events, regardless of treatment status
Outcomes	Any outcomes quantifying the costs and/or resource use requirements of the listed adverse events, as incurred by the NHS in the UK and Ireland	These are the appropriate methods for obtaining relevant costs and resource use
Language	Studies must be available in English.	
Exclusion criteria		
Category	**Criteria**	**Rationale**
Publication type	Systematic and non-systematic reviews, letters and comment articles	These study types are not appropriate.
Publication date	Studies published before 1 January 1990	The first Gaucher disease therapy, imiglucerase, only became available in 1997 when it was approved by the EMA
Key: EMA, European Medicines Agency; NHS, National Health Service.		

This review, however, identified no relevant studies and therefore the company opted include no adverse event costs in the model. This was justified on the basis that the majority rates of AEs applied in the model are not severe enough for additional costs to be incurred. The ERG does not consider the exclusion of adverse event costs to have been adequately justified and considers further efforts could have been made to identify the costs associated with the listed adverse events. For example, the company could have rerun the systematic review considering a broader range of disease areas where ERT is used or elicited values based on clinical expertise. The ERG, however, considered that the impact of excluding adverse event costs on total costs is likely to be small due given the significant drug acquisition costs associated with all treatments. Due to the limited time available to the ERG and the small impact on total costs the ERG do not present further analysis in Section 6 including adverse event costs.

5.2.9 Budget impact model

The budget impact model presented in the company submission calculates the cost implications to the NHS of NICE recommending eliglustat as treatment option for GD1 disease. The budget impact model assumes a five year time horizon and is based directly on estimates of total costs generated by the cost consequence model. It therefore implicitly makes all the same assumptions regarding the costs of eliglustat and the comparator ERT therapies, including assumptions about dosing of therapies, administration costs, and monitoring and management costs. All of the issues raised by the ERG in the previous sections relating to costs will therefore impact on the estimated budget impact.

The budget impact model assumes that the GD1 population is made up entirely of IM and EM patients. The size of the Gaucher population is calculated from prevalence data for GD1 in the UK obtained from company held market share data. This estimates the size of the Gaucher population to be [redacted] in the UK. Of these it is assumed that 200 (84%) reside in England and of these that 86% ([redacted]) are assumed to be over the age of 18 and therefore eligible for treatment with eliglustat. The budget impact additionally assumes that the prevalent population of Gaucher patients will increase by 0.4% per annum and that [redacted] new Gaucher patients will become eligible for treatment each year. The budget impact does not account for the impact of mortality in calculating the total size of the Gaucher population and therefore the total size of the Gaucher population increases over time.

In the scenario where eliglustat is not available total costs are calculated assuming all patients receive ERT. Based on Genzyme's (the company) market share datait is assumed that 48% of patients will receive imiglucerase and 52% velaglucerase. New Gaucher patients are similarly assumed to receive imiglucerase 48% of the time and velaglucerase 52% of the time. The number of patients each year receiving imiglucerase and velaglucerase where eliglustat is not available is presented in Table 47.

Table 47 Number of patients receiving imiglucerase and velaglucerase where eliglustat is not available

Treatment	2017	2018	2019	2020	2021
Stable on imiglucerase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stable on velaglucerase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initiating on imiglucerase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initiating on velaglucerase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative total patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In the scenario where eliglustat is available it assumed that a proportion of ERT stable patients switch from their current therapy to eliglustat. The proportion of switching patients is based on predicted uptake from market analysis carried out by the company. It is assumed that all newly diagnosed

Gaucher patients receive eliglustat. The number patients receiving each treatment each year is present in Table 48.

The ERG notes a number of issues with the budget impact beyond those identified in the evaluation of the cost-effectiveness. These relate to the size of the Gaucher population in the UK; the integration of estimates of cost from the cost-consequence model into the budget impact model; the treatment received by incidence patients in the absence of eliglustat; and, the composition of the Gaucher population. The ERG has not commented on the market share data used by the company as it has no means to verify these inputs. The ERG, however, considers the values used plausible.

Table 48 Number of patients receiving each treatment (where eliglustat is recommended)

Treatment	**2017**	**2018**	**2019**	**2020**	**2021**
Imiglucerase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Velaglucerase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eliglustat:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Switching from imiglucerase (ERT stable)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Switching from velaglucerase (ERT stable)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Naïve patients initiating in place of imiglucerase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Naïve patients initiating in place of velaglucerase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients per year initiating on eliglustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ERT, enzyme replacement therapy.					

5.2.9.1 The prevalence of Gaucher disease in UK and England

The size of the Gaucher population used in the CS is estimated from market share data collected by the company. This estimated the total size of the Gaucher disease population to be [redacted]. This figure is then adjusted to for the proportion of adult patients; the proportion of patients who have type 1 disease; and, the proportion of Gaucher patients that reside in England; see Table 49.

Table 49 Parameters used to estimate prevalence of type 1 Gaucher disease

Population parameters	**Estimate**
Gaucher disease patients in the UK	[redacted]
Proportion who reside in England	84%
Proportion over 18 years of age	86%
Proportion who have type 1 disease	91%
Estimated adult GD1 population the UK	156

Based on these assumptions the company estimates there to be [redacted] stable GD1 patients in England. The ERG, however, notes a number of inconstancies in this estimate. Firstly, the company appears to have made a calculation error as the reference provided to the ERG suggests that there are [redacted] patients in the UK with Gaucher disease not [redacted]. Based on the company's assumption, this would imply a total of [redacted] patients not [redacted] Secondly, this inconsistent with evidence present in Section 6 of the CS which suggest that there are 214 Gaucher disease patients in England, which re-weighted for the proportion of type patients predicts a total of 191 GD1 patients. Thirdly, this figure assumes that the distribution of GD1 patients across the UK is equal. This is unlikely to be the case as a significant proportion (35%)[70] of Gaucher disease patients in the UK are likely to be of Ashkenazi Jewish decent and the vast majority of Jews in the UK live in England (96%). With therefore expect the number of GD1 patients in in England to be disproportionate to its population size.

In addition to these inconsistencies evidence from other sources suggests the GD1 population is somewhat higher than estimated by the company. The UK Gaucher association in their submission to this appraisal report that they are in contact with 293 Type 1, 2 and 3 Gaucher disease patients in the UK including both adults and children. Based on the assumption of equal distribution of patients across the UK nations; re-weight for the adult population; and for the proportion of patients with type 1 this suggests a total of 193 patients in England. A second estimate can also be derived from a combination of estimates from the UK Gaucher Association and Burton et al (2009)[71] reported in NSCB [70] which suggest that in the UK there are 235 symptomatic Gaucher patients of non- Ashkenazi decent and 90 amongst the UK Ashkenazi Jewish population. Adjusting these figures for the distribution of these populations across the UK gives an estimate of 220 Gaucher patients in England. (This assumes that 91% have type 1 disease, 86% are adults; 84% (54.32 million/64.60milion) are of non-Ashkenazi Jewish patients live in England; and, that 96% of the Ashkenazi Jewish population live in England).

In light of the ERG considers there to be some uncertainty as to the size of the Gaucher disease population in the England and the UK, contrary to the company's statement on p.g.277 of the submission that there is certainty regarding the size of the Gaucher population due to the small number of patients. Given this uncertainty the ERG presents additional analysis on the budget impact model in Section 6 considering alternative estimates of the size of the Gaucher population.

5.2.9.2 The integration of the cost-consequence and budget impact model

The ERG has identified some issues in the way in which total costs from the cost-consequence model are used to estimate costs over five years. As described above, the budget impact model is linked directly to the cost effectiveness model and therefore total costs are based on those calculated by the cost-consequence model assuming a five year time horizon. While the ERG has no issue with this direct integration of the budget impact and the cost- effectiveness model in principal, the consequence in this case is that the effects of mortality and discontinuation are included in the estimated total costs. With respect to mortality, the cost consequence model calculates total costs of treating patients allowing the fact that some patients we die each year the total costs therefore represent the average cost of treating a patient over a life time rather the cost of treating one patient for a period of 5 years (the time horizon of the budget impact model). For the purposes of the budget impact model the latter figure is the more appropriate one as it reflects actual costs incurred. The impact of including mortality is to underestimate total costs as it assumes that a proportion of the patients will die each year. Given the short time horizon and the relatively low mortality rate of Gaucher patients, the impact of including the effects of mortality are small, but could easily have been accounted for in the model. With respect to discontinuation, the cost consequence model allows for a proportion of patients to discontinue treatment. It is, however, assumed that patients are not left untreated and instead switch to another treatment. The costs in the cost –consequence model therefore account for the fact that a proportion of patients switch treatments. The budget impact model, however, already accounts for the number of patients that switch treatment each year and therefore the effects of patients switching treatment are being double counted. Give these inconsistencies the ERG presents additional analysis in Section 6 which assumes removes the impact of mortality and discontinuation.

5.2.9.3 Treatment of incidence population

The company presents two scenarios regarding the treatment of incident patients when assuming eliglustat is not available. The first assumes that incident patients are treated in accordance with the current distribution of patients receiving imiglucerase and velaglucerase. The second assumes that all incidence patients are treated with velaglucerase in line with the CMU preference for velaglucerase over imiglucerase on the grounds of cost.[12] Advice form the clinical advisor to the ERG suggest that within her centre all patients receive velaglucerase and therefore this alternative scenario may

therefore be more plausible. The advisor, however, acknowledged there may be some variation in practice across the UK.

5.2.9.4 Composition of the Gaucher population

As described above the budget impact model assumes that the Gaucher population is made entirely of EM and IM patients. The model budget impact model therefore excludes PM patients. The CS states that PM patients make up 7% of the Gaucher population, however, no reference is given for this figure. This is however, in line with the proportion of PM patients recruited into the ENCORE trial. The ERG was not able to identify any other sources of evidence on the proportion of PM patients other than the ENGAGE trial where 3% of patients were PMs. Given that IM and EM patients make up the vast majority of the Gaucher population the budget impact model presented in the CS broadly reflects the NHS. The impact of excluding PM patients is to favour ERT as the treatment costs for PM patients with eliglustat is substantially less than for IM and EM patients. The budget impact model therefore somewhat overestimates the costs of treatment with eliglustat. The ERG therefore present additional analysis in Section 6 which incorporates PM patients into the budget impact model.

5.2.10 Cost effectiveness results

5.2.10.1 Base-case results

Eight different sets of base-case results were presented in the CS based on: patients' metaboliser status (IM/EM or PM), whether patients were ERT stable or treatment naïve, and the comparator used (imiglucerase or velaglucerase). Results were also presented using a weighted average of the comparator, assuming that 48% of patients were treated with imiglucerase and 52% of patients were treated with velaglucerase. The base-case analysis makes use of the list-price of velaglucerase and does not incorporate the confidential PAS which is unknown to the company. Results based on the non list prices provided to the ERG are presented in a confidential Appendix (separate to this report). The results for the estimated cost differences for each of the eight comparisons are summarised in Table 50. The CS results find eliglustat to generate lower overall costs in every base-case scenario, with cost differences ranging from £147,394 to £3,437,379 depending on the patient group treated and the comparator used.

Table 50: Incremental Costs for each Patient Group

Comparison	Incremental cost
ERT stable patients, IM and EM	
Patients switching from imiglucerase	-£147,394
Patients switching from velaglucerase	-£1,288,963
ERT stable patients, PM	
Patients switching from imiglucerase	-£2,116,154
Patients switching from velaglucerase	-£3,323,218
Treatment naïve patients, IM and EM	
Patients who would otherwise initiate on imiglucerase	-£212,299
Patients who would otherwise initiate on velaglucerase	-£1,352,367
Treatment naïve patients, PM	
Patients who would otherwise initiate on imiglucerase	-£2,297,310
Patients who would otherwise initiate on velaglucerase	-£3,437,379
Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; PM, poor metaboliser.	

The QALY results for each of the explored sub-groups are summarised in Table 51, with clinical outcomes equal for IM, EM and PM patients, as metaboliser status is assumed to determine only the dose of eliglustat and drug costs. The results show positive QALY gains in all groups, with marginally higher gains to be had in patients who are treatment naïve. All incremental differences are as a result of differences in HRQoL only, with the number of life-years gained being equal for patients treated with eliglustat and ERT treatments imiglucerase and velaglucerase.

Table 51: Incremental QALY's for each Patient Group

Comparison	Incremental QALYs
ERT stable patients	
Patients switching from imiglucerase	2.28
Patients switching from velaglucerase	2.28
Treatment naïve patients	
Patients who would otherwise initiate on imiglucerase	2.43
Patients who would otherwise initiate on velaglucerase	2.45
Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; PM, poor metaboliser.	

Tables 74-75 in the CS (pg. 232 to 233) summarise the QALY gains per health state, as well as the gains attributed to the treatment administration method, and adverse events for both the ERT stable

and ERT naïve patients respectively. When focussing on the sum of QALY gains from each of the nine health states there are no incremental differences in QALYs for the ERT stable group and only a 0.01 increment in the ERT naïve group when considering both comparators. There are small utility decrements of between 0.01-0.02 associated with adverse events, marginally favouring both ERT therapies relative to eliglustat. Almost all of the incremental differences in utility between eliglustat and ERT therapy can be attributed to the oral therapy utility increment, which is equal to 2.29 QALYS in the ERT stable group and 2.43 QALYs in the treatment naïve group.

5.2.10.2 Probabilistic cost-effectiveness analysis results

The CS included a PSA for both the ERT stable and treatment naïve populations, each with 1,000 simulations. Table 52 and Table 53 show the mean incremental costs and QALYS for each of the eight scenarios respectively. Although there are differences between the deterministic and the probabilistic results, the differences are relatively small which suggests the model appears to be linear function of the input parameters. This was confirmed by the ERG by running the PSA for both population groups for 5000 iterations and therefore, the majority of additional analysis carried out by the ERG in Section 6 uses the deterministic model.

Table 52: Summary of PSA Cost results

Comparison	Mean Incremental Costs
ERT stable patients, IM and EM	
Patients switching from imiglucerase	-£162,006
Patients switching from velaglucerase	-£1,394,994
ERT stable patients, PM	
Patients switching from imiglucerase	-£2,168,860
Patients switching from velaglucerase	-£3,445,021
Treatment naïve patients, IM and EM	
Patients who would otherwise initiate on imiglucerase	-£93,499
Patients who would otherwise initiate on velaglucerase	-£1,295,291
Treatment naïve patients, PM	
Patients who would otherwise initiate on imiglucerase	-£2,377,114
Patients who would otherwise initiate on velaglucerase	-£3,512,064
Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; PM, poor metaboliser.	

Table 53: Summary of PSA QALY results

Comparison	Mean Incremental QALYs
ERT stable patients, IM and EM	
Patients switching from imiglucerase	2.30
Patients switching from velaglucerase	2.30
ERT stable patients, PM	
Patients switching from imiglucerase	2.29
Patients switching from velaglucerase	2.29
Treatment naïve patients, IM and EM	
Patients who would otherwise initiate on imiglucerase	2.48
Patients who would otherwise initiate on velaglucerase	2.50
Treatment naïve patients, PM	
Patients who would otherwise initiate on imiglucerase	2.43
Patients who would otherwise initiate on velaglucerase	2.45
Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; PM, poor metaboliser.	

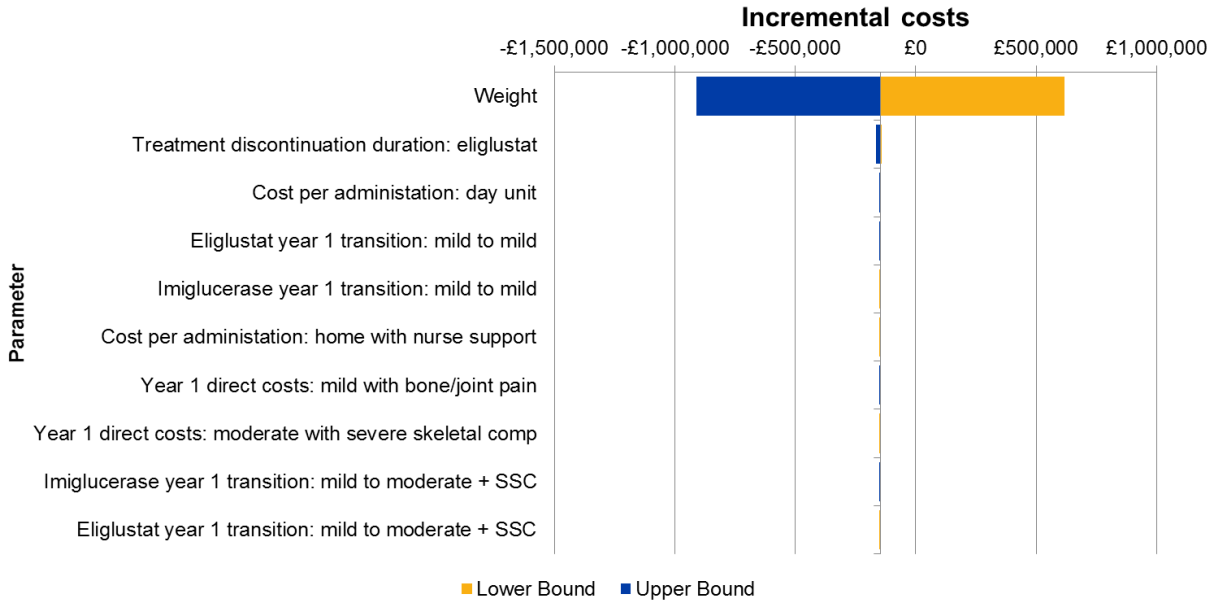
5.2.10.3 One way sensitivity analysis

The company presented the results of a variety of one-way deterministic sensitivity analyses to highlight how the uncertainty around different model input parameters impacts on the incremental costs and QALYs. The results of the analysis are presented using tornado diagrams in Figures 30-45 in the CS. This deterministic analysis was conducted for each of the eight different scenarios explored in the analysis. The lower and upper bounds of each value are based on the 95% confidence intervals, given the selected distribution type and the parameters. When distributions or transitions must sum to one, or there is covariance between parameters, the other inputs were adjusted to accommodate the upper and lower bound of each parameter. To avoid repetition, in this section only the results of the sensitivity analysis for eliglustat compared with imiglucerase in the IM/EM patient group are discussed. Results of the sensitivity analysis were largely independent of the patient group and comparator selected, there were however, some difference in the magnitude of the changes in results for some parameters and these are noted in the text below. Full results for all patient groups and comparators can be found on pg.246 to 254 of the CS.

Figures 6 and 7 show the ten most influential parameters on incremental costs and QALYs for IM/EM patients in the ERT stable group when imiglucerase is chosen as the comparator. The parameter with by far the largest impact on incremental costs when varied is average patient weight. This is because this has a significant impact on the dose of ERT people receive, and therefore the cost of treatment. The second largest impact on incremental costs results from varying the duration over which patients can discontinue eliglustat treatment. This is because patients discontinuing eliglustat move on to ERT

treatment and therefore incur additional drug acquisition and administration costs. The impact of varying the duration over which patients can discontinue eliglustat treatment has a larger effect when using velaglucerase as a comparator due to the higher drug acquisition costs associated with velaglucerase (note this only applies when list prices are used).

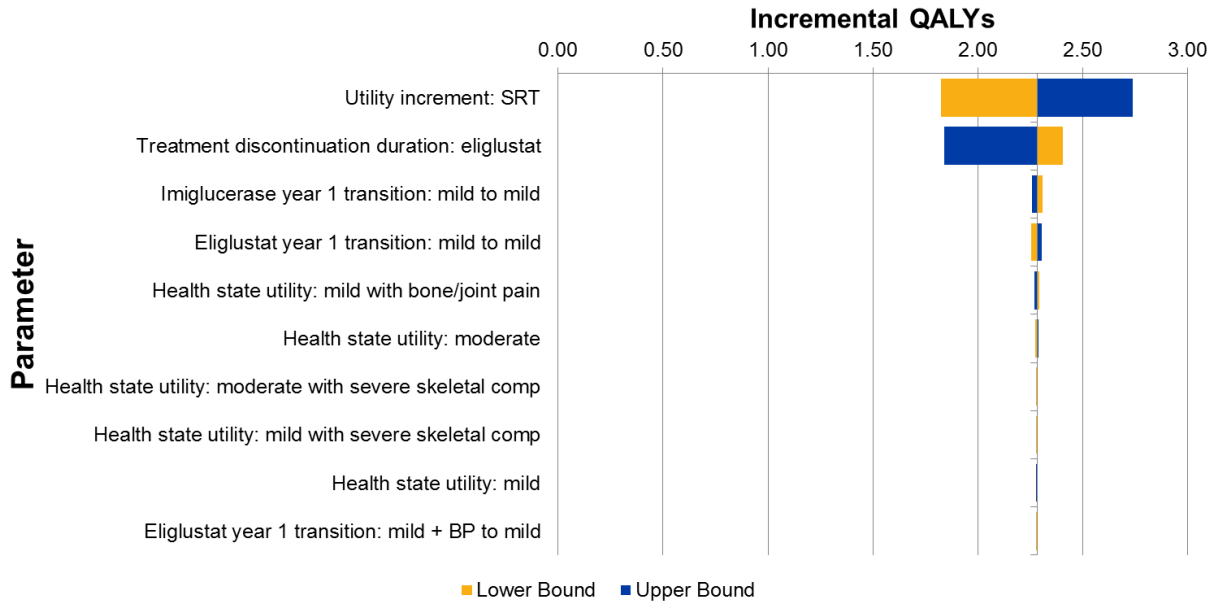
Figure 6: Tornado diagram of incremental cost – ERT stable, versus imiglucerase, IM/EM patients



Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; SSC, severe skeletal complications.

Varying the utility increment assigned to eliglustat for its more favourable administration method is the biggest driver of the difference in QALYs. The second most sensitive parameter is the treatment discontinuation duration of eliglustat, and these findings are the same for both PM patients and ERT comparators. Varying other parameters has very little impact on the results.

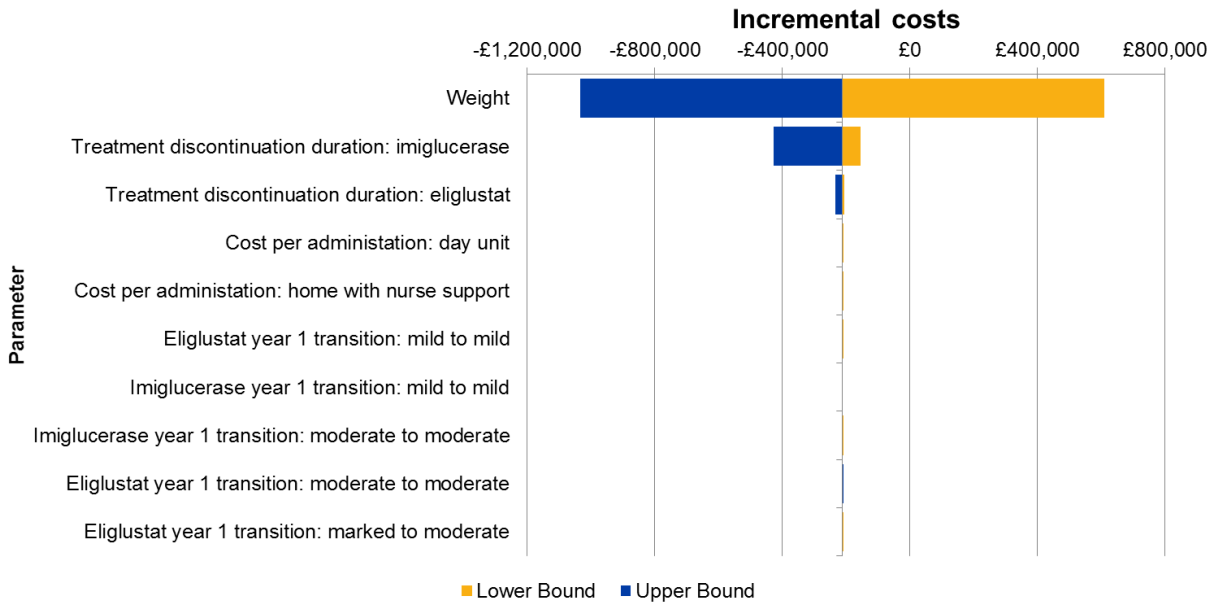
Figure 7: Tornado diagram of incremental QALYs – ERT stable, versus imiglucerase, IM/EM patients



Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

Figures 8 and 9 present the incremental costs and QALYs for treatment naïve patients who are with IM or EM, when imiglucerase is considered as the comparator. As with the treatment stable group changes in weight have y far the greatest impact on incremental costs. Varying the treatment discontinuation duration for imiglucerase has the second largest effect on incremental costs. This is slightly different to the stable patient group where the discontinuation duration for eliglustat is the second most influential parameter. This is because in the stable group discontinuation in ERT (imiglucerase) patients is assumed to be zero and not varied in the sensitivity analysis. In treatment naïve patients this parameter has a significant impact as patients in the ERT move to the more expensive velaglucerase treatment. Similar, but opposite results are observed when velaglucerase is the comparator, because velaglucerase patients are now moving to the cheaper imiglucerase.

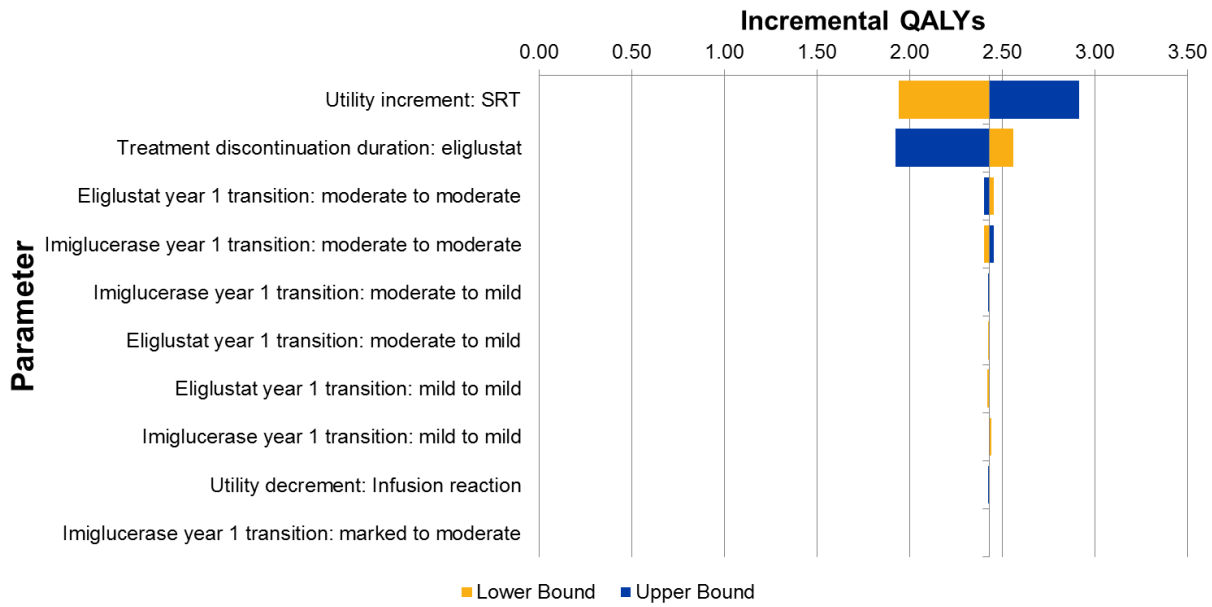
Figure 8: Tornado diagram of incremental cost – treatment naïve, versus imiglucerase, IM/EM patients



Key: EM, extensive metaboliser; IM, intermediate metaboliser.

For treatment naïve patients changes in the utility increment associated with substrate reduction therapy also has the biggest impact on incremental QALYs, with treatment discontinuation duration of eliglustat also having a sizeable impact. These findings are similar to the results for PM patients and when velaglucerase is selected as the comparator.

Figure 9: Tornado diagram of incremental QALYs – treatment naïve, versus imiglucerase, IM/EM patients



Key: EM, extensive metaboliser; IM, intermediate metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy

5.2.11 Model validation and face validity check

5.2.11.1 Validation by the company

The CS states that a number of quality control measures to validate the model including internal quality control process on behalf of the developers and review of the model by an external independent health economists not involved in the construction of the model.

The company externally validated the result of the model against predicted costs of imiglucerase treatment estimated by the model against a previous economic model van Dussen et al[40] and demonstrated similar life-time costs. No further external validation of the model was however, presented. This was justified on the basis that no comparisons of eliglustat with ERT have been published.

5.2.11.1 Validation by the ERG

The ERG undertook a review of the company's base-case and sensitivity analysis. This included the use of a check list to carry out a series of series of black box tests to evaluate the internal validity of the model. These black box tests check the internal logic of the model as well checking the predictive validity of parameter inputs (e.g. that increasing effectiveness of the treatment lowers cost-effectiveness) Further to this, the code of the model was examined for potential errors, this included

tracking how parameters fed into the model and an examination of the main calculation sheets, with a view to understanding how QALYs and costs are accumulated in the model. This review identified a number of minor errors in the model. These errors were highlighted to the company at the clarification stage and a revised model was supplied to the ERG. The impact of these calculation errors on the results of the model was very minor resulting in small differences in the total QALYs in the base case analysis. The errors within the model would have a more substantial impact on results where a PAS discount is applied to the price of the ERT treatments imiglucerase. This, however, does not affect any analysis presented in the CS as no such discount was included in the in the base-case or sensitivity analysis. After the points for clarification stage a further error was identified in the model relating to the application of PAS discounts for both ERT treatments. The errors, detailed below, have no impact on the base case analysis, but would impact on results where a PAS discount is applied to either ERT treatment.

Errors:

- On the sheet "Cost Inputs" Cell H110 should read "=F28"
- On the sheet "Cost Inputs" Cell H111 should read "=F30"

With regards to the external validity, the ERG considers that the efforts made by the company to externally validate the results of the predictions to be inadequate and largely superficial. The company's comparison with the van Dussen[40] is somewhat meaningless given the significant difference in the assumptions made and is too focussed on estimates of total costs, with any similarity in costs largely coincidental rather than evidence of external validly. The company also complete ignore the significant disparity in predicted life time costs in their model compared with Connock et al.[7] Further investigation of this disparity may have led the company to question its assumptions regarding the dose of ERT and to make alternative assumptions. Substantial further efforts by the company to externally validate the model could and should have been made.

5.3 Conclusions of the cost effectiveness section

A limited number of cost-effectiveness analyses were identified in the systematic review presented in CS. However, no economic assessments of eliglustat for the treatment of type 1 Gauchers disease in the UK setting were identified in the company's search. The de novo model presented by the company represents the most relevant source of evidence on the costs and consequences of implementing eliglustat in England. The economic model described in the CS is considered by the ERG to meet the NICE reference case and is broadly in-line with the decision problem specified in the scope, though the model does not include a comparison between eliglustat and milglustat which was stated as

relevant comparator in the NICE scope and is used by a small number of patients. The results of the costs consequence model presented in the CS suggest a reduction in costs of between £147,394 and £3,437,379depending on the population being treated and the comparator therapy. The company's model also estimates an increase in health benefits from implementing eliglustat of 2.28 QALYs over a 70 year time horizon. All of these QALY benefits are as a result of QoL benefits assumed to result from eliglustat being a oral therapy.

In its review of the company model the ERG identified a number of uncertainties surrounding assumptions made in the cost-consequence model presented in the CS which have a significant impact on estimated costs and benefits. These are outlined in brief below:

1. *Incorporation of clinical data in the economic model*

   The structure of the economic model along with a number of assumptions made about the comparative long term effectiveness of eliglustat and the comparator ERT therapies means that the model essentially assumes equal effectiveness between eliglustat and the comparator ERT treatments. The clinical evidence to support these assumptions is not considered by the ERG to be sufficient to support the assumptions made and the model structure used does not incorporate uncertainty regarding long term differences in the relative effectiveness of eliglustat with ERT.

2. *Dosing of ERT therapies*

   The company model assumes the dose of ERT therapy used will be the same as that used in the ENCORE trial. This dose is, however, significantly higher than is typically used in the UK and as such the economic model significantly over estimates the drug acquisition costs associated with ERT treatments.

3. *Benefits of oral therapy*

   The company model assumes an incremental utility benefit of 0.12 QALYs to represent the benefits of oral therapy. While the ERG acknowledges that there may be some HRQoL benefits resulting from oral therapy, the ERG considers the magnitude of these benefits to be unreasonably large when compared with QALY decrements from adverse events and QALY benefits of other oral therapies estimated in previous NICE submissions.

With regards to the budget impact the ERG also identified a number of issues the most significant of these were the estimates of the size of the Gaucher population in the UK. Alternative, estimates of the Gaucher population which significantly includes Gaucher patients of Ashkenazi Jewish decent suggest that the Gaucher population is more than 30% larger than that estimated by the company. The budgetary impact model therefore underestimates the impact of recommending eliglustat.

In summary, the ERG considers the company's base-case to be over optimistic and is likely to significantly overestimate the benefits of eliglustat therapy and the costs of comparator therapies. Additional analyses undertaken by the ERG are presented in Section 6, in which the impact of alternative assumptions on the results of the cost-consequence and budget impact models is explored.

The annual costs based on the mean dose of ERT assumed in the model are summarised in Table 54 assuming both the list prices and the discounted price.

Table 54: Dosing and drug cost per year for ERT

Drug	Total dose required	Number of doses per year	Total drug cost per year at list price
Imiglucerase	2862U (42.4U/kg)	26.09	£199,976
Velaglucerase	2862U(42.4U/kg)	26.09	£263,203

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

This section summarises the ERG's further exploration of the issues and uncertainties highlighted in the review and critique of the company's cost-consequence analysis and budget impact presented in section 5. This additional analysis addresses the following issues and uncertainties:

- Discontinuation rates associated with eliglustat and ERT treatment;
- Assumptions regarding the mortality of Gaucher patients;
- Assumptions regarding the HRQoL benefits associated with oral therapy.
- Assumptions made regarding the administrative costs of eliglustat and ERT;
- The dose of eliglustat and ERT treatment assumed in the model;
- Assumptions regarding the short-term effectiveness of eliglustat in treatment naïve patients;
- Assumptions regarding the prevalence of Type 1 Gaucher disease in England.

These are analyses are concluded with the presentation of alternative ERG base-case which the ERG believes is as at least as plausible the base-case presented by the company. All analyses in this section are based on the list prices of imiglucerase and velaglucerase. A confidential appendix replicates the analyses presented in this section using the prices for imiglucerase and velaglucerase currently faced by the NHS. To keep the analyses focused, the scenarios presented in this section assume a treatment stable population who are IM/EM metaboliser status. Full results are presented for all populations in the Appendix .

6.2 Additional ERG analyses

6.2.1 Discontinuation

The company base-case analysis assumes an annual discontinuation of 1.89% for all ERT naïve patients, and ERT stable patients who are treated with eliglustat for three years until they are considered being stable on treatment. In order to address the uncertainty surrounding the selected discontinuation rate in the company's analysis highlighted in Section 5.2.3.1, two scenarios were explored. The first assumed that there was no discontinuation in each patient group. The second used an annual discontinuation rate of 2.36% which was calculated from the rate in the 104 week extension period of the ENCORE trial. The impacts of adjusting this assumption on incremental QALYs and costs are presented in Table 55 and Table 56.

Table 55: Impact of excluding discontinuation (ERT Stable IM/EM Patients)

	Comparator		Incremental QALYs		Incremental Cost	
Company base-case	**Imiglucerase**		2.28		-£ 147,394	
	Velaglucerase		2.28		-£ 1,354,457	
No discontinuation	**Imiglucerase**		2.40		-£ 142,258	
	Velaglucerase		2.40		-£ 1,414,232	
Budget Impact						
	2017	**2018**	**2019**	**2020**	**2021**	**Cumulative Total**
Company base-case	-£1,873,401	-£2,987,521	-£3,622,848	-£4,242,818	-£4,846,357	-£17,572,946
No discontinuation	-£1,898,211	-£3,039,542	-£3,715,424	-£4,375,437	-£5,008,718	-£18,037,331

Table 56 Impact of higher discontinuation Rate from ENCORE extension period

	Comparator		Incremental QALYs		Incremental Cost	
Company base-case	**Imiglucerase**		2.28		-£ 147,394	
	Velaglucerase		2.28		-£ 1,354,457	
Higher discontinuation	**Imiglucerase**		2.24		-£ 148,624	
	Velaglucerase		2.24		-£ 1,340,142	
Budget Impact						
	2017	**2018**	**2019**	**2020**	**2021**	**Cumulative Total**
Company base-case	-£1,873,401	-£2,987,521	-£3,622,848	-£4,242,818	-£4,846,357	-£17,572,946
Higher discontinuation	-£1,867,324	-£2,974,848	-£3,600,490	-£4,210,940	-£4,807,379	-£17,460,981

6.2.2 Mortality

A scenario was explored related to mortality, in order to address some of the issues highlighted in Section 5.2.3.2. This scenario involved adjusting general population mortality estimates to incorporate an elevated morality risk associated with Gaucher disease. This method differs from that from the analysis presented by the company which fitted a parametric function to Gaucher morality data, and one to the general population mortality data. The model was then set to select the curve over time which generated the highest morality rate.

The ERG instead used ONS data to calculate the proportion of the UK population in each age group [72]. These proportions were multiplied by the age stratified Gaucher mortality data presented in the CS (p.g. 331-332) to calculate a weighted overall Gaucher morality rate. The same method was used on

the data presented in the life tables in the company's analysis to calculate a weighted overall general population mortality rate. A relative risk was then calculated using these rates, which was applied to the general mortality rates to model mortality in the Gaucher population.

Two results of two variations of this scenario are presented. The first variation applied this elevated Gaucher mortality rate to every patient regardless of their DS3 score, and the second was applied only to those with DS3 scores classified as 'Marked' or 'Severe'. This method results in a lower mortality rate compared to the Gaucher mortality previously calculated in the company's economic model. The results are presented below in Table 57 and Table 58.

In addition the budget impact analysis presented in the CS incorporated morality, so a scenario was also conducted which removed morality from the analysis. The results are presented below in Table: 59.

Table 57 Impact of ERG calculated mortality applied to all GD1 patients

	Comparator		**Incremental QALYs**		**Incremental Cost**	
Company base-case	**Imiglucerase**		2.28		-£ 147,394	
	Velaglucerase		2.28		-£ 1,354,457	
Revised mortality	**Imiglucerase**		2.40		-£ 155,778	
	Velaglucerase		2.40		-£ 1,424,776	
Budget Impact						
	2017	**2018**	**2019**	**2020**	**2021**	**Cumulative Total**
Company base-case	-£1,873,401	-£2,987,521	-£3,622,848	-£4,242,818	-£4,846,357	-£17,572,946
Revised mortality	-£1,873,401	-£3,003,435	-£3,679,279	-£4,350,921	-£5,022,528	-£17,929,564

Table 58 Impact of ERG calculated applied to 'Marked' and 'Severe' states

	Comparator	Incremental QALYs	Incremental Cost
Company base-case	**Imiglucerase**	2.28	-£ 147,394
	Velaglucerase	2.28	-£ 1,354,457
Revised mortality applied to 'Marked' and 'Severe' states	**Imiglucerase**	2.53	-£ 163,517
	Velaglucerase	2.53	-£ 1,501,459

Budget Impact

	2017	2018	2019	2020	2021	Cumulative Total
Company base-case	-£1,873,401	-£2,987,521	-£3,622,848	-£4,242,818	-£4,846,357	-£17,572,946
Revised mortality applied to 'Marked' and 'Severe' states	-£1,873,401	-£3,005,751	-£3,687,544	-£4,366,946	-£5,049,320	-£17,982,962

Table: 59 Impact of no mortality

Budget Impact

	2017	2018	2019	2020	2021	Cumulative Total
Company base-case	-£1,873,401	-£2,987,521	-£3,622,848	-£4,242,818	-£4,846,357	-£17,572,946
No mortality applied to 'Marked' and 'Severe' states	-£1,873,401	-£3,009,786	-£3,702,033	-£4,395,291	-£5,097,050	-£18,077,561

6.2.3 HRQoL: Impact of Oral Therapy Increment

In order to address the uncertainty surrounding the oral therapy utility increment of '0.12' implemented in the company's analysis highlighted in section **Error! Reference source not found.**, three alternative values were used. The first value of '0.025' was taken from a study conducted by Tabberer et al. 2006[49] which was used in TA162[50]. The second and third values of '0.09' and '0.05' were taken from the vignette study commissioned by the company[46]. These alternative values differ from the company base-case value of '0.12' as the health state valued by patients included a more comprehensive list of treatment related adverse events and state a higher dose frequency of eliglustat. The impact of these adjustments on the incremental QALY values are summarised in Table 60:

Table 60 Impact of Oral therapy Increment

	Comparator	Incremental QALYs	Incremental Cost
Company base-case Oral therapy Increment (0.12)	**Imiglucerase**	2.28	-£ 147,394
	Velaglucerase	2.28	-£ 1,354,457
Oral therapy Increment (0.025)	**Imiglucerase**	0.47	-£ 147,394
	Velaglucerase	0.47	-£ 1,354,457
Oral therapy Increment (0.09)	**Imiglucerase**	1.71	-£ 147,394
	Velaglucerase	1.71	-£ 1,354,457
Oral therapy Increment (0.05)	**Imiglucerase**	0.94	-£ 147,394
	Velaglucerase	0.94	-£ 1,354,457

Budget Impact

	2017	2018	2019	2020	2021	Cumulative Total
Company base-case	-£1,873,401	-£2,987,521	-£3,622,848	-£4,242,818	-£4,846,357	-£17,572,946
Oral therapy Increment (0.025)	-£1,873,401	-£2,987,521	-£3,622,848	-£4,242,818	-£4,846,357	-£17,572,946
Oral therapy Increment (0.09)	-£1,873,401	-£2,987,521	-£3,622,848	-£4,242,818	-£4,846,357	-£17,572,946
Oral therapy Increment (0.05)	-£1,873,401	-£2,987,521	-£3,622,848	-£4,242,818	-£4,846,357	-£17,572,946

6.2.4 Administration Costs

6.2.4.1 Alternative administration costs for ERT

The company's base-case analysis assumes that the administration costs of treating patients with ERT at home are higher than the costs of treating patients in hospital, as discussed in section **Error! Reference source not found.**. The ERG believes this assumption is not reasonable, and therefore a scenario was explored where the administration cost of home ERT with or without nurse support was set as being equal to the administration cost of hospital therapy. This was implemented by setting the proportion of patients who were treated in hospital to 100%. The impact of this scenario on incremental costs is presented in Table 61.

Table 61 Impact of alternative admin costs for ERT

	Comparator		Incremental QALYs		Incremental Cost	
Company base-case	**Imiglucerase**		2.28		-£ 147,394	
	Velaglucerase		2.28		-£ 1,354,457	
Alternative admin costs for ERT	**Imiglucerase**		2.28		-£ 25,013	
	Velaglucerase		2.28		-£ 1,232,077	
Budget Impact						
	2017	**2018**	**2019**	**2020**	**2021**	**Cumulative Total**
Company base-case	-£1,873,401	-£2,987,521	-£3,622,848	-£4,242,818	-£4,846,357	-£17,572,946
Alternative admin costs for ERT	-£1,591,631	-£2,531,704	-£3,054,831	-£3,563,821	-£4,059,895	-£14,801,882

6.2.4.2 Dispensary Costs for Eliglustat (£14.40)

As discussed in Section 5.2.8.2, in line with the recent NICE appraisal of Ceritinib the ERG considers at a minimum monthly pharmacy dispensary cost of £14.40 should be included to represent the cost of administering eliglustat. The impact of this is shown in Table 62.

Table 62: Impact of including dispensary costs for eliglustat

	Comparator		Incremental QALYs		Incremental Cost	
Company base-case	**Imiglucerase**		2.28		-£ 147,394	
	Velaglucerase		2.28		-£ 1,354,457	
Dispensary Costs for Eliglustat (£14.40)	**Imiglucerase**		2.28		-£ 144,095	
	Velaglucerase		2.28		-£ 1,351,158	
Budget Impact						
	2017	**2018**	**2019**	**2020**	**2021**	**Cumulative Total**
Company base-case	-£1,873,401	-£2,987,521	-£3,622,848	-£4,242,818	-£4,846,357	-£17,572,946
Dispensary Costs for Eliglustat (£14.40)	-£1,865,274	-£2,974,518	-£3,606,982	-£4,224,111	-£4,824,765	-£17,495,651

6.2.5 Dosing

6.2.5.1 Vial wastage for ERT

As discussed in Section 5.2.8.3 the ERG considered that some level of vial wastage should potentially be assumed. A scenario is therefore presented where each dose of ERT given is rounded up to the

nearest vial. The smallest vial size available of 200 units was assumed to be used in this scenario. The results of this analysis are presented in Table 63.

Table 63 Impact of vial wastage for ERT

	Comparator	Incremental QALYs	Incremental Cost
Company base-case	**Imiglucerase**	2.28	-£ 147,394
	Velaglucerase	2.28	-£ 1,354,457
Vial wastage	**Imiglucerase**	2.28	-£ 281,562
	Velaglucerase	2.28	-£ 1,531,045

6.2.5.2 Exploration of the doses of ERT in the model

The base-case analysis assumed that patients either received eliglustat at a dose of 100mg twice daily, or an average ERT dose of 42U/kg, assuming a mean weight of 67.5kg. There are inconsistencies in the dosing selected in the company's base-case analysis which are discussed further in Sections **Error! Reference source not found.** and **Error! Reference source not found.**. The mean dose of ERT was selected based on the dose used in the ENCORE trial, while the eliglustat dose is based on what is most commonly used in practice.

Therefore three different scenarios are presented which make use of different data on the dosing of all treatments. Firstly, a scenario is presented which shows the impact of using dosing and weight data used in a cost-minimisation study conducted by the AWMSG, which was highlighted in the CS. This study assumed a mean dose of 32U/kg based on consultation with several Welsh clinicians, and an average weight of 75kg. This resulted in a mean dose of 2,400 units, which is similar to mean dose of 2,395 units adopted in a health technology assessment conducted by Connock et al. 2006.[7] The impact of this scenario on incremental costs is presented in Table 64.

The second scenario used the average dose of eliglustat used in the ENCORE trial. To obtain the average dose of eliglustat we took the mean dose after the titration period of the trial which equated to 114mg. The impact of this scenario on incremental costs is presented in Table 64.

The third scenario related to dosing makes use of data obtained on what is commonly used in UK clinical practice. The average dose of ERT was assumed to be 25U/kg in this scenario, which was taken from the CS (p.g. 141). This figure was calculated from prescribing data which reported that in clinical practice in England adult imiglucerase patients receive 3,873 units per month, which equates to 25U/kg if the average weight from the ENCORE trial is used. The impact on incremental costs of this scenario is summarised in Table 64.

Table 64 Impact of Dosing Changes

	Comparator	Incremental QALYs	Incremental Cost
Company base-case	**Imiglucerase**	2.28	-£ 147,394
	Velaglucerase	2.28	-£ 1,354,457
AWSG dose of 2400U every two weeks	**Imiglucerase**	2.28	£ 512,583
	Velaglucerase	2.28	-£ 499,629
Trial dosage of Eliglustat	**Imiglucerase**	2.28	£ 403,859
	Velaglucerase	2.28	-£ 803,204
ERT dose to 25 U/KG	**Imiglucerase**	2.28	£ 1,530,403
	Velaglucerase	2.28	£ 818,691

Budget Impact

	2017	2018	2019	2020	2021	Cumulative Total
Company base-case	-£1,873,401	-£2,987,521	-£3,622,848	-£4,242,818	-£4,846,357	-£17,572,946
AWMSG dose of 2400U every two weeks	-£3,192	£3,004	£22,343	£50,138	£100,351	£172,644
Trial dosage of Eliglustat	-£515,371	-£814,757	-£971,609	-£1,116,857	-£1,238,395	-£4,656,989
ERT dose to 25 U/KG	£2,881,060	£4,615,015	£5,643,986	£6,670,768	£7,729,203	£27,540,032

6.2.6 Efficacy

In the CS the treatment effectiveness data from the ENGAGE study for eliglustat was used to calculate the transition probabilities for both treatment arms of the treatment naïve population in the first cycle of the analysis. This resulted in an assumption of equal efficacy in the first cycle. A scenario is presented where the data from the ENCORE trial was used in the first cycle of the analysis for the treatment naïve population. This results in differential efficacy being assumed in the first cycle of the analysis. The results of this scenario are presented in Table 65.

In the absence of long-term trial data the company's base-case analysis assumed that the transition probabilities for eliglustat and ERT were equal beyond the first year. This assumption was based on data from the ENCORE trial which had demonstrated that eliglustat was non-inferior to imiglucerase. However, the long-term difference between the two treatments is unclear and there are issues regarding the assumption of non-inferiority as discussed further in Section 5.2.7. The ERG attempted to incorporate differential efficacy into the analysis in order to demonstrate the impact on the results if the assumption of non-inferiority did not hold in the long-term. However, the ERG was unable to explore this scenario as any attempt to remove the assumption of non-inferiority resulted in

inconsistent results, and a lack of transparency in the cost-effectiveness model prevented the identification of any errors.

Table 65 Impact of using ENCORE effectiveness data in treatment naïve population

	Comparator	Incremental QALYs	Incremental Cost
Company base-case	**Imiglucerase**	2.28	-£ 147,394
	Velaglucerase	2.28	-£ 1,354,457
ENCORE data	**Imiglucerase**	2.28	-£ 201,180
	Velaglucerase	2.30	-£ 1,284,245

Budget Impact

	2017	2018	2019	2020	2021	Cumulative Total
Company base-case	-£1,873,401	-£2,987,521	-£3,622,848	-£4,242,818	-£4,846,357	-£17,572,946
ENCORE data	-£1,757,825	-£2,801,339	-£3,384,498	-£3,950,686	-£4,510,514	-£16,404,862

6.2.7 Population Size

As discussed in Section 5.2.9.1 the ERG believe alternative estimates of the size of the GD1 population should be tested. The estimates used are: [redacted] (ERG estimate after correcting calculation error) and 293 (UK Gaucher association submission). The results of these are presented in Table 66.

6.2.7.1 Estimates of the size of the Gaucher Patient Population in England

Table 66 Impact of increasing UK Gaucher population

Budget Impact

	2017	2018	2019	2020	2021	Cumulative Total
Company base-case	-£1,873,401	-£2,987,521	-£3,622,848	-£4,242,818	-£4,846,357	-£17,572,946
UK Gaucher population [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UK Gaucher population 293	-£1,873,401	-£2,994,340	-£3,636,465	-£4,263,154	-£4,873,365	-£17,640,725

6.3 ERG Base-Case Analysis

The ERG has a number of concerns regarding the company's base-case analysis and consider it overoptimistic with respect to a number of assumptions. Therefore, an alternative ERG-base case

which is based on a combination of a number of the scenarios presented in Section 6.2. The ERG base-case made the following assumptions:

- Additional administration costs for eliglustat (£14.40 monthly dispensary cost);
- Revised administration costs for ERT treatments (Home therapy cost equal to hospital cost);
- Revised estimate of the QALY benefits of oral therapy (Estimate of '0.05');
- Revised modelling of mortality to allow for increased mortality risk for marked and severe patients;
- Reduction in dose of ERT to bring it in-line with UK practice (25 units per kilogram);
- Using ENCORE effectiveness data in the treatment naïve population during the first cycle

The results of the analysis are presented in Table 67 and Table 68. The ERG-base budget impact analysis additionally assumed zero mortality, zero discontinuation and a UK Gaucher population of 293. The results are the ERG base-case budget impact analysis are presented in Table 69.

Table 67: Incremental QALYs and Costs (Eliglustat vs Imiglucerase)

Patient Group	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Health states: 0.00	Drug acquisition: £ 1,869,333
	AE events: -0.01	Administration: -£ 157,025
	Oral therapy increment: 1.06	Management/ social service costs: £ 193
	Total: 1.05	**Total: £ 1,712,502**
ERT stable PM	Health states: 0.00	Drug acquisition: -£ 312,889
	AE events: -0.01	Administration: -£ 157,025
	Oral therapy increment: 1.06	Management/ social service costs: £ 193
	Total: 1.05	**Total: -£ 469,721**
ERT naïve IM/EM	Health states: -0.02	Drug acquisition: £ 1,833,454
	AE events: 0.00	Administration: -£ 157,635
	Oral therapy increment: 1.06	Management/ social service costs: £ 504
	Total: 1.04	**Total: £ 1,676,323**
ERT naïve PM	Health states: -0.02	Drug acquisition: -£ 357,252
	AE events: 0.00	Administration: -£ 157,635
	Oral therapy increment: 1.06	Management/ social service costs: £ 504
	Total: 1.04	**Total: -£ 514,382**

Table 68: Incremental QALYs and Costs (Eliglustat vs Velaglucerase)

Patient Group	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Health states: 0.00	Drug acquisition: £ 1,080,452
	AE events: -0.01	Administration: -£ 157,025
	Oral therapy increment: 1.06	Management/ social service costs: £ 193
	Total: 1.05	**Total: £ 923,621**
ERT stable PM	Health states: 0.00	Drug acquisition: -£ 1,101,770
	AE events: -0.01	Administration: -£ 157,025
	Oral therapy increment: 1.06	Management/ social service costs: £ 193
	Total: 1.05	**Total: -£ 1,258,602**
ERT naïve IM/EM	Health states: -0.02	Drug acquisition: £ 1,127,802
	AE events: 0.02	Administration: -£ 157,635
	Oral therapy increment: 1.06	Management/ social service costs: £ 504
	Total: 1.06	**Total: £ 970,671**
ERT naïve PM	Health states: -0.02	Drug acquisition: -£ 1,062,904
	AE events: 0.02	Administration: -£ 157,635
	Oral therapy increment: 1.06	Management/ social service costs: £ 504
	Total: 1.06	**Total: -£ 1,220,035**

Table 69: Budget Impact (ERT Stable IM/EM Patients)

	2015	2016	2017	2018	2019
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**£2,961,673**	**£4,784,125**	**£5,928,950**	**£7,073,317**	**£8,219,694**
Cumulative Total	**£2,961,673**	**£7,745,798**	**£13,674,748**	**£20,748,065**	**£28,967,758**

6.4 Conclusions from ERG analyses

In this section the ERG has presented a number of additional analyses to explore a number of issues raised in Section 5. These analyses include an exploration of alternative assumptions regarding the mean dose of ERT patients receive and the assumed QoL benefits resulting from oral therapy.

An alternative base-case was also presented combining a number scenarios presented by the ERG. The alternative base-case conducted by the ERG showed a dramatic increase in incremental costs Based on list prices of imiglucerase the impact of the ERG's assumptions is to increase incremental costs of implementing eliglustat from an estimated saving of £147,394 per patient in the company's model to an increase in total costs of £ 1,712,502 per patient in the ERG's base-case. With respect to velaglucerase, again based on list prices, the ERG's assumptions increase incremental costs from an estimated saving of £1,288,963 in the company's base-case to an increase in total cost of £ 923,621 in the ERG's base-case. The majority of this change incremental costs results from alternative assumption regarding the dose of ERT treatment used. Based on these revised cost assumptions the budget impact of eliglustat is £28,967,758 over 5 years.

Similarly, large effects are also observed with respect to QALY benefits, in the company QALY benefits are estimated increase of approximately 2.28 per patient over the model 70 time horizon. In the ERG base-case this is reduced to 1.05 QALYs. The reason for the significant change is due to alternative assumptions about the size of the incremental benefit for oral therapy.

The ERG considers these estimates of the costs to be substantially more plausible than those in the company's base-case which the ERG considers makes a number of overly optimistic assumptions regarding the dose of ERT used in the UK, two of which the ERG was able to address; the administration costs of eliglustat; and the administration cost associated with ERT. With respect to estimated incremental QALYs the ERG considers its base-case analysis to be at least as plausible as the company's base-case. Further ERG emphasise that the estimated benefits are based on very strong assumptions regarding the long-term clinical effectiveness of eliglustat. The ERG was unfortunately unable to explore this uncertainty as it could not identify the transition probabilities used in the company's base-case analyses due to a lack of transparency in the model.

Based on the ERG's analysis, implementing eliglustat in the NHS would result in significantly increased costs with highly uncertain health benefits.

7 Submissions from practitioner and patient groups

This section presents a summary of additional submissions received from patients, patient organisations, clinicians and NHS England.

7.1 Clinician and NHS England perspective

This section presents a summary of the submissions from Addenbrooke's Hospital Cambridge UK, Royal Free lysosomal storage disorder (LSD) unit, Royal College of Physicians and the NHS England.

Patients eligible for eliglustat

According to the perspective of clinicians, at least 70% of the adult patients with GD1 in England would be expected to receive and be eligible to receive eliglustat therapy. The submission of Addenbrooke's Hospital Cambridge UK and Royal Free LSD unit indicated that there are about 300 to 350 known patients with Gaucher disease in England. However, the submission by Royal College of Physicians estimated that there are approximately 400 patients in the UK, but would expect only 50 to 100 patients to receive eliglustat.

Approximately 5% of adult patients with GD1 would not be suitable for eliglustat based on the frequency of CYP2D6 genotypes (ultrarapid or indeterminate metabolisers). It is also pointed out that young adults, who wish to start a family, are pregnant, or who are breast feeding should not take eliglustat. Patients who are taking a range of co-medication would also not be suitable for eliglustat as the co-medications can substantially change the bioavailability of eliglustat.

Current management of GD1

Currently there are eight specialist centres for Gaucher disease in the UK, including three centres where children are treated and monitored. The formal arrangements for transitioning patients from paediatric to adult care have been long-established.

All specialist centres aim to provide continuity of care with active shared-care arrangements with referring specialist practitioners (e.g. consultant staff) local to the patient. It is stated that agreed protocols for the treatment of Gaucher disease ensure that clinical practice is built on a strong consensus, thereby minimising variations in the treatment of GD patients across the UK. It is also pointed out that if NICE recommends adoption of eliglustat, the principle of long-term disease management and clinical monitoring for this disease should not change. These specialist centres will continue to provide treatment services for patients with Gaucher disease.

Monitoring of the disease is usually performed at least every six months in most patients with agreed protocols for blood testing, radiological review and other necessary investigations (e.g.

multidisciplinary care provided by orthopaedic surgical consultants). The comprehensive treatment of Gaucher disease in the UK clinical practice requires coordinated interdisciplinary care and monitoring of this disease.

The current standard therapy for most diagnosed patients is ERT. Most patients receive doses of 20 to 40 U/kg. ERT is initiated in the hospital setting and transferred to home care after 1 to 3 hospital infusions. The majority of patients receive the ERT infusion biweekly at home, either self-administered or with the help of a clinician (e.g. visiting healthcare nurse) or a carer. Therefore, delivery of ERT is associated with costs of staff time and medical equipment. Some patients would need to travel to local GP surgery (Health Centre) or local hospital for infusions. It takes about two hours for the infusion process. It is also pointed out that patients who receive ERT reported a social burden for infusion related to having to take time off work or school, and/or a psychological burden associated with cannulation.

Both imiglucerase and velaglucerase are the ERT products that have marketing approval in the EU. The submissions did not comment on the equivalence of, or differences between imiglucerase and velaglucerase. It is stated that over the past 4-5 years, the drive for efficiency gains and price competition has promoted the market position of velaglucerase alfa and currently velaglucerase alfa appears to be the ERT of majority use in England. Patients new to ERT in England will receive velaglucerase as a result of an NHS England tender and a cost advantage.

For those who are not suitable to be treated with ERT there is the option of miglustat, a first-in-class with a novel mode of action as a substrate-reduction agent. Miglustat was the first orally active therapy for Gaucher disease and is the second-line agent for those patients with mild-to-moderate disease unable or unwilling to be treated with enzyme replacement therapy. It is pointed out that the use of miglustat in adult patients with GD1 has been limited by moderate efficacy and concerns on side effects such as gastrointestinal symptoms (e.g.diarrhoea) and peripheral neuropathy. There are probably fewer than ten adult patients with Gaucher disease who are currently taking this drug in the UK.

Eliglustat

Whilst eliglustat has not as yet been used in clinical practice outside of clinical trials in England the clinicians' submissions were supportive of the clinical evidence of the effectiveness and tolerability of eliglustat. The evidence presented in phase 2 and 3 clinical trials is consistent with UK practice for patients starting therapy and the outcome measure relevant, meaningful and those used to monitor patients in the UK according to the NHS England SOP**.** The submissions also mentioned the beneficial effects on biomarkers stating that the rapid changes in their expression are highly

supportive of specific biological effects. The submissions stated that no consistent serious unwanted effects were identified in the trials that materially affect management beyond the potential interactions and cardiac toxicity that would result from prescribing inappropriate co-medication sharing metabolism by CYP 2D6 or in patients predicted by genotyping to be indeterminate or ultra-rapid metabolizers. The clinicians were unaware of any adverse effects associated with eliglustat not identified in the clinical trials.

Subgroups

Clinical trial data does not suggest the existence of subgroups of GD1 patients who would benefit heterogeneously from eliglustat. Patients with a rare subtype of Gaucher disease, resulting from deficiency of the activator protein saponsin C, cannot respond to exogenous enzyme therapy. Although eliglustat has not been tested in this subtype, theory suggests it should have a salutary biological effect through reducing production of substrate.

It is pointed out that the following subgroups of patients are associated with an increased risk of osteonecrosis:

- Patients with early-onset of clinical manifestations;
- Those with established bone disease;
- Those whose disease has been treated by splenectomy to improve health and rescue them from the consequences of hypersplenism and cytopenias.

Other specific subgroups of patients who are likely to have a different prognosis from the typical patient are:

- Those patients with poor or absent venous access and needle phobia who attend infrequently may need intensification of care but have been put off by the need for ERT
- Those patients who develop strong and persistently high antibody titres and/or infusion reactions to enzyme preparations
- Those patients (around 30% with type 1 Gaucher disease) who develop monoclonal gammopathy that is a risk factor for the eventual development of multiple myeloma.
- Those patients who have cardiovascular and pulmonary manifestations of Gaucher disease. Macrophage-targeted enzyme therapy is not taken up by the expanded populations of pathological alveolar macrophages; a systemically active small molecular inhibitor of glucosylceramide biosynthesis would be likely to have critical beneficial.effects in this life-threatening complication

- Those patients with type 1 Gaucher disease and Parkinsonism. The disability of this subgroup of patients renders home care and independence from hospital services for infusions is particularly difficult and may lead to premature termination of Gaucher-specific therapy.

It is stated that all of the above sub-groups of patients should have the potential enhanced benefit from the availability of the technology of eliglustat; particularly prevention of the malignant complications of Gaucher disease may provide more than niche value for this new technology.

It is pointed out that the advantage of eliglustat therapy is that this is an orally active drug approved as a first-line therapy for adults with type 1 Gaucher disease. The advantages of an oral therapy can be attested from the viewpoint of patient choice and preferences. The enzyme therapy infusion is an undoubted burden and a financial cost for the NHS. Furthermore, infusions are painful and inconvenient for patients. Patients who receive intravenous therapies are also at risk of developing needle-phobia, poor venous access through damaged veins, and impaired compliance, as well as a small risk of septic infection. As such, compared with the ERT infusions, compliance with eliglustat therapy is likely to be increased. The submission stated that the cost of ERT administration is £500 per 4 weeks compared to £35 per 4 weeks for an oral therapy.

Changes to service delivery and resources required if eliglustat recommended

It is stated that because most UK patients diagnosed with GD are eligible for eliglustat treatment and currently receive ERT, the delivery of care with eliglustat would not generate increased numbers of treated patients or require additional specialist nurses or physicians. On the contrary, it is likely that home nursing and storage requirements will be reduced. The new technology of eliglustat requires cytochrome CYP2D6 genotype testing to see if the patient is a rapid or slow metabolizer. This testing could be made available through industry. An EMA approved reference centre for the CYP2D6 predictive genotyping has been established by the company for approved use. Currently the company aims to provide this service, but the arrangement in the long-term needs to be established. There is a need for consideration of plasma drug monitoring at the initiation of therapy or if an interacting medication is initiated. There is also a need for a 24-hour help line to advise on drug interactions. No further resources additional to the lysosomal storage disorder (LSD) specialist centres will be required. Based on the NHS England perspective, it will be important for patients to remain under the care of expert centres for initiation and monitoring of eliglustat therapy if this drug is to be recommended.

Conclusion

It is stated that eliglustat in clinical practice will be used as an alternative first-line therapeutic option to naive or enzyme-experienced adult patients with GD1 without limitations by disease severity or suitability for ERT. Given the obvious advantages, of eliglustat as an oral therapy there is an

expectation that, should eliglustat be approved for treating adult patients with GD1there will be a rapid transfer of patients from ERT to eliglustat.

7.2 Patient support group submission

A submission was made by Gauchers Association Limited. This has been summarised by the ERG in Section 7.2.1 below. This patient association had conducted a patient survey and the results were submitted to NICE. The ERG presents a summary of the findings in Section 7.2.2.

7.2.1 Gauchers Association Ltd HST Submission Summary

Established in 1991, the Gauchers Association aims to represent and provide support and information to patients, families, and carers of those suffering from Gaucher diseases to ensure all have access to best practice in diagnosis, treatment and care. The Association is in contact with 236 of the 310 identified Gaucher patients in the UK & Ireland and lobby the research industry and Government on their behalf.

The opinions of patients in this submission were gathered from a survey of 39 Gauchers patients undertaken in 2014, and a third-party study of the experiences of 22 Gaucher patients commissioned by the GA and Shire to more efficiently target resources and help diagnose the disease earlier.

The latter study found patients often experienced symptoms from a young age, however, 18% of respondents were not referred beyond their GP for 11+ years, with only 40% of patients receiving an accurate diagnosis within a year of symptom onset. The mean time between onset of symptoms and diagnosis was 7 years, it was not uncommon for patients to see 3-4 different healthcare professionals before diagnosis, occurring up to 31 years after the appearance of symptoms. Those symptoms that lead to final diagnosis included bone pain, fatigue, and enlarged spleen or liver, and Gauchers was often suggested only after diagnosis and tests for leukaemia or lymphoma.

The impact upon the quality of life of patients, families, and carers falls into two categories depending on when the patient was diagnosed. Those diagnosed prior to the introduction of enzyme replacement therapy (ERT) suffered debilitating pain, mobility issues, fatigue, and were highly dependent on carers, often having to make major adjustments to work, children, and social lives, or even having to forego these altogether. Many of these patients have suffered irreversible bone damage and have undergone splenectomy, leaving them with varying degrees of disability and even those now on ERT have a relatively poor quality of life; still experiencing fractures and requiring hip replacements. ERT treatment was approved for use in 1994, those diagnosed after ERT and substrate reduction therapy (SRT) were made available reported significant improvement in quality of life, and are often able to work and have a family with minimal issues. UK patients are now prescribed VPRIV upon new diagnosis based on the current NHS drugs framework, however clinicians can still request that a

patient receives Cerezyme on a case by case basis. Two patients have been prescribed SRT due to illegibility for ERT treatment or on compassionate grounds.

Establishment of the Gauchers Association facilitated patients' contact with specialist doctors and improved general availability of information, but understanding outside of the patient community remains low, even among doctors. Patients report many challenges of living with an 'invisible' disease, and often have difficulty accessing care, disability benefits, and employment support such as reduced working hours and time off for appointments and illness. Frequent ERT infusion and specialist clinic appointments can interfere with work and presents an additional financial burden, limiting patient freedom for holiday and studying. Once physical symptoms subside after commencing treatment, many patients are able to live a relatively normal life with no emotional effects of Gaucher, though living with a long term genetic condition can have a significant effect upon the psychological wellbeing of some patients and their families, particularly when family is also responsible for treatment and care. Some patients suffer from depression and confidence issues as a result of their disease; anxiety is common due to a heightened awareness of future health and morbidity, with uncertainty about the severity of disease manifestation in later life.

Oral treatment would have several benefits to patients. Many have been receiving regular intravenous ERT infusion for over 20 years and as such report increasing difficulty performing cannulation as veins collapse. The longer they receive ERT, the more difficult venous access will become, placing additional stress and pressure on whomever is administering the treatment, usually family members. Some patients also start producing antibodies against ERT which results in allergic reactions to the infusion, causing many to withdraw from treatment and a relapse of their disease. Availability of an equally effective oral therapy would mean patients in these cases, with needle phobia or on palliative care would have another option for treatment, and would allow a reduction of the homecare burden and eliminating the need for venous access. The logistics of the ERT cold-chain and equipment management also pose an inconvenience; frequent drug deliveries, a controlled drugs fridge and sharps bins would no longer be required when on oral therapy; allowing greater freedom to travel and study, and the potential to keep the condition private. This is a commonly cited benefit of oral therapy; many patients would like the ability to incorporate treatment into their daily routine without disruption to work, family, and social life. For those patients unable to use ERT, eliglustat offers an effective, better tolerated alternative to miglustat.

Patients perceive there to be a number of disadvantages to the oral therapy, however. It is only suitable for a limited number of Gaucher patients; pregnancy and medications associated with many co-morbidities preclude its prescription, as do existing cardiac diseases, renal impairment, and hepatic impairment. SRT Eliglustat does not address the neurological aspects of Gaucher disease in type 2

and 3 patients. Due to known side effects of miglustat (Zavesca), uptake of existing oral therapy has been low; there are currently only 6 patients in the UK on SRT eliglustat, four of whom were part of the original clinical trial, suggesting interest in new oral treatments may be limited. Genotyping must be carried out on potential eliglustat recipients, ultra-rapid CYP2D6 metabolisers and indeterminate metabolisers are not eligible for treatment as the drug will be ineffective for these individuals. Compliance may also be an issue; planning, drug delivery, and nurse visits provide built-in compliance for ERT, whereas tablets must be taken once or twice a day on the patient's own volition. Having to avoid certain foods may also result in compliance issues. Many patients voiced concern about forgetting or getting into the habit of skipping treatment, particularly when they are not feeling unwell, while several have said they prefer the less frequent infusions over taking tablets daily. Most patients are concerned about the potential side effects associated with SRT eliglustat and this could pose a major obstacle to uptake, those on highly efficacious ERT currently experience very few side effects and want reassurance they could switch back to this treatment if the oral therapy is less effective or they start experiencing side effects.

7.2.2 Gauchers Association Ltd Patient Survey Responses Summary

This survey was commissioned by the Gaucher's Association in 2014 and was sent to all Gaucher's disease patients currently living in England for whom the Association had an email address, receiving 39 responses. The survey asked for patients' views and experiences with the condition and their thoughts on the new oral technology.

Q1 Describe your diagnosis journey, who did you see, how long did it take, was there a delay, were you diagnosed with something else before getting a diagnosis? If you were a child when you were diagnosed, it would be helpful to ask your parents to help complete this question.

60% of those patients reporting age of diagnosis were first diagnosed with Gaucher's disease as children, often initially diagnosed as leukaemia or lymphoma until further testing. Diagnosis in later life is also common, with diagnosis in adulthood occurring from age 19 to into the 60s. Those reporting an exact age of diagnosis were on average 17 years old (SD 15.5). 9 of the 39 respondents report undergoing splenectomy.

Q2 Can you tell us what challenges you have faced living with a rare disease?

Responses varied often based on time since diagnosis and availability of treatments, many patients report feeling socially isolated and unable to work or carry out day to day tasks, particularly those

who remained untreated for much of their lives. Lack of understanding of Gaucher's in the medical community and among family and friends caused anxiety and loneliness for many. For those diagnosed more recently to whom ERT treatment was available a relatively normal and productive life was possible.

Q3 Where did you go to find information on Gaucher Disease once you got your diagnosis, was it easy to find information, did it tell you everything you needed to know? Were there things you couldn't find the answer to?

Again responses varied widely depending on when they were diagnosed. Older patients report knowing very little about the disease prior to the foundation of the Gaucher's Association and the internet. Access to information was dependent on the expertise of the patients' doctors, now it is much easier to find.

Q4 Can you tell us how your diagnosis impacted on you and your family?

For many the diagnosis placed a significant psychological burden upon their family, as a rare genetic condition it caused anxiety and guilt among parents and the implications of chronic illness and care requirements place strain on relationships. Diagnosis and the prospect of treatment was a relief for others after nameless symptoms and earlier suggestions of terminal disease.

Q5 You will be treated at one of the designated centres for your Gaucher disease, can you describe the advantages and disadvantages of this set up.

Many patients have to travel a long way to their designated treatment centres, causing disruption to work and life balance, requiring time off work for themselves and those attending with them. Consistency and level of expertise available at the specialist clinics cited as main advantages.

Q6 Can you tell us how having Gaucher Disease affects your daily life, have you had to adapt the way you live in anyway? e.g. physical, emotional, ability to go to school, work, college, go out to social gatherings etc.

26% of respondents reported being unable to work or having great difficulty doing so due to their disease, a further 21% found they had to make major adaptations to their work and lifestyle.

Q7 Are you on Enzyme Replacement Therapy?

Yes – 37 (94.9%)
No – 5 (5.1%)

One respondent receives miglustat.

Q8 If you answered yes to Q7 do you still have any unmet medical needs that you feel ERT has not helped with?

31 respondents (79.5%) said they had no further unmet medical needs or were unsure. Most of those who felt ERT was insufficient for their needs had already experienced extensive bone damage and permanent disability prior to the introduction of ERT, or had other comorbidities causing their health issues.

Q9 Were you diagnosed before Enzyme Replacement Therapy was available?

Yes – 23 (59%)
No – 16 (41%)

Q10 If you answered Yes to Q9 then please describe to us the physical and emotional challenges of living with a condition that did not have a treatment.

General reduced quality of life, psychological issues and depression common before treatment.

Q11 Have you heard about the new oral therapy that Genzyme have developed for Type 1 adults with Gaucher disease?

Yes – 36 (92.3%)
No – 3 (7.7%)

Q12 Would you consider taking an oral treatment for your Gaucher disease rather than regular enzyme replacement therapy infusions, subject to a full consultation with your doctor?

Yes – 37 (94.9%)
No – 2 (5.1%)

Q13 What do you consider to be the advantages of taking an oral therapy? What difference do you think it would make to you?

Most believe oral therapy would give more freedom to travel for work and pleasure, convenience and more general lifestyle flexibility. Would prevent damage caused by regular ERT infusion and risks attached which are a concern for many respondents.

Q14 What disadvantages do you consider an oral therapy would have?

Most respondents had concerns about side effects or reduced efficacy of the oral therapy compared to ERT, compliance also considered a challenge for some.

Q15 Is there anything else that you would like to share with us that would provide a unique perspective on what it is like for you and your family living with Gaucher disease?

Most points repeated those covered by the earlier questions. One respondent expressed a fear of developing Parkinson's disease.

8 Overall conclusions

8.1 Summary of clinical effectiveness issues

A key concern for the ENCORE trial was the lack of adequate justification for the choice of the non-inferiority margin which was chosen in the data analysis. The non-inferiority margin of 25% was higher than the more usual 15%. This and the assumption that a lower efficacy with eliglustat of up to 10% compared with imiglucerase is not clinically important was not justified, statistically or clinically. Therefore, whether eliglustat is clinically non-inferior to imiglucerase in treating ERT-stable patients remains uncertain.

Data for the effectiveness of eliglustat in untreated patients is limited. Whilst the results from the ENGAGE placebo controlled RCT and single-arm Phase II studies are positive, the number of patients studied is small, only 66 in total.

Data for the effectiveness of eliglustat in the long-term is limited. The 4 year follow-up data from ENCORE and the Phase II trial are based on only small number of patients (63 in total), with no clear information regarding patients not included in the analysis. Furthermore, as GD1 is a lifelong condition, 4 years follow-up is short compared to life-long administration. This uncertainty is compounded by the long-term implications of a possible small reduction in efficacy with eliglustat compared with ERT.

The evaluation of the adverse effects of eliglustat was primarily limited to the short-term data from two RCTs of adult GD1 patients. Long-term adverse effect data were from on a single arm Phase II trial with a small sample size. While the short-term adverse effect data indicate that eliglustat appears to be generally well tolerated, the long-term adverse effect profile remains uncertain because the company failed to provide longer term follow-up data from controlled studies.

There is uncertainty regarding the doses of ERT used in clinical practice. This has implications for the generalisability of the findings of the ENCORE trial: In ENCORE nearly 60% of patients were receiving doses of at least 35 U/kg every two weeks. SPCs for imiglucerase and velaglucerase recommend higher starting dose of 60 U/kg every two weeks however the SOP, developed by expert consensus reports that a maintenance dose of 15-30 U/kg is appropriate for most patients on either imiglucerase or velaglucerase, though this may be increased to 60 U/kg. Expert opinion suggests typical doses of 25 U/kg (range: 15-28 U/kg) or 20-40 U/kg (practitioner submission to NICE). Across the observational studies mean doses of ERT reported ranged from 34.2 U/kg/4 weeks to 67.5 U/kg 4 weeks.

8.2 Summary of cost-effectiveness issues

The economic model presented in CS contained a number of significant weaknesses. The most significant of these relates to the structure of the model and assumptions made regarding the comparative effectiveness of eliglustat and ERT treatments. The model structure adopted by the company is based on the GD1 DS3 score. While the DS3 score is a validated measure of disease severity, the ERG questions the appropriateness of using this scoring system as the basis of the model structure as the DS3 score system appears to be a relative insensitive measure of disease severity and as such apparent differences in the clinical effectiveness of eliglustat and ERT observed in the ENCORE trial are not observed as differences in DS3 score. Furthermore, the model makes the very strong assumption of equal effectiveness in the long-term, basing long term transitions on those observed in a registry study. This assumption is not supported by any clinical data other than the 12 month trial data from the ENCORE which, as discussed above, appears to indicate a small difference in clinical effectiveness in favour of the ERT treatment, imiglucerase.

In addition to the significant structural issues noted above the, the ERG did not consider that the company had adequately justified a number of critical assumptions underpinning their base-case analysis. The most significant of which related to the dose of ERT assumed and the HRQoL benefits associated with oral treatment. Both of these assumptions have a significant impact on estimated cost benefits estimated by the model.

8.3 Conclusions of ERG critique

Based on the ERG's analysis, implementing eliglustat in the NHS would result in significantly increased costs with highly uncertain health benefits.

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10 Appendices

11 Appendices

11.1.1 Discontinuation

Zero Discontinuation

Table 70: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

Patient Group	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Health states: 0.00	Drug acquisition: £ 126,197
	AE events: -0.01	Administration: -£ 268,648
	Oral therapy increment: 2.41	Management/ social service costs: £193
	Total: 2.40	**Total: -£ 142,258**
ERT stable PM	Health states: 0.00	Drug acquisition: -£ 1,948,435
	AE events: -0.01	Administration: -£ 268,648
	Oral therapy increment: 2.41	Management/ social service costs: £193
	Total: 2.40	**Total: -£ 2,216,890**
ERT naïve IM/EM	Health states: 0.00	Drug acquisition: £ 133,687
	AE events: 0.00	Administration: -£ 284,594
	Oral therapy increment: 2.56	Management/ social service costs: £0
	Total: 2.56	**Total: -£ 150,907**
ERT naïve PM	Health states: 0.00	Drug acquisition: -£ 2,064,085
	AE events: 0.00	Administration: -£ 284,594
	Oral therapy increment: 2.56	Management/ social service costs: £0
	Total: 2.56	**Total: -£ 2,348,679**

Table 71: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

Patient Group	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Health states: 0.00	Drug acquisition: -£ 1,145,778
	AE events: -0.01	Administration: -£ 268,648
	Oral therapy increment: 2.41	Management/ social service costs: £193
	Total: 2.40	**Total: -£ 1,414,232**
ERT stable PM	Health states: 0.00	Drug acquisition: -£ 3,220,410
	AE events: -0.01	Administration: -£ 268,648
	Oral therapy increment: 2.41	Management/ social service costs: £193
	Total: 2.40	**Total: -£ 3,488,864**
ERT naïve IM/EM	Health states: 0.00	Drug acquisition: -£ 1,213,785
	AE events: 0.02	Administration: -£ 284,594

	Oral therapy increment: 2.56	Management/ social service costs: £0
	Total: 2.58	**Total: -£ 1,498,379**
ERT naïve PM	Health states: 0.00	Drug acquisition: -£ 3,411,558
	AE events: 0.02	Administration: -£ 284,594
	Oral therapy increment: 2.56	Management/ social service costs: £0
	Total: 2.58	**Total: -£ 3,696,151**

Table 72: Budget Impact (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**-£1,898,211**	**-£3,039,542**	**-£3,715,424**	**-£4,375,437**	**-£5,008,718**
Cumulative Total	**-£1,898,211**	**-£4,937,752**	**-£8,653,177**	**-£13,028,613**	**-£18,037,331**

Discontinuation from 104 week ENCORE trial

Table 73: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

Patient Group	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Health states: 0.00	Drug acquisition: £ 117,772
	AE events: -0.01	Administration: -£ 266,942
	Oral therapy increment: 2.25	Management/ social service costs: £193
	Total: 2.24	**Total: -£ 148,976**
ERT stable PM	Health states: 0.00	Drug acquisition: -£ 1,818,368
	AE events: -0.01	Administration: -£ 266,942
	Oral therapy increment: 2.25	Management/ social service costs: £193
	Total: 2.24	**Total: -£ 2,085,116**
ERT naïve IM/EM	Health states: 0.00	Drug acquisition: £ 55,575
	AE events: 0.00	Administration: -£ 269,563
	Oral therapy increment: 2.39	Management/ social service costs: £0
	Total: 2.39	**Total: -£ 213,988**

ERT naïve PM	Health states: 0.00	Drug acquisition: -£ 1,994,617
	AE events: 0.00	Administration: -£ 269,563
	Oral therapy increment: 2.39	Management/ social service costs: £0
	Total: 2.39	**Total: -£ 2,264,180**

Table 74: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

Patient Group	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Health states: 0.00	Drug acquisition: -£ 1,069,291
	AE events: -0.01	Administration: -£ 266,942
	Oral therapy increment: 2.25	Management/ social service costs: £193
	Total: 2.24	**Total: -£ 1,336,040**
ERT stable PM	Health states: 0.00	Drug acquisition: -£ 3,005,431
	AE events: -0.01	Administration: -£ 266,942
	Oral therapy increment: 2.25	Management/ social service costs: £193
	Total: 2.24	**Total: -£ 3,272,179**
ERT naïve IM/EM	Health states: 0.00	Drug acquisition: -£ 1,063,145.26
	AE events: 0.02	Administration: -£ 269,563.08
	Oral therapy increment: 2.39	Management/ social service costs: £0
	Total: 2.41	**Total: -£ 1,332,708**
ERT naïve PM	Health states: 0.00	Drug acquisition: -£ 3,113,337
	AE events: 0.02	Administration: -£ 269,563
	Oral therapy increment: 2.39	Management/ social service costs: £0
	Total: 2.41	**Total: -£ 3,382,900**

Table 75: Budget Impact (ERT Stable IM/EM patients)

	2015	2016	2017	2018	2019
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**-£1,867,324**	**-£2,974,848**	**-£3,600,490**	**-£4,210,940**	**-£4,807,379**
Cumulative Total	**-£1,867,324**	**-£4,842,172**	**-£8,442,662**	**-£12,653,602**	**-£17,460,981**

11.1.2 Mortality

Revised mortality applied to all GD1 patients

Table 76: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

Patient Group	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Health states: 0.00	Drug acquisition: £ 125,903
	AE events: -0.01	Administration: -£ 281,874
	Oral therapy increment: 2.41	Management/ social service costs: £ 194
	Total: 2.40	**Total: -£ 155,778**
ERT stable PM	Health states: 0.00	Drug acquisition: -£ 1,943,869
	AE events: -0.01	Administration: -£ 281,874
	Oral therapy increment: 2.41	Management/ social service costs: £ 194
	Total: 2.40	**Total: -£ 2,225,550**
ERT naïve IM/EM	Health states: 0.00	Drug acquisition: £ 57,294
	AE events: 0.00	Administration: -£ 285,879
	Oral therapy increment: 2.57	Management/ social service costs: £0
	Total: 2.57	**Total: -£ 228,586**
ERT naïve PM	Health states: 0.00	Drug acquisition: -£ 2,150,408
	AE events: 0.00	Administration: -£ 285,879
	Oral therapy increment: 2.57	Management/ social service costs: £0
	Total: 2.57	**Total: -£ 2,436,287**

Table 77: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

Patient Group	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Health states: 0.00	Drug acquisition: -£ 1,143,095
	AE events: -0.01	Administration: -£ 281,874
	Oral therapy increment: 2.41	Management/ social service costs: £194
	Total: 2.40	**Total: -£ 1,424,776**
ERT stable PM	Health states: 0.00	Drug acquisition: -£ 3,212,867
	AE events: -0.01	Administration: -£ 281,874
	Oral therapy increment: 2.41	Management/ social service costs: £194
	Total: 2.40	**Total: -£ 3,494,548**
ERT naïve IM/EM	Health states: 0.00	Drug acquisition: -£ 1,142,272
	AE events: 0.02	Administration: -£ 285,879

	Oral therapy increment: 2.57	Management/ social service costs: £0
	Total: 2.59	**Total: -£ 1,428,151**
ERT naïve PM	Health states: 0.00	Drug acquisition: -£ 3,349,973
	AE events: 0.02	Administration: -£ 285,879
	Oral therapy increment: 2.57	Management/ social service costs: £0
	Total: 2.59	**Total: -£ 3,635,853**

Table 78: Budget Impact (ERT Stable IM/EM Patients)

	2015	2016	2017	2018	2019
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**-£1,873,401**	**-£3,005,751**	**-£3,687,544**	**-£4,366,946**	**-£5,049,320**
Cumulative Total	**-£1,873,401**	**-£4,879,152**	**-£8,566,696**	**-£12,933,642**	**-£17,982,962**

Revised mortality applied to 'Marked' and 'Severe' states

Table 79: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

Patient Group	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Health states: 0.00	Drug acquisition: £ 132,735
	AE events: -0.01	Administration: -£ 296,445
	Oral therapy increment: 2.54	Management/ social service costs: £193
	Total: 2.53	**Total: -£ 163,517**
ERT stable PM	Health states: 0.00	Drug acquisition: -£ 2,049,488
	AE events: -0.01	Administration: -£ 296,445
	Oral therapy increment: 2.54	Management/ social service costs: £193
	Total: 2.53	**Total: -£ 2,345,740**
ERT naïve IM/EM	Health states: 0.00	Drug acquisition: £ 63,234
	AE events: 0.00	Administration: -£ 298,593

	Oral therapy increment: 2.68	Management/ social service costs: £0
	Total: 2.68	**Total: -£ 235,359**
ERT naïve PM	Health states: 0.00	Drug acquisition: -£ 2,242,648
	AE events: 0.00	Administration: -£ 298,593
	Oral therapy increment: 2.68	Management/ social service costs: £0
	Total: 2.68	**Total: -£ 2,541,242**

Table 80: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

Patient Group	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Health states: 0.00	Drug acquisition: -£ 1,205,207
	AE events: -0.01	Administration: -£ 296,445
	Oral therapy increment: 2.54	Management/ social service costs: £193
	Total: 2.53	**Total: -£ 1,501,459**
ERT stable PM	Health states: 0.00	Drug acquisition: -£ 3,387,430
	AE events: -0.01	Administration: -£ 296,445
	Oral therapy increment: 2.54	Management/ social service costs: £193
	Total: 2.53	**Total: -£ 3,683,682**
ERT naïve IM/EM	Health states: 0.00	Drug acquisition: -£ 1,196,464
	AE events: 0.02	Administration: -£ 298,593
	Oral therapy increment: 2.68	Management/ social service costs: £0
	Total: 2.70	**Total: -£ 1,495,057**
ERT naïve PM	Health states: 0.00	Drug acquisition: -£ 3,502,347
	AE events: 0.02	Administration: -£ 298,593
	Oral therapy increment: 2.68	Management/ social service costs: £0
	Total: 2.70	**Total: -£ 3,800,940**

Table 81: Budget Impact (ERT Stable IM/EM Patients)

	2015	2016	2017	2018	2019
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**-£1,873,401**	**-£3,005,751**	**-£3,687,544**	**-£4,366,946**	**-£5,049,320**

Cumulative Total	**-£1,873,401**	**-£4,879,152**	**-£8,566,696**	**-£12,933,642**	**-£17,982,962**

Zero Mortality

Table 82: Budget Impact (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**-£1,873,401**	**-£3,009,786**	**-£3,702,033**	**-£4,395,291**	**-£5,097,050**
Cumulative Total	**-£1,873,401**	**-£4,883,188**	**-£8,585,220**	**-£12,980,511**	**-£18,077,561**

11.1.3 HRQoL: impact of increment for oral administration

Increment equal to '0.025'

Table 83: Incremental QALYs (Eliglustat vs. Imiglucerase)

Patient Group	Incremental QALYs
ERT stable IM/EM	Health states: 0.00
	AE events: -0.01
	Oral therapy increment: 0.48
	Total: 0.47
ERT stable PM	Health states: 0.00
	AE events: -0.01
	Oral therapy increment: 0.48
	Total: 0.47
ERT naïve IM/EM	Health states: 0.00
	AE events: 0.00
	Oral therapy increment: 0.51
	Total: 0.51
ERT naïve PM	Health states: 0.00
	AE events: 0.00
	Oral therapy increment: 0.51

	Total: 0.51

Table 84: Incremental QALYs (Eliglustat vs. Velaglucerase)

Patient Group	Incremental QALYs
ERT stable IM/EM	Health states: 0.00
	AE events: -0.01
	Oral therapy increment: 0.48
	Total: 0.47
ERT stable PM	Health states: 0.00
	AE events: -0.01
	Oral therapy increment: 0.48
	Total: 0.47
ERT naïve IM/EM	Health states: 0.00
	AE events: 0.02
	Oral therapy increment: 0.51
	Total: 0.53
ERT naïve PM	Health states: 0.00
	AE events: 0.02
	Oral therapy increment: 0.51
	Total: 0.53

Increment equal to '0.09'

Table 85: Incremental QALYs (Eliglustat vs. Imiglucerase)

Patient Group	Incremental QALYs
ERT stable IM/EM	Health states: 0.00
	AE events: -0.01
	Oral therapy increment: 1.72
	Total: 1.71
ERT stable PM	Health states: 0.00
	AE events: -0.01
	Oral therapy increment: 1.72
	Total: 1.71
ERT naïve IM/EM	Health states: 0.00
	AE events: 0.00
	Oral therapy increment: 1.82
	Total: 1.82

ERT naïve PM	Health states: 0.00
	AE events: 0.00
	Oral therapy increment: 1.82
	Total: 1.82

Table 86: Incremental QALYs (Eliglustat vs. Velaglucerase)

Patient Group	Incremental QALYs
ERT stable IM/EM	Health states: 0.00
	AE events: -0.01
	Oral therapy increment: 1.72
	Total: 1.71
ERT stable PM	Health states: 0.00
	AE events: -0.01
	Oral therapy increment: 1.72
	Total: 1.71
ERT naïve IM/EM	Health states: 0.00
	AE events: 0.02
	Oral therapy increment: 1.82
	Total: 1.84
ERT naïve PM	Health states: 0.00
	AE events: 0.02
	Oral therapy increment: 1.82
	Total: 1.84

Increment equal to '0.05'

Table 87: Incremental QALYs (Eliglustat vs. Imiglucerase)

Patient Group	Incremental QALYs
ERT stable IM/EM	Health states: 0.00
	AE events: -0.01
	Oral therapy increment: 0.95
	Total: 0.94
ERT stable PM	Health states: 0.00
	AE events: -0.01
	Oral therapy increment: 0.95
	Total: 0.94

ERT naïve IM/EM	Health states: 0.00
	AE events: 0.00
	Oral therapy increment: 1.01
	Total: 1.01
ERT naïve PM	Health states: 0.00
	AE events: 0.00
	Oral therapy increment: 1.01
	Total: 1.01

Table 88: Incremental QALYs (Eliglustat vs. Velaglucerase)

Patient Group	Incremental QALYs
ERT stable IM/EM	Health states: 0.00
	AE events: -0.01
	Oral therapy increment: 0.95
	Total: 0.94
ERT stable PM	Health states: 0.00
	AE events: -0.01
	Oral therapy increment: 0.95
	Total: 0.94
ERT naïve IM/EM	Health states: 0.00
	AE events: 0.02
	Oral therapy increment: 1.01
	Total: 1.03
ERT naïve PM	Health states: 0.00
	AE events: 0.02
	Oral therapy increment: 1.01
	Total: 1.03

11.1.4 Administration Costs

Alternative administration costs for ERT (home therapy cost equal to hospital cost)

Table 89: Incremental Costs (Eliglustat vs. Imiglucerase)

Patient Group	Incremental Cost
ERT stable IM/EM	Drug acquisition: £ 119,757
	Administration: -£ 144,963
	Management/ social service costs: £193

	Total: -£ 25,013
ERT stable PM	Drug acquisition: -£ 1,849,004
	Administration: -£ 144,963
	Management/ social service costs: £193
	Total: -£ 1,993,774
ERT naïve IM/EM	Drug acquisition: £ 57,693
	Administration: -£ 153,523
	Management/ social service costs: £0
	Total: -£ 95,830
ERT naïve PM	Drug acquisition: -£ 2,027,318
	Administration: -£ 153,523
	Management/ social service costs: £0
	Total: -£ 2,180,841

Table 90: Incremental Costs (Eliglustat vs. Velaglucerase)

Patient Group	**Incremental Cost**
ERT stable IM/EM	Drug acquisition: -£ 1,087,307
	Administration: -£ 144,963
	Management/ social service costs: £193
	Total: -£ 1,232,077
ERT stable PM	Drug acquisition: -£ 3,056,068
	Administration: -£ 144,963
	Management/ social service costs: £193
	Total: -£ 3,200,838
ERT naïve IM/EM	Drug acquisition: -£ 1,082,375
	Administration: -£ 153,523
	Management/ social service costs: £0
	Total: -£ 1,235,898
ERT naïve PM	Drug acquisition: -£ 3,167,387
	Administration: -£ 153,523
	Management/ social service costs: £0
	Total: -£ 3,320,910

Table 91: Budget Impact (ERT Stable IM/EM Patients)

	2017	**2018**	**2019**	**2020**	**2021**
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**-£1,591,631**	**-£2,531,704**	**-£3,054,831**	**-£3,563,821**	**-£4,059,895**
Cumulative Total	**-£1,591,631**	**-£4,123,335**	**-£7,178,166**	**-£10,741,987**	**-£14,801,882**

Dispensary Costs for Eliglustat (£14.40 per month)

Table 92: Incremental Costs (Eliglustat vs. Imiglucerase)

Patient Group	Incremental Cost
ERT stable IM/EM	Drug acquisition: £ 119,757
	Administration: -£ 264,045
	Management/ social service costs: £193
	Total: -£ 144,095
ERT stable PM	Drug acquisition: -£ 1,849,004
	Administration: -£ 264,045
	Management/ social service costs: £193
	Total: -£ 2,112,855
ERT naïve IM/EM	Drug acquisition: £ 57,693
	Administration: -£ 266,498
	Management/ social service costs: £0
	Total: -£ 208,805
ERT naïve PM	Drug acquisition: -£ 2,027,318
	Administration: -£ 266,498
	Management/ social service costs: £0
	Total: -£ 2,293,816

Table 93: Incremental Costs (Eliglustat vs. Velaglucerase)

Patient Group	Incremental Cost
ERT stable IM/EM	Drug acquisition: -£ 1,087,307
	Administration: -£ 264,045
	Management/ social service costs: £193
	Total: -£ 1,351,158

ERT stable PM	Drug acquisition: -£ 3,056,068
	Administration: -£ 264,045
	Management/ social service costs: £193
	Total: -£ 3,319,919
ERT naïve IM/EM	Drug acquisition: -£ 1,082,375
	Administration: -£ 266,498
	Management/ social service costs: £0
	Total: -£ 1,348,874
ERT naïve PM	Drug acquisition: -£ 3,167,387
	Administration: -£ 266,498
	Management/ social service costs: £0
	Total: -£ 3,433,885

Table 94: Budget Impact (ERT Stable IM/EM Patients)

	2017	**2018**	**2019**	**2020**	**2021**
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**-£1,865,274**	**-£2,974,518**	**-£3,606,982**	**-£4,224,111**	**-£4,824,765**
Cumulative Total	**-£1,865,274**	**-£4,839,793**	**-£8,446,775**	**-£12,670,886**	**-£17,495,651**

11.1.5 Dosing

Vial wastage for ERT

Table 95: Incremental Costs (Eliglustat vs. Imiglucerase)

Patient Group	**Incremental Cost**
ERT stable IM/EM	Drug acquisition: -£ 14,411
	Administration: -£ 267,344
	Management/ social service costs: £193
	Total: -£ 281,562
ERT stable PM	Drug acquisition: -£ 1,983,172
	Administration: -£ 267,344
	Management/ social service costs: £193

	Total: -£ 2,250,322
ERT naïve IM/EM	Drug acquisition: -£ 77,146
	Administration: -£ 269,992
	Management/ social service costs: £0
	Total: -£ 347,138
ERT naïve PM	Drug acquisition: -£ 2,162,157
	Administration: -£ 269,992
	Management/ social service costs: £0
	Total: -£ 2,432,149

Table 96: Incremental Costs (Eliglustat vs. Velaglucerase)

Patient Group	Incremental Cost
ERT stable IM/EM	Drug acquisition: -£ 1,263,895
	Administration: -£ 267,344
	Management/ social service costs: £193
	Total: -£ 1,531,045
ERT stable PM	Drug acquisition: -£ 3,232,656
	Administration: -£ 267,344
	Management/ social service costs: £193
	Total: -£ 3,499,806
ERT naïve IM/EM	Drug acquisition: -£ 1,259,847
	Administration: -£ 269,992
	Management/ social service costs: £0
	Total: -£ 1,529,839
ERT naïve PM	Drug acquisition: -£ 3,344,858
	Administration: -£ 269,992
	Management/ social service costs: £0
	Total: -£ 3,614,850

AWMSG Study Dosage and Weight inputs

Table 97: Incremental Costs (Eliglustat vs.Imiglucerase)

Patient Group	Incremental Cost
ERT stable IM/EM	Drug acquisition: £ 736,041
	Administration: -£ 223,652
	Management/ social service costs: £193

	Total: £ 512,583
ERT stable PM	Drug acquisition: -£ 1,232,719
	Administration: -£ 223,652
	Management/ social service costs: £193
	Total: -£ 1,456,178
ERT naïve IM/EM	Drug acquisition: £ 721,528
	Administration: -£ 226,082
	Management/ social service costs: £0
	Total: £ 495,446
ERT naïve PM	Drug acquisition: -£ 1,363,483
	Administration: -£ 226,082
	Management/ social service costs: £0
	Total: -£ 1,589,565

Table 98: Incremental Costs (Eliglustat vs. Velaglucerase)

Patient Group	**Incremental Cost**
ERT stable IM/EM	Drug acquisition: -£ 276,171
	Administration: -£ 223,652
	Management/ social service costs: £195
	Total: -£ 499,629
ERT stable PM	Drug acquisition: -£ 2,244,932
	Administration: -£ 223,652
	Management/ social service costs: £193
	Total: -£ 2,468,391
ERT naïve IM/EM	Drug acquisition: -£ 234,504
	Administration: -£ 226,082
	Management/ social service costs: £0
	Total: -£ 460,586
ERT naïve PM	Drug acquisition: -£ 2,319,515
	Administration: -£ 226,082
	Management/ social service costs: £0
	Total: -£ 2,545,597

Table 99: Budget Impact (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**-£3,192**	**£3,004**	**£22,343**	**£50,138**	**£100,351**
Cumulative Total	**-£3,192**	**-£188**	**£22,155**	**£72,293**	**£172,644**

Trial Dosage of Eliglustat

Table 100: Incremental Costs (Eliglustat vs. Imiglucerase)

Patient Group	Incremental Cost
ERT stable IM/EM	Drug acquisition: £ 671,010
	Administration: -£ 267,344
	Management/ social service costs: £193
	Total: £ 403,859
ERT stable PM	Drug acquisition: -£ 1,573,378
	Administration: -£ 267,344
	Management/ social service costs: £193
	Total: -£ 1,840,528
ERT naïve IM/EM	Drug acquisition: £ 641,496
	Administration: -£ 269,992
	Management/ social service costs: £0
	Total: £ 371,504
ERT naïve PM	Drug acquisition: -£ 1,735,417
	Administration: -£ 269,992
	Management/ social service costs: £0
	Total: -£ 2,005,409

Table 101: Incremental Costs (Eliglustat vs. Velaglucerase)

Patient Group	Incremental Cost
ERT stable IM/EM	Drug acquisition: -£ 536,054
	Administration: -£ 267,344

	Management/ social service costs: £195
	Total: -£ 803,204
ERT stable PM	Drug acquisition: -£ 2,780,441
	Administration: -£ 267,344
	Management/ social service costs: £193
	Total: -£ 3,047,591
ERT naïve IM/EM	Drug acquisition: -£ 498,572
	Administration: -£ 269,992
	Management/ social service costs: £0
	Total: -£ 768,564
ERT naïve PM	Drug acquisition: -£ 2,875,485
	Administration: -£ 269,992
	Management/ social service costs: £0
	Total: -£ 3,145,477

Table 102: Budget Impact (ERT Stable IM/EM Patients)

Cost category	2017	2018	2019	2020	2021
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**-£515,371**	**-£814,757**	**-£971,609**	**-£1,116,857**	**-£1,238,395**
Cumulative Total	**-£515,371**	**-£1,330,128**	**-£2,301,737**	**-£3,418,594**	**-£4,656,989**

ERT dosing used in practice

Table 103: Incremental Costs (Eliglustat vs. Imiglucerase)

Patient Group	Incremental Cost
ERT stable IM/EM	Drug acquisition: £ 1,686,481
	Administration: -£ 156,271
	Management/ social service costs: £193
	Total: £ 1,530,403
ERT stable PM	Drug acquisition: -£ 282,280
	Administration: -£ 156,271

	Management/ social service costs: £193
	Total: -£ 438,358
ERT naïve IM/EM	Drug acquisition: £ 1,745,300
	Administration: -£ 158,364
	Management/ social service costs: £0
	Total: £ 1,586,936
ERT naïve PM	Drug acquisition: -£ 339,711
	Administration: -£ 158,364
	Management/ social service costs: £0
	Total: -£ 498,075

Table 104: Incremental Costs (Eliglustat vs. Velaglucerase)

Patient Group	**Incremental Cost**
ERT stable IM/EM	Drug acquisition: £ 974,769
	Administration: -£ 156,271
	Management/ social service costs: £195
	Total: £ 818,691
ERT stable PM	Drug acquisition: -£ 993,992
	Administration: -£ 156,271
	Management/ social service costs: £193
	Total: -£ 1,150,070
ERT naïve IM/EM	Drug acquisition: £ 1,073,090
	Administration: -£ 158,364
	Management/ social service costs: £0
	Total: £ 914,726
ERT naïve PM	Drug acquisition: -£ 1,011,921
	Administration: -£ 158,364
	Management/ social service costs: £0
	Total: -£ 1,170,285

Table 105: Budget Impact (ERT Stable IM/EM Patients)

	2017	**2018**	**2019**	**2020**	**2021**
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**£2,881,060**	**£4,615,015**	**£5,643,986**	**£6,670,768**	**£7,729,203**
Cumulative Total	**£2,881,060**	**£7,496,075**	**£13,140,061**	**£19,810,829**	**£27,540,032**

11.1.6 Efficacy

ENCORE transition probabilities applied to first cycle in treatment naïve patients

Table 106: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

Patient Group	Incremental QALYs	Incremental Cost
ERT naive IM/EM	Health states: -0.02	Drug acquisition: £ 54,809
	AE events: 0.00	Administration: -£ 256,492
	Oral therapy increment: 2.30	Management/ social service costs: £ 504
	Total: 2.28	**Total: -£ 201,180**
ERT naive PM	Health states: -0.02	Drug acquisition: -£ 1,925,952
	AE events: 0.00	Administration: -£ 256,492
	Oral therapy increment: 2.30	Management/ social service costs: £ 504
	Total: 2.28	**Total: -£ 2,181,941**

Table 107: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

Patient Group	Incremental QALYs	Incremental Cost
ERT naive IM/EM	Health states: -0.02	Drug acquisition: -£ 1,028,257
	AE events: 0.02	Administration: -£ 256,492
	Oral therapy increment: 2.30	Management/ social service costs: -£ 504
	Total: 2.30	**Total: -£ 1,284,245**
ERT naive PM	Health states: -0.02	Drug acquisition: -£ 3,009,017
	AE events: 0.02	Administration: -£ 256,492
	Oral therapy increment: 2.30	Management/ social service costs: -£ 504
	Total: 2.30	**Total: -£ 3,265,006**

Table 108: Budget Impact (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**-£1,757,825**	**-£2,801,339**	**-£3,384,498**	**-£3,950,686**	**-£4,510,514**
Cumulative Total	**-£1,757,825**	**-£4,559,164**	**-£7,943,662**	**-£11,894,348**	**-£16,404,862**

11.1.7 Population Size

[redacted] ***Gaucher Patients***

Table 109: Budget Impact (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

293 Gaucher Patients

Table 110: Budget Impact (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**-£1,873,401**	**-£2,994,340**	**-£3,636,465**	**-£4,263,154**	**-£4,873,365**
Cumulative Total	**-£1,873,401**	**-£4,867,741**	**-£8,504,206**	**-£12,767,360**	**-£17,640,725**

11.2 ERG Base-Case Analysis

Table 111: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

Patient Group	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Health states: 0.00	Drug acquisition: £ 1,869,333
	AE events: -0.01	Administration: -£ 157,025
	Oral therapy increment: 1.06	Management/ social service costs: £ 193
	Total: 1.05	**Total: £ 1,712,502**
ERT stable PM	Health states: 0.00	Drug acquisition: -£ 312,889
	AE events: -0.01	Administration: -£ 157,025
	Oral therapy increment: 1.06	Management/ social service costs: £ 193
	Total: 1.05	**Total: -£ 469,721**
ERT naïve IM/EM	Health states: -0.02	Drug acquisition: £ 1,833,454
	AE events: 0.00	Administration: -£ 157,635
	Oral therapy increment: 1.06	Management/ social service costs: £ 504
	Total: 1.04	**Total: £ 1,676,323**
ERT naïve PM	Health states: -0.02	Drug acquisition: -£ 357,252
	AE events: 0.00	Administration: -£ 157,635
	Oral therapy increment: 1.06	Management/ social service costs: £ 504
	Total: 1.04	**Total: -£ 514,382**

Table 112: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

Patient Group	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Health states: 0.00	Drug acquisition: £ 1,080,452
	AE events: -0.01	Administration: -£ 157,025
	Oral therapy increment: 1.06	Management/ social service costs: £ 193
	Total: 1.05	**Total: £ 923,621**
ERT stable PM	Health states: 0.00	Drug acquisition: -£ 1,101,770
	AE events: -0.01	Administration: -£ 157,025
	Oral therapy increment: 1.06	Management/ social service costs: £ 193
	Total: 1.05	**Total: -£ 1,258,602**
ERT naïve IM/EM	Health states: -0.02	Drug acquisition: £ 1,127,802
	AE events: 0.02	Administration: -£ 157,635
	Oral therapy increment: 1.06	Management/ social service costs: £ 504
	Total: 1.06	**Total: £ 970,671**
ERT naïve PM	Health states: -0.02	Drug acquisition: -£ 1,062,904
	AE events: 0.02	Administration: -£ 157,635

	Oral therapy increment: 1.06	Management/ social service costs: £ 504
	Total: 1.06	**Total: -£ 1,220,035**

Table 113: Budget Impact (ERT Stable IM/EM Patients)

	2017	**2018**	**2019**	**2020**	**2021**
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**£2,961,673**	**£4,784,125**	**£5,928,950**	**£7,073,317**	**£8,219,694**
Cumulative Total	**£2,961,673**	**£7,745,798**	**£13,674,748**	**£20,748,065**	**£28,967,758**

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Eliglustat for treating type 1 Gaucher disease [ID 709]

You are asked to check the ERG report from Centre for Reviews and Dissemination and Centre for Health Economics – York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Tuesday 26 July 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

General comments

Issue 1 General comment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Throughout the document there are a number of typographical errors and missing words		We have focused here factual inaccuracies but would like to highlight a number of typographical errors and missing words throughout the document.	The ERG thanks the company for identifying the typographical errors within the ERG report.

Factual inaccuracies

Issue 2 Clarification that patients were not lost to follow up in the 4 year data for ENCORE

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 14/15 *Long-term follow-up data from ENCORE demonstrated that for patients who remain on eliglustat stability on all four composite parameters is maintained over 4 years. Although very few patients withdrew due to adverse events the number of patients in the analysis at 4 years was only 44 out of an original 159 patients: the unexplained loss of patients from follow-up raises a question of how to interpret these long-term results.*	Long-term follow-up data from ENCORE demonstrated that, for patients who remain on eliglustat, stability on all four composite parameters is maintained over 4 years. ~~Although~~ Very few patients withdrew due to adverse events. **Due to the trial protocol, 51 (US) patients were withdrawn from the trial and switched to commercial eliglustat when it became available in the US. A further 48 patients did not have 4 years' worth of data due to the timing of their enrollment and/or the group they were in during the primary analysis. Therefore,** the number of patients in the analysis at 4 years was only 44 out of an original 159 patients~~: the unexplained loss of patients from follow-up raises a question of how to interpret these long-term results.~~	Incorrect interpretation of the apparent loss-to-follow up of patients at the 4 year time point. Patients were compelled to withdraw from the trial to continue on commercially available product as per the protocol. We have provided the poster publication (Cox *et al.,* 2016) that reports the detail of the patient disposition in the long-term follow up for ENCORE. This appears not to have been requested at the clarification stage, so we have taken this opportunity to share these data. Please note, the ERG's concern about loss-to-follow-up, implying a negative effect on eligulstat treatment continuation and	Although the ERG accepts the company's amendment may be true, we were not previously given access to the relevant information stated by the company. At this stage of the process we believe that we cannot incorporate new information or data into the report, and that the statement made by the ERG remains accurate based on the information we had available to us at the time.

		efficacy is repeated throughout the document. We would request that all mentions are appropriately amended based on this clarification.	

Issue 3 Efficacy of outcome measures in the ENCORE trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 14. Section *Encore* *The results for individual outcomes of spleen and liver volume, haemoglobin levels and platelet counts indicate a small reduction in efficacy with eliglustat, although this reached statistical significance only for haemoglobin levels (-0.28 (95% CI (-0.52, -0.03)).*	The results for individual outcomes of spleen and liver volume and platelet counts **indicate a small, statistically non-significant improvement in efficacy with eliglustat**. **Least-square mean absolute change for haemoglobin concentration showed a small, statistically significant reduction favouring imiglucerase (p=0·03). However, the lower bound of the CI (–5·2 g/L) is still within normal range for haemoglobin levels for the general population. As such it is unlikely to be clinically significant**.	Incorrect interpretation of the data/unclear phrasing. Extract from Cox *et al.,* 2015: *Figure 2 also shows stability of the individual components of the composite primary endpoint. Differences between treatment groups in the percentage of patients maintaining stable individual variables were not significant. Figure 3 shows individual variables over time. The between group least-square mean percentage changes from baseline in platelet count, liver volume, and spleen volume did*	Text changed to: "The results for individual outcomes of spleen and liver volume and platelet counts indicate a small, statistically non-significant improvement in efficacy with eliglustat. However, haemoglobin concentration showed a small, statistically significant improvement favouring imiglucerase (p=0·03)."

		not differ significantly (p>0·2 for all). We noted a small but significant difference in least-square mean absolute change for haemoglobin concentration favouring imiglucerase (p=0·025); however, the lower bound of the CI (–5·2 g/L) of this difference is not clinically significant (appendix).” The appendix is provided for completeness. It reports the data already provided in the submission in Table 17.	

Issue 4 Description of outcome measures

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 41. Section 4.2.3.1 of ≤ 1.5g/dl from baseline), *platelet counts (a decrease of ≤ 25% from baseline), spleen volume (a decrease of ≤ 25% from baseline) and liver volume (a decrease of ≤ 20% from baseline).*	of ≤ 1.5g/dl from baseline), platelet counts (a decrease of ≤ 25% from baseline), spleen volume (**an increase** of ≤ 25% from baseline) and liver volume (**an increase** of ≤ 20% from baseline).	Clarification	Amendment accepted, changed as company suggests.

Issue 5 Uncertainty in long-term efficacy of eliglustat in the ENCORE trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 15 *As treatment for GD1 is life-long, there is uncertainty regarding the long-term implications of a possible small reduction in efficacy with eliglustat compared with ERT*	Delete sentence	As described above eliglustat retains efficacy compared with ERT. Haemoglobin concentration results show a statistically significant, but not a clinically significant, reduction in efficacy with eliglustat.	The statement refers to the primary outcome measure of the trial was the percentage of patients stable in the composite endpoint. Although eliglustat met the pre-specified criteria for non-inferiority, a smaller percentage of patients were stable on eliglustat compared to imiglucerase. Also, when individual outcomes are considered the only statistically significant difference was in haemoglobin levels, which demonstrated a reduction in efficacy for eliglustat compared to imiglucerase. In addition, due to the length of follow-up in the trial it remains unclear what the long-term differences are between the two treatments in terms of efficacy, and although in the short-term any differences may be clinically insignificant, the may become more significant over a patient's lifetime.

Issue 6 Clarification that patients were not lost to follow up in the 4 year data for ENCORE

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 16. Section 1.3 *Although the long-term follow-up data from ENCORE demonstrated that for patients who remain on eliglustat stability on all four composite parameters is maintained over 4 years the unexplained loss of patients from follow-up (only 44 out of 159 remaining at 4 years) raises a question of how to interpret these long-term results. As treatment for GD1 is life-long, there is uncertainty regarding the long-term implications of a possible small reduction in efficacy with eliglustat compared with ERT.*	The long-term follow-up data from ENCORE demonstrated that for patients who remain on eliglustat stability on all four composite parameters is maintained over 4 years.	This conclusion appears to be based on incomplete information about the apparent loss-to-follow-up that was, in fact, protocol driven transfer to commercially available product. This comment also relies on the assumption of a reduction in relative efficacy in eliglustat compared with ERT over time discussed above. The data for the individual outcomes: spleen and liver volume and platelet counts indicate a small, statistically non-significant improvement in efficacy with eliglustat. The statistically significant change in haemoglobin concentration, favouring imiglucarase is not clinically significant, even at the lower bound of the CI.	This is not a factual inaccuracy.

Issue 7 Clarification of the non-inferiority margin used in ENCORE

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response

Page 21. Section 1.7.1.1 (also referred to on: page 41, Section 4.2.3; page 51, section 4.2.3.4; page 83, section 4.8) *The ERG raises that a key concern of ENCORE was the lack of adequate justification for the choice of the non-inferiority margin used in the data analysis. The non-inferiority margin of 25% was higher than the more usual 15%. This and the assumption that a lower efficacy with eliglustat of up to 10% compared with imiglucerase is not clinically important, were not justified, statistically or clinically. Therefore, whether eliglustat is clinically non-inferior to imiglucerase in treating ERT-stable patients remains uncertain.*	Delete text and replace with: The non-inferiority margin in the ENCORE trial was based on a 95% imiglucerase response rate and an 85% eliglustat response rate (as established by results from the Phase II study). This margin was accepted as sufficient by the regulatory bodies, EMEA and FDA.	This was provided in the original submission and the clarification response: this margin was acceptable to the regulatory bodies. Further, it is important to note that the criteria for stability in ENCORE is stricter than the international treatment guidelines for GD1. Therefore, patients who were being adequately treated according to International Guidelines were deemed not to be stable in the trial. According to the international guidelines, 93% of eliglustat patients in ENCORE maintained stability in the composite endpoint (all four treatment goals) at year 1, 92% at year 2, 93% at year 3 and 96% at year 4. For individual endpoints, 97% of eliglustat patients maintained their Hb treatment goal, 96% their platelet treatment goal, 100% their spleen size treatment goal and 99% their liver size treatment goal at year 1. If trial endpoints had been based	The ERG understands the basis for the non-inferiority margin, but still raises questions around the clinical importance of the margin and the justification for why the margin appears to wider than those commonly seen in the literature. Although the margin may have been accepted by the EMEA, the EPAR highlighted concerns with the selected margin, and further concerns were raised in the PBAC report. Therefore, the ERG believes it is justified in highlighting this potential issue.

		on these International Guidelines ENCORE results would have been well within the margin for non-inferiority. For information we've attached a poster presented at World (Cox *et al.,* 2016), and direct you to the graph, "Stability with Respect to Published Therapeutic Goals (absolute value)".	

Issue 8 Clarification of loss to follow up in the Phase II study

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 15/16 Section Supporting Evidence *Due to the lack of control group in this study, the small sample size and the unexplained loss of patients from the later time points, the treatment effects observed over the four year follow-up are uncertain.*	Due to the lack of control group in this study, the small sample size ~~and the unexplained loss of patients from the later time points,~~ the treatment effects observed over the four year follow-up are uncertain.	Clarification: the CONSORT diagram in the submission: Figure 13, section 9.4.5 reports patient numbers at different times points and gives reasons for withdrawal.	Changed as company suggest.

Issue 9 Clarification of loss to follow up in the Phase II study

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 17. Section 1.3. *In addition, the small sample size and the unexplained loss of patients from the later time points add to the uncertainty of the Phase II results*.	Delete sentence	Loss of patients is explained (Figure 13 in section 9.4.5 in the submission document). Absolute patient numbers are small, as expected in orphan diseases. It is worth noting that the complete eliglustat trial programme provides the greatest volume of data in this disease area to date.	Text changed from: "*In addition, the small sample size and the unexplained loss of patients from the later time points add to the uncertainty of the Phase II results*." To "*In addition, the small sample size adds to the uncertainty of the Phase II results*."

Issue 10 Common adverse events associated with eliglustat

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 16. Section Supporting Evidence *The most common AEs were headache, arthralgia, nasopharyngitis, diarrhoea,*	The most common AEs were headache, arthralgia, nasopharyngitis, diarrhoea, **upper respiratory tract infection and dizziness**, most were of mild severity	For completeness, these AEs should be included upper respiratory tract infection (11%), and dizziness (10%)	Changed as company suggest.

most were of mild severity			

Issue 11 Availability of bone and HRQL data at 4 years

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 15. Section Supporting Evidence *Bone parameter and HRQL data suggested some small improvements by 2 years, but were not reported at 4 years*	*Bone parameter and HRQL data suggested some small improvements by 2 years, some bone and QoL data were available at years 3 and 4.*	Four year bone endpoint data were provided in Table 19 and Figure 17 in section 9.6.1 of the submission. Four year HRQL improvements are mentioned in sections 7.2, 8.5 and 9.9.1 of the submission document. In response to question A1 in the clarification question, we provided three year data for bone and HRQL outcomes.	Changed as company suggest.

Issue 12 Spleen volume measures in both ENCORE and ENGAGE

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 32 Section 3.4 *In the supporting ENGAGE trial there was only one primary outcome spleen volume which differed to the composite endpoint in ENCORE involving four key measures.*	In the supporting ENGAGE trial there was only one primary outcome spleen volume which differed to the composite endpoint in ENCORE involving four key measures, **although spleen volume was also measured in ENCORE, in response to an FDA request**.	Accuracy of statement	Text changed from: "*In the supporting ENGAGE trial there was only one primary outcome spleen volume which differed to the composite endpoint in ENCORE involving four key measures."* *To:* In the supporting ENGAGE trial there was only one primary outcome spleen volume which differed to the composite endpoint in ENCORE involving four key measures, although spleen volume was also measured in ENCORE.

Issue 13 Search strategy terms

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 34. Section 4.1.1 *The search strategy for CENTRAL included terms to remove any systematic reviews, meta-analyses or indirect/mixed treatment comparisons from the results.*	The search strategy for CENTRAL included terms to remove any **reviews. Systematic reviews, meta-analyses or indirect/mixed treatment comparisons were included in the results**	Appears to be a misinterpretation of the double negative in the following search string: *NOT (review NOT (systematic OR meta-analy* OR ((indirect OR mixed) AND "treatment comparison"))))* This means that general, non-systematic reviews would be excluded but systematic reviews, meta-analyses and indirect comparisons would be retained because of the double negative.	Text changed to: "The search strategy for CENTRAL included terms to remove any reviews from the results. However this limit is unnecessary as CENTRAL only contains clinical trials. The same search strategy was used to search DARE and CDSR. As both databases only contain systematic reviews, it was unnecessary to attempt to remove reviews from the results, and it could have led to relevant systematic reviews not being identified by the search."

Issue 14 Comparator products in the SLR

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 36. Section Clinical Efficacy	The submission did not differentiate clearly between the intervention and comparators in the inclusion criteria: the submission listed both the intervention (eliglustat) and	This appears not to have been queried at the clarification stage, however, we can clarify for the ERG that the SLR was	Not a factual inaccuracy

The submission did not differentiate clearly between the intervention and comparators in the inclusion criteria: the submission listed both the intervention (eliglustat) and other comparators as interventions. The inclusion criteria specified that eligible comparators were imiglucerase, velaglucerase alfa, miglustat, alglucerase, and taliglucerase alfa. The ERG noted that two of these comparators (alglucerase, and taliglucerase alfa) were not in line with those relevant comparators specified by the NICE scope nor the company's decision problem, and it is unclear why these two comparators were included in the inclusion criteria, although the company did not present the evidence relating to them	other comparators as interventions. The inclusion criteria specified that eligible comparators were imiglucerase, velaglucerase alfa, miglustat, alglucerase, and taliglucerase alfa. The ERG noted that two of these comparators (alglucerase, and taliglucerase alfa) were not in line with those relevant comparators specified by the NICE scope nor the company's decision problem.	conducted to meet the needs of multiple countries, and as such, any potential treatment for GD1 in any country were included in the search terms. However, only those relevant to the NICE decision problem were presented in the CS.	

Issue 15 SLR outcomes inclusion criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 38. Section 4.1.6 *There was also a lack of transparency on the selection of outcomes being considered.*	Delete this sentence	As stated in the response to the clarification questions (Question A3), articles were included if they reported *any* efficacy, safety or PRO outcomes. In addition, given the paucity of data in this disease area the search was purposefully broad to encompass publications with *any* relevant outcomes data. Studies were excluded only if the following outcomes were included: in vitro, animal, foetal, molecular, genetic, PD/PK, biopsy findings, plasma or serum levels of antibodies, lipids and proteins only.	Changed as company suggest.

Issue 16 ENCORE type of endpoints

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 39. Table 5	ENCORE, Type of Endpoint Composite +	In addition to the composite endpoint spleen volume was	Changed as company

ENCORE, Type of Endpoint: Composite	Single	captured as an endpoint	suggest.

Issue 17 Clarification on inclusion criteria according to prior ERT exposure

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 41. *The key patient inclusion and exclusion criteria for the trial were adults with confirmed diagnosis of GD1, with documented deficiency of acid beta-glucosidase activity; had received treatment with ERT (including velaglucerase or imiglucerase) for at least 3 years (for at least 6 of the 9 months before randomisation the patient had received a total monthly dose of 30 U/kg to 130 U/kg of ERT);*	The key patient inclusion and exclusion criteria for the trial were adults with confirmed diagnosis of GD1, with documented deficiency of acid beta-glucosidase activity; had received treatment with ERT (including velaglucerase or imiglucerase) for at least 3 years (**patients were required to receive a total monthly dose of 30-130U/kg of ERT at least 6 of the 9 months prior to randomization);**	For clarification	Changed as company suggest.

Issue 18 Trial inclusion criteria: Phase II trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 61. Section 4.2.5.1 *The ERG noticed that there did not appear to be an age restriction in this trial. Also, unusually, patients with a negative pregnancy test were not a pre-specified inclusion criterion: pregnant patients were excluded from all the other trials, and the SPC clearly states that these patients should not be included. In general the inclusion criteria appeared to be less restrictive than ENCORE and ENGAGE.*	**The age range for this trial was patients aged 16-65 years. Pregnant and lactating women were excluded from the trial, in line with study protocol. In general, the inclusion criteria are similar to ENCORE and ENGAGE.**	According to the study protocol the proposed amended text is more accurate.	Although the ERG accepts the company's amendment may be true, we were not previously given access to the protocol, and therefore the information stated by the company. At this stage of the process we believe that we cannot incorporate new information or data into the report, and that the statement made by the ERG remains accurate based on the information we had available to us at the time.

Issue 19 Clarification of table content

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 63. Table 20 and Section 4.2.5.3 *Table: Patients lost to follow-up were not reported in the*	No patients were lost to follow-up Losses of patients due to follow-up were not reported in the CSR, **however, they**	Clarification	Text changed from: "*Losses of patients due to follow-up were not reported in the CSR"*

CSR *Text:* *Losses of patients due to follow-up were not reported in the CSR*	**were described in Figure 13 in section 9.4.5**		*To* *"*Losses of patients due to follow-up were not reported in the CSR, however, they were described in Figure 13 in section 9.4.5 in the CS."

Issue 20 Missing value provided

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 22	Missing value: Wyatt study, % male = 43%	Clarification	Changed as company suggest.

Issue 21 Clarification of evaluation time points in ENGAGE

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 74. Section 4.5.1 *However the ERG has assessed the risk differences for the AEs reported in the placebo-controlled trial ENGAGE, where only two AEs (Arthralgia at 32 weeks and Nasopharyngitis at 109 weeks) were found to be statistically*	However the ERG has assessed the risk differences for the AEs reported in the placebo-controlled trial ENGAGE, where only two AEs (Arthralgia at **39** weeks and Nasopharyngitis at **78** weeks) were found to be statistically significant.	Clarification of evaluation time points	Minor typographical error, changed as company suggests.

significant.			

Cost-effectiveness section

Issue 22 Text clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 91. Table 34 states *"The ENGAGE study is the only RCT comparing eliglustat with ERT therapy in stable Gaucher disease patients"*	The **ENCORE** study is the only RCT comparing eliglustat with ERT therapy in stable Gaucher disease patients	Clarification	Changed as company suggest.

Issue 23 Table 36 value amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 101. Table 36 ENCORE: Treatment Naïve patient aged 27.9	Amend table values	There were no treatment naïve patients in the ENCORE trial	Minor typographical error, changed as company suggests.

Issue 24 Clarification of implementation of utility values

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
Page 113 *The utility increment is applied in every cycle of the analysis regardless of treatment duration*	The utility increment is applied in every cycle of the analysis regardless of treatment duration, **while the patient remains on treatment.**	For clarity	Changed as company suggests.

Issue 25 Utility calculation correction

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
Page 115 *If an extreme scenario is assumed in which patients experience '0' utility for the two hours they spend each fortnight receiving ERT and a utility of '1' otherwise, then the decrement each fortnight would be equal to '-0.005'*	then the decrement each fortnight would be equal to **'-0.006'**	Clarification: from our estimates is -0.00595 (-0.006 to 3.d.p)	Minor typographical error, changed as company suggests.

Issue 26 Table 42, incomplete costing calculation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 120 Table 42 *Day unit (Haematology) £309.45*26.09 =*	Day unit (Haematology) £309.45*26.09 **= £8073.81**	Missing value	Minor typographical error, changed as company suggests.

Economic model

Issue 27 Validation of ERG analyses in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
It was possible to replicate the ERGs analyses, once the ERG amended model had been received. *Page 143* *The first assumed that there was no discontinuation in each patient group. The second used an annual discontinuation rate of 2.36% which was calculated from the rate in the 104 week extension period of the ENCORE trial*	No amendment	We were not able to replicate this 2.3% calculation. We would request more information about how this value was calculated be included in the ERG report.	An additional sentence has been added to Page 143 to provide additional information regarding the calculation: "Five patients out of 106 who were enrolled onto eliglustat from the start of the trial discontinued therapy over the 104 week extension period, resulting in an annual discontinuation rate of 2.36 %."

Typographical errors

Issue 28 Use of "GD population" rather than "GD1 population"

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 13. Section 1.1 *Approximately 3% of the GD population are ultra-rapid metabolisers and are excluded currently from the treatment with eliglustat*.	Should read Approximately 3% of the **GD1** population are ultra-rapid metabolisers and are excluded currently from the treatment with eliglustat.	Typographical error	Minor typographical error, changed as company suggests.

Issue 29 Liver volume reduction, typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 15. Section ENGAGE. *Eliglustat was also associated with a reduction in liver volume of 55.2% compared with an increase of 1.4% on placebo*	*Eliglustat was also associated with a reduction in liver volume of **5.2%** compared with an increase of 1.4% on placebo*	Typographical error	Minor typographical error, changed as company suggests.

Issue 30 Typographical error, should be greater than rather than less than

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 53. Section 4.2.4.1 *The key patient inclusion and exclusion criteria for the ENGAGE trial were ≤ 16 years with confirmed diagnosis of GD1*	The key patient inclusion and exclusion criteria for the ENGAGE trial **were ≥ 16** years with confirmed diagnosis of GD1	Typographical error should be ≥	Minor typographical error, changed as company suggests.

Issue 31 Typographical error in outcome: organ volume

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 84 *Eliglustat was also associated with a reduction in liver volume of 55.2% compared with an increase of 1.4% on placebo (statistically significant mean reduction of 66.64% (95% -11.37% to -1.91%).*	Eliglustat was also associated with a reduction in liver volume **of 5.2%** compared with an increase of 1.4% on placebo (statistically significant mean reduction **of 6.64%** (95% -11.37% to -1.91%).	Typographical error	Minor typographical error, changed as company suggests.

References

Cox TM, Drelichman G, Cravo R, et al. Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial. *Lancet*. 2015; 385(9985):2355-62.

Cox TM, Drelichman G, Cravo R, et al. Appendix to: Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial. *Lancet*. 2015; 385(9985):2355-62

Cox TM, Drelichman G, Cravo, et al. Four year follow-up from the ENCORE trial or Oral Eliglustat in Patients with Gaucher Disease Type 1 Stablized on Enzyme Replacement Therapy. Poster presented at World 2016

1 Summary

This report represents the ERG's assessment of the company's (Sanofi Genzyme) submission to NICE on the use of eliglustat for the treatment of adult patients with Gaucher disease type 1 (GD1). The report includes an assessment of both the clinical and cost effectiveness evidence submitted by the company. The report also includes a summary of additional submissions received from patients, patient organisations, clinicians and NHS England: submissions from Addenbrooke's Hospital Cambridge UK, Royal Free lysosomal storage disorder (LSD) unit, Royal College of Physicians, NHS England; and Gauchers Association Limited.

The company's evaluation of clinical efficacy included evidence relating to eliglustat therapy versus placebo, evidence relating to eliglustat therapy versus enzyme replacement therapy (imiglucerase), an indirect comparison of relative efficacy between eliglustat, imiglucerase and velaglucerase, and a decision analysis assessing the cost-effectiveness of eliglustat compared with enzyme replacement therapy (imiglucerase and velaglucerase).

1.1 Critique of the decision problem in the company's submission

The company's decision problem reflects the population specified in the NICE scope: adult patients with symptomatic GD1. The evidence presented in the Company's submission was derived from patients who were treatment naive or not currently on ERT, and others who were stable on ERT.

The submission presented data on therapy initiated with eliglustat tartrate 50 mg or 100 mg once or twice daily for oral administration, which is not precisely reflective of the product licence. The current licensed dose of eliglustat is 84 mg (equivalent to 100mg eliglustat tartrate) twice daily or once daily depending on the CYP2D6 metaboliser status. The EMA licence is granted for patients with PM, IM and EM metabolism status. The majority of patients in the eligible eliglustat trials in the CS are IM or EM status. Approximately 3% of the GD1 population are ultra-rapid metabolisers and are excluded currently from the treatment with eliglustat.

Imiglucerase and velaglucerase alfa were the comparators of interest addressed in the company submission, reflecting the NICE scope. However, the submission excluded miglustat as a relevant comparator, stating that it was only used in a very small proportion of adult GD1 patients for whom ERT was not suitable. The ERG suggests it is likely that, if recommended, eliglustat would be used in place of miglustat, as it is better tolerated.

The company's decision problem addressed each of the relevant outcomes: GD1 therapeutic goals (based on four measures: haemoglobin level, platelet count, spleen volume and liver volume), mortality, adverse effects of treatment, and patients' health-related quality of life (HRQL). The primary outcome of the key trial of eliglustat (ENCORE) was proportion of patients who remained

stable for the GD1 therapeutic goal (based on the composite measure of platelet count, haemoglobin level, liver and spleen volumes).

The primary measure of cost-effectiveness was incremental cost per quality-adjusted life year (QALY) gained.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company submission presented three RCTs (ENCORE, ENGAGE and EDGE) and one single arm Phase II study to demonstrate clinical efficacy and safety of eliglustat.

ENCORE is a phase III RCT comparing eliglustat with imiglucerase for treating adults with symptomatic GD1 already controlled by ERT therapy. ENGAGE is another phase III RCT comparing eliglustat with placebo in untreated patients. Supporting long-term evidence was provided from a Phase II, single-arm trial of eliglustat. Single-arm data are also presented from the lead-in phase of a third RCT (EDGE) that assessed once daily with twice daily dosing with eliglustat.

The synthesis of adverse effects in the company's submission comprised a summary of adverse effects from ENCORE, ENGAGE, EDGE and the Phase II study.

ENCORE

ENCORE, an open-label RCT, conducted in 159 ERT stable patients demonstrated that when patients switched from ERT therapy, eliglustat maintained haematological and organ volume stability over 52 weeks. At 52 weeks eliglustat met the criteria of being non-inferior to imiglucerase in terms of the primary outcome and maintaining stability, as the non-inferiority lower 95% CI was -17.6% which was within the pre-specified threshold of -25% (lower 95% CI for the composite endpoint confirmed non-inferiority at the 20% acceptance margin).

The results for individual outcomes of spleen and liver volume and platelet counts indicate a small, statistically non-significant improvement in efficacy with eliglustat. However, haemoglobin concentration showed a small, statistically significant improvement favouring imiglucerase (p=0·03). There were no significant changes in DS3 scores or measures of bone health. Eliglustat was not associated with any improvement in quality of life despite patients expressing a marked preference for an oral therapy. A post hoc analysis showed that eliglustat efficacy was similar both post-imiglucerase and post-velaglucerase treatment.

Long-term follow-up data from ENCORE demonstrated that for patients who remain on eliglustat stability on all four composite parameters is maintained over 4 years. Although very few patients withdrew due to adverse events the number of patients in the analysis at 4 years was only 44 out of an original 159 patients: the unexplained loss of patients from follow-up raises a question of how to

interpret these long-term results. As treatment for GD1 is life-long, there is uncertainty regarding the long-term implications of a possible small reduction in efficacy with eliglustat compared with ERT.

ENGAGE

ENGAGE was a placebo-controlled RCT in 40 patients who were not treated with ERT. At 39 weeks, eliglustat was associated with a reduction in spleen volume of 27.8% compared with an increase of 2.3% on placebo (statistically significant mean difference of -30.03%; 95% CI -36.82% to -23.24%). Eliglustat was also associated with a reduction in liver volume of 5.2% compared with an increase of 1.4% on placebo (statistically significant mean difference of -6.64%; 95% -11.37% to -1.91%). The effect sizes of point estimates for spleen and liver volumes were moderate to large, implying that these treatment effects could be clinically significant. Compared with placebo eliglustat achieved a statistically significant increase in haemoglobin level (1.22 g/dL; 95% CI 0.57 to 1.88) and platelet count (41.06%; 95% CI 23.95% to 58.17%). Nineteen out of the 20 patients in the eliglustat treatment group met at least one of the 1-year therapeutic goals established for Gaucher patients (9 met 2 goals, and 2 met 3 goals). Improvements were also seen in DS3 scores, though none achieved the minimum clinically significant threshold for improvement. At 39 weeks, eliglustat also demonstrated beneficial effects on a number of bone-related outcomes and some reached statistical significance. Eliglustat showed some positive effects on health-related quality of life measures, being associated with a significant improvement in disease-specific quality of life outcome (fatigue severity score 0.7; 95% CI 0.02 to 1.33) compared with placebo but there was no statistically significant difference in brief pain inventory (BPI)(average pain) (-0.2; 95% CI -0.81 to 0.36) between the treatment and placebo groups nor for the SF-36 general health score (-2.4; 95% CI -9.84 to 4.94), physical component score (3.3; 95% CI -0.67 to 7.29) or mental component score (-2.2; 95% CI -7.01 to 2.59) at week 39.

The open-label extension data indicated that the beneficial effects on organ volumes, haemoglobin level and platelet count were sustained at 78 weeks; there were no drop outs. There was also an indication of continued small improvements in some but not all bone parameters. Results for DS3 scores, biomarker measures and health-related quality of life outcomes at 78 weeks were not reported.

Supporting evidence

The results of the two RCTs are supported by a single-arm phase II study which included 26 patients. At year 1, 77% of the 26 patients achieved a composite outcome requiring improvements from baseline in at least two of spleen volume, haemoglobin level and platelet count. At year 2, this was 85% of 20 patients remaining in the analysis. At 4 years all 19 patients included at this point met their therapeutic goals for spleen volume and haemoglobin level, 94% met the goal for liver volume and 47% met the goal for platelet count. Bone parameter and HRQL data suggested some small improvements by 2 years, some bone and HRQL data were available at years 3 and 4. Due to the lack

of control group in this study, the small sample size the treatment effects observed over the four year follow-up are uncertain.

Supportive evidence also came from the single-arm open label lead-in period trial EDGE, in which 83% of the 170 patients achieved all five therapeutic goals during the lead-in period.

The adverse effects profile from all four of these trials suggests that eliglustat is well tolerated. There were no deaths reported, very few discontinuations and few eliglustat related SAEs. Most AEs were reported as mild (78%) or moderate (44%). The most common AEs were headache, arthralgia, nasopharyngitis, diarrhoea, upper respiratory tract infection and dizziness, most were of mild severity.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The clinical effectiveness evidence in the company's submission was based on a systematic review of eliglustat for the treatment of adult patients with GD1. The ERG is confident that all relevant trials (including trial extensions) were included in the submission.

ENCORE was a well conducted trial with a clinically relevant composite primary outcome based on four measures: haemoglobin level, platelet count, spleen volume and liver volume. The primary efficacy endpoint was the percentage of patients whose organ volumes and haematological variables remained stable after 12 months. This outcome reflects the targeting of therapeutic goals used in clinical practice. However, because the comparator imiglucerase is administered by infusion and eliglustat is an oral therapy, the trial was open label. This means that the trial was at high risk of bias for any subjective outcomes.

Whilst eliglustat met the criteria of being non-inferior to imiglucerase in terms of the primary outcome and maintaining stability, this non-inferiority margin is somewhat wider than would normally be accepted: a margin of 15% would have been more robust. Furthermore, the 25% non-inferiority margin assumes that a 10% reduction in efficacy is clinically insignificant, an assumption that was not justified by any clinical argument. The ERG notes the EMA accepted the broader margin due to the rare nature of the disease: the conduct of a larger trial (as would be necessary with a 15% margin) would not be feasible.

Although the long-term follow-up data from ENCORE demonstrated that for patients who remain on eliglustat stability on all four composite parameters is maintained over 4 years the unexplained loss of patients from follow-up (only 44 out of 159 remaining at 4 years) raises a question of how to interpret these long-term results. As treatment for GD1 is life-long, there is uncertainty regarding the long-term implications of a possible small reduction in efficacy with eliglustat compared with ERT.

ENGAGE was a well conducted placebo-controlled RCT in patients not being treated with ERT. However the sample size was small (40 patients), the primary outcome was spleen volume, rather than a more clinically relevant composite outcome, and the randomised phase was only 39 weeks. It should be noted that in the company submission the trial population are referred to as treatment naïve, but this was not the case for all patients: the inclusion criteria encompassed those who had had previous, though terminated at the time of recruitment, treatment with ERT.

As far as can be determined from limited data sets, the generalisability of findings from the two main Phase III trials (ENGAGE and ENCORE) to routine practice in England is adequate. There is nothing to suggest that the beneficial effects observed in these trials would not be reflected in practice except for a lack of information on the treatment of ERT stable patients with very large spleens and some question over the ERT dosing.

No data comparing eliglustat with imiglucerase or veleglucerase in treatment naive or untreated patients were presented, nor any making a direct comparison of eliglustat with velaglucerase in ERT stable patients. There are no pertinent data to enable an indirect comparison analysis to be performed. It is generally accepted that imiglucerase and velaglucerase are equivalent, though the trial data to support this are limited to one small non-inferiority trial with haemoglobin levels as the primary outcome.

Due to the lack of control group in both the Phase II trial and the lead-in phase of the EDGE trial the results from these trials cannot be considered robust, but are supportive of the findings from the RCTs. In addition, the small sample size adds to the uncertainty of the Phase II results. The treatment effects observed over the four year follow-up are uncertain.

The adverse effects of eliglustat were based on the limited available evidence from ENCORE, ENGAGE and the Phase II trial. The evidence from ENCORE shows a higher number of patients experiencing treatment related AEs and severe TEAEs. However, this apparent difference in tolerability may be due to the fact that patients were stable on ERT at recruitment into the trial. The evidence was mostly limited to the short-term data although some data up to 4 years demonstrate that eliglustat is generally well tolerated.

1.4 Summary of cost effectiveness submitted evidence by the company

The *de novo* economic analysis presented by the company consisted of a cost-consequence and budget impact analysis. The models compared eliglustat with two enzyme replacement therapies: imiglucerase and velaglucerase, in the treatment of Gaucher disease. Four different populations were considered in the cost-consequence model:

patients who remained stable for the GD1 therapeutic goal (a composite measure). Secondary outcomes included changes in haemoglobin level, platelet count and organ volumes. The health-related quality of life was measured by the Short Form 36 Health Survey (SF-36) and the disease specific quality of life measure (fatigue severity score). The safety outcomes were mortality and the incidence of adverse events. In the supporting ENGAGE trial there was only one primary outcome spleen volume which differed to the composite endpoint in ENCORE involving four key measures, although spleen volume was also measured in ENCORE.

The primary measure of cost-effectiveness was incremental cost per quality-adjusted life year (QALY) gained.

3.5 Other relevant factors

Equity issues were not specified in the NICE scope nor in the decision problem. The submission states that no equity issues relating to socio-economic status, ethnicity and gender are anticipated for the appraisal of eliglustat. Other factors relating to patients' metabolism status and dosing in clinical practice were presented in this section.

3.5.1 Metabolism status

The EMA licence is granted for patients with PM, IM and EM metabolism status. The majority of patients as were found in the eligible eliglustat trials in the CS are IM or EM status. Approximately 3% of the GD population are ultra-rapid metabolisers and are excluded currently from the treatment with eliglustat.

reviewers working independently. Any discrepancies with regard to inclusion or exclusion of an article were resolved by a third reviewer.

4.1.5 Evidence synthesis

The company did not undertake a formal meta-analysis mainly because of the diverse nature of the clinical and methodological characteristics of the included studies, for example, considerable heterogeneity relating to patient population (e.g. treatment-naïve and treatment stable), study design and intervention. As a result, the company performed a narrative synthesis of the evidence. Despite the lack of a transparent pre-specified approach to the narrative synthesis, the ERG considers that theapproach undertaken by the company was acceptable.

4.1.6 Summary statement

Although the company's search strategies were likely to have identified all the evidence relevant to the decision problem, the ERG had concerns about how the studies were selected in the submission. For the evaluation of clinical efficacy, it appears that all relevant trials have been included. The ERG identified one additional relevant article, [20] which was published after the company's literature search in their review. This study provides a descriptive comparison of patients receiving eliglustat or miglustat after switching from ERT. Details are given in Section 4.5.There was a lack of clarity regarding the study selection for the safety evaluation, as the company did not clearly pre-specify the study design in their inclusion criteria. Appropriate criteria were used to assess the study validity. Limiting a systematic review to English language studies may have introduced the potential for language bias. A narrative synthesis approach undertaken by the company was considered appropriate.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 The included trials of eliglustat

Table 1 presents the included trials of the evaluation of clinical efficacy and safety of eliglustat, including three RCTs (ENCORE, ENGAGE and EDGE) and one single arm Phase II study.

Table 1: The included studies of the evaluation of clinical efficacy and safety

Study	Study Design	Intervention and comparator
ENCORE	RCT	Eliglustat versus imiglucerase
ENGAGE	RCT	Eliglustat versus placebo
EDGE	RCT	Eliglustat versus Eliglustat (once daily vs. twice daily)
Phase II trial	Non-randomised,, single arm trial	A single arm of eliglustat (no comparator)

Direct trial evidence of the efficacy of eliglustat: ENCORE is a phase III RCT comparing eliglustat with imiglucerase for treating adults with symptomatic GD1 already controlled by ERT therapy. ENGAGE is another phase III RCT comparing eliglustat with placebo in patients not on therapy. Supporting long-term evidence was provided from a Phase II, single-arm trial of eliglustat. Further single-arm data are presented from the lead-in phase of a third RCT (EDGE) trial that assessed once daily with twice daily dosing with eliglustat.

Safety evaluation: The synthesis of adverse effects in the company's submission comprised a pooled descriptive summary of adverse effects from ENCORE, ENGAGE, EDGE and the Phase II study.

4.2.2 Outcomes in the trials

There were some variations in the outcomes used in the trials. In particular, the included trials used different primary outcomes. Table 2 presents the primary outcomes in measuring the achievement of therapeutic goals in individual trials. These outcomes will be discussed further in the individual trial sections.

Table 2 Primary outcomes in measuring the achievement of therapeutic goals in trials

	ENCORE	ENGAGE	EDGE	Phase II
Type of endpoint	Composite + Single	Single	Composite	Composite
Primary outcome	Percentage of patients who remained stable for 52 weeks on the composite endpoint of a combination of haematological parameters and organ volumes defined as: Haemoglobin level does not decrease >1.5g/dl from baseline; platelet count does not decrease >25% from baseline; spleen volume does not increase >25% from baseline; liver volume does not increase >20% from baseline	The primary efficacy endpoint was the percentage change in spleen volume (MN) from baseline (Mean baseline spleen volume 13.89 MN) to Week 39 of treatment.	The lead-in period therapeutic goals included: ≤1 bone crisis and no symptomatic bone disease during previous 6 months of the lead-in period Haemoglobin ≥11 g/dL for females and ≥12 g/dL for males Platelet count ≥100,000/mm^3 Spleen volume ≤10 MN (if applicable) Liver volume ≤1.5 MN	Improvement from baseline to Week 52 in at least 2 of the 3 main efficacy parameters: - Spleen volume - Haemoglobin level - Platelet count

However it should be noted that a composite primary outcome of haemoglobin level, platelet count, spleen volume and liver volume is more applicable to routine practice since therapy dosing regimen are based on the achievement of therapeutic goals (as measured by spleen and liver volumes, haemoglobin level and platelet count).

of ≤ 1.5g/dl from baseline), platelet counts (a decrease of ≤ 25% from baseline), spleen volume (an increase of ≤ 25% from baseline) and liver volume (an increase of ≤ 20% from baseline). These outcomes were assessed for both treatment groups separately along with the difference between two treatment groups and the measurement represented the accepted therapeutic goal in treating Gaucher disease in clinical practice for treatment-stable patients. There were a number of reported secondary outcomes which are listed in Table 9 of the CS, they include Total T and Z-SCORES for BMD of femur and lumber spine, normal haemoglobin levels, platelet counts, spleen volume and liver volume.

The key patient inclusion and exclusion criteria for the trial were adults with confirmed diagnosis of GD1, with documented deficiency of acid beta-glucosidase activity; had received treatment with ERT (including velaglucerase or imiglucerase) for at least 3 years (patients were required to receive a total monthly dose of 30-130U/kg of ERT at least 6 of the 9 months prior to randomisation); and had reached Gaucher disease therapeutic goals prior to randomisation (spleen volume <10 times normal or total splenectomy (if occurred >3 years prior to randomisation), and liver volume <1.5 times normal). The full criteria are found in Table 9 in the CS. The trial inclusion criteria appear to be appropriate and follow SPC special warnings and precautions for eliglustat use. However patients taking strong or moderate CYP2D6 inhibitors concomitantly with a strong or moderate CYP3A inhibitor were not excluded. The ERG notes that the use of eliglustat under these conditions could substantially elevate eliglustat plasma concentrations and these patients should be excluded from trials of eliglustat.

The statistical design of the ENCORE trial was to test non-inferiority, where the difference in the percentage of patients remaining stable in terms of the primary outcome was to be evaluated with 95% CI, computed at 52 weeks for both eliglustat and imiglucerase. If the lower-bound of the 95% CI for the difference was within the pre-specified non-inferiority margin of 25%, then eliglustat treatment was to be declared non-inferior to imiglucerase treatment. This non-inferiority margin was based on a 95% imiglucerase response rate and an 85% eliglustat response rate (as established by the results from the Phase II study).[22] The 95% CI for the primary composite outcome for non-inferiority difference was calculated using the statistical method of Agresti and Caffo's adjusted Wald. This is a common approach used when there are two independent samples with different proportions of responses.

ERG comments on the test for non-inferiority

The underlying assumptions and hypothesis for the non-inferiority margin was specified in the CS as 25%. Non-inferiority margins are often derived based on sound clinical judgement which usually include statistical principles, [23] however this was not clearly explained or visible within the CS. Nor

Study details	Description
Secondary outcomes	• Absolute change from baseline in haemoglobin level (in g/dL), • percentage change from baseline in liver volume (in MN) • percentage change from baseline in platelet count (in/mm^3) within patient changes from baseline to 39 weeks of eliglustat treatment for percentage changes in spleen volume, liver volume, and platelet count

Unlike the ENCORE trial the primary outcome was not a composite one but was percentage change in spleen volume (measured in MN) from baseline to 39 weeks in untreatedpatients. Measures of absolute change from baseline in haemoglobin level, percentage change from baseline in liver volume and platelet count were then considered as secondary outcomes in the ENGAGE trial. It should be noted that a number of tertiary outcomes were also evaluated in this trial: bone parameters, biomarkers and health related quality of life. The bone-related outcomes included change in lumbar spine BMD, total spine T-score, total spine Z-score, total femur BMD, total femur T-score, total femur Z-score, and absolute change in spine bone marrow burden (BMB), femur BMB, and total BMB. The biomarker outcomes included changes in normalised chitotriosidase, plasma glucosylceramide, plasma GM3 ganglioside, plasma macrophage inflammatory protein, plasma ceramide and plasma sphingomyelin. The health related quality of life outcomes included fatigue severity score, bone pain inventory and 36-item SF-36 measures. In addition a summary measure of disease activity DS3 (domain and total scores) was assessed and reported in the CS.

The key patient inclusion and exclusion criteria for the ENGAGE trial were $\geq$ 16 years with confirmed diagnosis of GD1, with documented deficiency of acid beta-glucosidase activity. Although the CS refers to the patients in this trial as 'treatment-naïve', this is not strictly correct. At the time of recruitment patients were not on SRT or ERT therapy, but were allowed to have taken these therapies in the past. Specifically, patients receiving SRT within 6 months prior to randomisation or ERT within 9 months prior to randomisation were excluded. In the trial, five patients (out of a total of 40) had received prior ERT with either alglucerase or imiglucerase: two patients in the eliglustat group and three in the placebo group. Four of these five patients had also received prior treatment with miglustat. As consistent with the inclusion and exclusion criteria, all these patients discontinued treatment with ERT and miglustat at least 9 months and 6 months prior to randomization. However, it was unclear whether these patients failed to respond adequately to the ERT or miglustat therapy.

Furthermore, patients who had the following symptoms during the screening period were included: 1) haemoglobin level of 8.0 to 11.0 g/dL for females or 8.0 to 12.0 g/dL for males and/or platelet count of 50,000 to 130,000/mm3 (based on the mean of two measurements obtained at least 24 hours apart). 2) Splenomegaly (defined as a spleen volume of 6 to 30 MN); 3) If hepatomegaly was present, liver

4.2.5.3 Quality Assessment

A quality assessment was carried out using the Downs and Blacks checklist for non-randomised trials. The checklist produced by the company includes 24 of the 29 original items that were possible to assess (See CS, Table 125). The ERG performed their own assessment on these 24 items using the Downs and Blacks and identified only four discrepancies as indicated in Table 3.

Table 3: Study quality assessment for Phase II trial using Downs and Black criteria

Description of criteria	CS assessment	ERGs assessment	ERGs Comment
Have the characteristics of patients lost to follow-up been described?	Yes	No	Patients lost to follow-up were not reported in the CSR, however, they were described in Figure 13 in section 9.4.5 in the CS.
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Unclear	No	30 day follow-up period following completion or patient withdrawal
Were losses of patients to follow-up taken into account?	Yes	No	Not clearly reported in the CSR
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance?	Yes	No	CSR reports that the trial was too small and that the lack of a control comparator (single-arm) limits the power

The characteristics of patients lost at follow-up were not clearly reported in the CS, CSR or journal publication. There were no adjustments for variable follow-up time lengths for patients, this was just specified as 30-days or when patients withdrew. Losses of patients due to follow-up were not reported in the CSR, however, they were described in Figure 13 in section 9.4.5 in the CS. Most importantly the ERG discovered from the CSR that the trial did not have sufficient power due to the limited sample size, the reasons for this were not explained in the CS.

4.2.5.4 Summary of efficacy results from Phase II trial

The clinical effectiveness results of the Phase II trial are provided in **Error! Reference source not found.**. Of the 26 patients who entered the trial, 22 completed the primary 52 week period and 20 patients completed year 2 and 19 completed Year 4 (The full CONSORT diagram is given in the CS Figure 13). Year 3 results were not included in the submission but provided on request to the ERG.

For changes in bone related outcomes, lumber spline data were collected from 19 patients. The lumber spine Z-score showed a statistically significant change at 2 years and 3 years follow up with p=0.003, however the 4 year follow up was not reported. The T-score showed a statistically significant change at the 3 year and 4 year follow-up, with 31% and 9.9% change from baseline respectively (p=0.0285 and p=0.014). Femur Z-score and T-score were followed up at years 1, 3 and 3, and there were very small changes from baseline -0.1 and 0 respectively. The outcomes bone crisis, bone lesions and bone infarctions showed no change from baseline (Table 19 in CS).

[redacted]

Year 3 data provided in the Company's response to the ERG reported a median DS3 of 5 (range 1.4, 8.6) with a median reduction of 1.5 at 3 years (range -5.0 to 2.0).

Patient HRQL outcomes in Phase II

HRQL data was collected in the Phase II trial using version 2 of the SF-36 instrument. These results were reported in the CSR and not the CS.

[redacted]

4.2.5.5 Summary of critique of the Phase II trial

The Phase II trial was single-arm phase II study including 26 patients who were not being treated with ERT. The trial provides supporting data for one, two and 4 years of treatment with eliglustat, although not all patients remained in the analysis beyond one year and, not all outcomes were reported at 4 years. At year 1, 77% of the 26 patients achieved a composite outcome requiring improvements from baseline in at least two of spleen volume, haemoglobin level and platelet count. At year 2, this was 85% of 20 patients remaining in the analysis. At 4 years all 19 patients included at this point met their therapeutic goals for spleen volume and haemoglobin level, 94% met the goal for liver volume and 47% met the goal for platelet count. Bone parameter and HRQL data suggested some small improvements by 2 years, some bone and HRQL data were available at years 3 and 4. Due to the lack

Table 4 Comparison of basic demographic details across all sources of evidence presented in the CS (ERG constructed)

Study	Treatment status	N	Age	% Male
ENCORE	ERT stable	159 (randomised)	Mean 37.6	45%
ENGAGE	Treatment naive	40 (randomised)	Mean 32	50%
Phase II	No ERT for 12 months prior to study	26	Mean 34	38%
Edge (lead in Phase)	Mixed patient group	170	Median 33.5	52%
Royal Free Hospital Cohort	1st presentation at Royal free clinic (mixed patient group)	86	Median 26	57%
Wyatt study	Mixed patient group	150	Mean 46.4	43%
Gaucher international registry	Patients treated with ERT	757	Unknown	45%

The submission presented a comparison of baseline characteristics of treatment-naïve patients between the ENGAGE trial and those patients at diagnosis of GD1 at the Royal Free Hospital, London (n=45). As seen in Table 5, there was a substantially higher rate of patients who experienced bone pain in the ENGAGE trial than those in the Royal Free Hospital (67% vs. 36%). A higher rate of hepatomegaly was also seen in the ENGAGE trial: 63% with moderate or severe disease vs. 44% (without indication of disease severity in the data from the Royal Free Hospital). Thus, the trial participants in the ENGAGE trial were likely to have more severe disease of GD1 compared to patients at first diagnosis. The clinical advisor to the ERG confirmed that in England there is unlikely to be a delay between diagnosis and the start of ERT therapy. Therefore the patients in the ENGAGE trial are not exactly generalisable to clinical practice in England and it remains unclear that the beneficial effects observed in the ENGAGE trial participants would be reflected in routine clinical practice.

Table 5 Patient characteristics in ENGAGE compared with Royal Free Hospital newly diagnosed cohort (adapted from CS Table 30)

	Royal Free Hospital London – Cohort at time of diagnosis	ENGAGE
Number of patients	45	40
Splenomegaly	87%	100%
Hepatomegaly	44%	63% moderate or severe
Bone pain	36%	67%
Avascular necrosis	11%	Not reported (note: prior bone crisis was an exclusion criterion, and only 1 patient had severe bone disease)

4.5 Adverse effects

The data on adverse events presented in the CS were derived from three Phase III trials (ENCORE, ENGAGE and EDGE) and the long-term Phase II trial. In particular, the ENCORE trial was a large-scale trial with 160 patients randomised over a relatively long period of 52 weeks, then followed by an extension period of a minimum of a further 52 weeks. It also provides a comparison of the adverse effects patients experience when switching from ERT to eliglustat with those of remaining on imiglucerase (or velaglucease).

In the three trials (ENCORE, ENGAGE and EDGE) and the long-term Phase II trial, safety was specified as a secondary outcome. In each of the four trials the MedDRA coding dictionary for AEs was used, however the version of the dictionary was not specified, which could lead to heterogeneity in coding when pooling the safety data.

The pooled safety data were presented in the CS and these are outlined below

4.5.1 Descriptive pooled analysis of adverse effect data

A descriptive pooled safety analysis was presented in the CS, where the AEs data from ENCORE, ENGAGE, EDGE and the phase II trial have been grouped together. As the trial populations and designs were regarded too heterogeneous, a pooled meta-analysis was not possible. However the ERG has assessed the risk differences for the AEs reported in the placebo-controlled trial ENGAGE, where only two AEs (Arthralgia at 39 weeks and Nasopharyngitis at 78 weeks) were found to be statistically significant. A sensitivity analysis was performed on these events and they were classified as mild and not treatment related (Table 6).

Table 6: Risk differences for adverse events in ENGAGE trial

MedDRA terms	39 Weeks		109 weeks	
System Organ classification Preferred term	RD	95% CI	RD	95% CI
Infections and infestations	0	(-0.3083; 0.3083)	0	(-0.3083; 0.3083)
Nasopharyngitis	0.15	(-0.0222; 0.3222)	0.2	(0.0128; 0.3872)
Musculoskeletal and connective tissue disorders	0.15	(-0.1464; 0.4464)	0.15	(-0.1528; 0.4528)
Arthralgia	0.35	(0.0954; 0.6046)	0.25	(-0.0298; 0.5298)

In total across all four of these trials there were 393 patients with GD1 who received eliglustat, the vast majority for over 6 months 349 (%), but only 19 (%) for 4 years or more (**Error! Reference source not found.**). Table 17 displays the pooled results for the AEs and SAEs with a breakdown for the severity grading and treatment relatedness. Of the 334 AEs reported across all four trials, the majority were mild or moderate with only 11% classified as severe. In total 40% of the reported AEs

were treatment related, and 12 patients (3%) experienced AEs leading to study drug discontinuation, with 10 of the AEs

reported in the CS, the ERG requested further detail from the company. The company stated that thirteen of the SAEs were graded as severe events with three possibly related to eliglustat (Table 7). These preferred term AEs include hepatic neoplasm malignant, neuropathy peripheral and intestinal obstruction where they received eliglustat doses of 50 mg, 150mg and 150 mg respectively. There were no deaths in either treatment arm during the whole study.

Table 7: Summary of patients with treatment-emergent SAEs in ENCORE

Patient number	System Organ Class (S) Preferred term (P)	Severity	Relation to study drug/G. disease	Eliglustat dose
9	S: Neoplasm benign, malignant and unspecified (including cysts and polyps) P: Hepatic neoplasm malignant	Severe	Possible	50mg BID
17	S: Nervous system disorders P: Neuropathy peripheral	Moderate	Possible	150mg BID
18	S: Gastrointestinal disorders P: Intestinal obstruction	Severe	Possible	150mg BID

4.5.3 Summary

The adverse effects profile from the four trials suggests that eliglustat is well tolerated. There were no deaths reported, very few discontinuations (3%) and minimal SAEs (9%) and eliglustat related SAEs (1%) reported across the trials. Most AEs were reported as mild (78%) or moderate (44%), with 79% of AEs considered not related. The most common AEs were headache, arthralgia, nasopharyngitis, diarrhoea, upper respiratory tract infection and dizziness, most were of mild severity.

In the ENCORE trial adverse events, including serious and severe ones were more common on eliglustat than on imiglucerase. However, this difference in tolerability may be due to the fact that patients were stable on ERT at recruitment into the trial.

In the economic model, a subgroup of AEs was included in the cost-consequence analysis in section 12.2.6 of the CS (See table 52 of CS). These include the AEs that occurred in at least 15\5 of patients on eliglustat, imiglucerase or velaglucerase: back pain, abdominal pain and joint pain, fever, weakness, infusion reaction, URTI, dizziness and headache. Potentially more severe AEs or those more relevant to eliglustat were not considered. The event rate per year for all of these events included in the economic model was highest in the patients receiving velaglucerase. This is discussed further in the health economics Section 5.

4.6 Doses of eliglustat, imiglucerase or velaglucerase in clinical practice

The ERG present the recommended doses of eliglustat, imiglucerase or velaglucerase from the trials in the CS, the SPCs, the European public assessment report (EPAR), the UK standard operating

volume, rather than a more clinically relevant composite outcome, and the randomised phase was only 39 weeks. At 39 weeks, eliglustat was associated with a reduction in spleen volume of 27.8% compared with an increase of 2.3% on placebo (statistically significant mean difference of -30.03%; 95% CI -36.82% to -23.24%). Eliglustat was also associated with a reduction in liver volume of 5.2% compared with an increase of 1.4% on placebo (statistically significant mean reduction of 66.64% (95% -11.37% to -1.91%). The effect sizes of point estimates for spleen and liver volumes were moderate to large, implying that these treatment effects could be clinically significant. Compared with placebo eliglustat achieved a statistically significant increase in haemoglobin level (1.22 g/dL; 95% CI 0.57 to 1.88) and platelet count (41.06%; 95% CI 23.95% to 58.17%). Nineteen out of the 20 patients in the eliglustat treatment group met at least one of the 1-year therapeutic goals established for Gaucher patients (9 met 2 goals, and 2 met 3 goals). Improvements were also seen in DS3 scores, though none achieved the minimum clinically significant threshold for improvement. At 39 weeks, eliglustat also demonstrated beneficial effects on a number of bone-related outcomes and some reached statistical significance. Eliglustat showed some positive effects on health-related quality of life measures, being associated with a significant improvement in disease-specific quality of life outcome (fatigue severity score 0.7; 95% CI 0.02 to 1.33) compared with placebo but there was no statistically significant difference in BPI (average pain) (-0.2; 95% CI -0.81 to 0.36) between the treatment and placebo groups nor for the SF-36 general health score (-2.4; 95% CI -9.84 to 4.94), physical component score (3.3; 95% CI -0.67 to 7.29) or mental component score (-2.2; 95% CI -7.01 to 2.59) at week 39.

The open-label extension data indicated that the beneficial effects on organ volumes, haemoglobin level and platelet count were sustained at 78 weeks; there were no drop outs. There was also an indication of continued small improvements in some but not all bone parameters. Results for DS3 scores, biomarker measures and health-related quality of life outcomes at 78 weeks were not reported.

The results of the two RCTs are supported by the single-arm phase II study in 26 patients. At year 1, 77% of the 26 patients achieved a composite outcome requiring improvements from baseline in at least two of spleen volume, haemoglobin level and platelet count. At year 2, this was 85% of 20 patients remaining in the analysis. At 4 years all 19 patients included at this point met their therapeutic goals for spleen volume and haemoglobin level, 94% met the goal for liver volume and 47% met the goal for platelet count. Bone parameter and HRQL data suggested some small improvements by 2 years, but were not reported at 4 years, some bone and HRQL data were available at years 3 and 4. Due to the lack of control group in this study and the small sample size, the treatment effects observed over the four year follow-up were uncertain.

Supportive evidence also came from the single-arm open label lead-in period of the EDGE trial in which 83% of the 170 patients achieved all five therapeutic goals during the lead-in period.

As far as can be determined from limited data sets, the generalisability of findings from the two main Phase III trials (ENGAGE and ENCORE) to routine practice in England is adequate. There is nothing to suggest that the beneficial effects observed in these trials would not be reflected in practice except for a lack of information on the treatment of ERT stable patients with very large spleens and some question over the ERT dosing.

No data comparing eliglustat with imiglucerase or veleglucerase in treatment naive or untreated patients was presented, nor any making a direct comparison of eliglustat with velaglucerase in ERT stable patients. There are no pertinent data to enable an indirect comparison analysis to be performed. It is generally accepted that imiglucerase and velaglucerase are equivalent, though the trial data to support this are limited to one small non-inferiority trial with haemoglobin levels as the primary outcome.

The adverse effects of eliglustat were based on the limited available evidence from ENCORE, ENGAGE and the Phase II trial. The adverse effects profile from the trials suggests that eliglustat is well tolerated. There were no deaths reported, very few discontinuations and few eliglustat related SAEs. Most AEs were reported as mild (78%) or moderate (44%). The most common AEs were headache, arthralgia, nasopharyngitis, diarrhoea, upper respiratory tract infection and dizziness; most were of mild severity. The evidence from ENCORE shows a higher number of patients experiencing treatment related AEs and severe TEAEs. However, this apparent difference in tolerability may be due to the fact that patients were stable on ERT at recruitment into the trial. The evidence was mostly limited to the short-term data although some longer-term data up to 4 years demonstrate that eliglustat is generally well tolerated.

5.2 ERG's summary and critique of company's submitted economic evaluation

A summary of the company's approach and signposts to the relevant sections in the company's submission are reported in Table 8 below:

Table 8 Summary of the company's economic evaluation (and signposts to CS)

	Approach	Source / Justification	Signpost (location in CS)
Model	A cost consequence analysis using a 10 health state Semi-Markov model	No justification of model structure given.	Section 12.1.3 Pg. 179 to 182
States and events	The model contains 9 health states plus death. The 9 living health states were based on the GD DS3 severity scoring system.	The model health states were designed to represent the heterogeneity of the Gaucher disease population.	Section 12.1.3 and 12.1.4 Pg. 179 to Pg. 182
Comparators	Eliglustat is compared with the ERT therapies imiglucerase and velaglucerase.	The choice of comparators is based on the Standard Operating Procedures (SOP) for Gaucher disease in England.	Section12.1.2 Pg. 179
Subgroups	IM and EM Gaucher disease patients were analysed separately from patients with PM Gaucher disease. Stable and treatment naïve patients.	These subgroups were presented separately due to differential drug acquisition costs for IM/EM patients compared with PM patients.	Section 12.1.4 Pg. 182
Treatment effectiveness	For stable patients transition probabilities in the first year were based on the ENCORE trial and therefore after based on data from the DS3 score study. For treatment naïve patient's treatment effectiveness was assumed equal and based on the eliglustat arm of the ENGAGE study. In both patient groups clinical effectiveness was based on the GD-DS3 score and mapped directly to the respective health state. The effectiveness of the two ERT therapies imiglucerase and velaglucerase was assumed to be equal in all analyses.	The ENCORE study is the only RCT comparing eliglustat with ERT therapy in stable Gaucher disease patients. There have been no comparisons of eliglustat with ERT therapies in treatment naïve patients.	Section 12.1 Pg. 186 to pg. 188.
Adverse events	Adverse events were included if they occurred in 15% of patients or greater. Patients were only at risk of AE during the first 36 months of the model and thereafter were assumed to experience no further AEs.	Adverse event rates were taken from a pooled analysis of a number of studies including the ENGAGE and ENCORE trials. No adverse events were assumed after 36 months on the basis that that patients are stable on treatment after this time and will not discontinue due to AEs.	Section 12.2.4 Pg. 188 to 189
Health related quality of life	Utility values were assigned to each of the 9 health states based on SF 36 QoL data collected in the DS3 Score study and mapped	Utility values for each health state were sourced from a regression analysis of QoL data collected in the DS3 scoring studies.	Section 10 Pg. 146 to 164

	to EQ-5D. A QoL of life increment was assumed for eliglustat patients to represent the benefits of oral therapy this was based on a TTO study of 100 members of the UK general public Disutilites were applied for a number of AEs.	A QoL increment assigned to eliglustat patients to represent the benefits of oral therapy was sourced from Mapi (2015) a company sponsored study. Disutilises associated with AE were sourced from a number of published studies.	
Resource utilisation and costs	Cost categories were as follows: drug acquisition, administration and monitoring/disease management.	Drug acquisition costs for eliglustat were sourced form the company. For imiglucerase costs were sourced from the BNF and for velaglucerase from MIMS. Drug administration costs were sourced from data on file and NHS reference costs (2014 to 2015). Unit costs for monitoring were taken from NHS reference costs (2014 to 2015). Resource use items were obtained mainly based on expert opinion, but also based on previous economic analyses.	Section 12.3 Pg. 195 to 217
Discount rates	Costs and benefits were discounted at 3.5% per annum	In accordance with the NICE reference case.	Section 12.4.4 Pg. 222
Sensitivity analysis	Probabilistic sensitivity analysis was performed. Deterministic univariate probabilistic analysis was performed on a series of model parameters. A series of scenario analyses was also performed.	In accordance with the NICE reference case.	Section 12.5.11 to 12.5.13. Pg. 246 to 259

5.2.1 Model structure

The de novo cost consequence analysis presented by the company considers two different patient groups: those who are treatment-naïve and those who were taking ERT and are considered clinically stable. Within these groups, further sub-groups are analysed based on metaboliser status, with intermediate and extensive metabolisers (IM and EM) receiving 100mg of eliglustat tartrate twice daily, and poor metabolisers (PM) receive 100mg once daily. The structure of the model is presented in Figure 3. The analysis uses a ten-health state semi-Markov model structure. The model is a semi-Markov structure because, unlike a normal Markov model which is memoryless, the transition probabilities used in the model depend on a patient's initial health state. The health states used in the model are defined by a patients score on the GD-DS3, a validated measure used to score the severity of GD1 in clinical practice (described briefly in Section 2.2.2 of this report). Patients are grouped by: mild (DS3 = 0-3.5), moderate (DS3 = 3.5-6.5), marked (DS3 = 6.5-9.5), and severe (DS3 >9.5) disease. Within these categories, patients are also divided by the presence of bone symptoms, based

metabolisers and 7.5% were indeterminate. Therefore, eliglustat is licensed for the vast majority of the GD1 population, and the impact on the trial results of including these patients is likely to be small.

The starting age of patients in the treatment-naïve population was assumed to be 32 years based on the mean age of the ENGAGE trial, while the starting age of patients in the ERT stable population who switch to eliglustat was assumed to be 38 years. Starting age impact on the model results as it influences survival rates within the time horizon of the model, and therefore affects number of QALYs and costs that patients accrue. Underestimating the starting age therefore has the effect of overestimating lifetime differences and vice versa.

The ERG notes that there is significant variability in the age of patients enrolled in different studies and predicted age at initiating treatment. Table 9 presents an overview of data on the age of patients from the ENGAGE and ENCORE trials as well as other published studies. The Wyatt et al[28] study is particularly noteworthy as this was UK based cohort of 150 patients and likely to be the most representative of the UK GD1 patients. This suggests that the age values used in the model potentially underestimate the mean age at which treatment is initiated and the mean age of stable patients. The ERG considers that this patient group is likely to have more representative of the age of patients in the UK than the trial data and as such presents additional scenario analysis using these alternative values in Section 6.

Table 9Age of patient in published studies

Study	Treatment naïve	Treatment stable
ENGAGE	32	NA
ENCORE	NA	37.6
Phase II	38.0	NA
Wyatt (UK cohort)	35.2	46.4
DS3 score study	44.5	57.8

The initial distribution of patients across health states is summarised in **Error! Reference source not found.**. These are based on the baseline DS3 score patients enrolled in the ENGAGE and ENCORE studies respectively for treatment naïve and treatment stable patients. The base-line distribution of patients in the model is particular important as it determines the transition probabilities that are used in the model and therefore the impacts both on total QALYs and total costs.

As noted in Section 5.2.3.3 the model also excludes a number of serious , but less common adverse events. These serious adverse events include a number of serious adverse events experienced primarily by eliglustat patients including

However, the ERG believes that due to the lack of data available that making use of additional published literature is reasonable, and is likely to have minimal impact on the results due to the adverse event profile being comparable between the intervention and comparator arms.

5.2.7.3 Oral Therapy Increment

The cost-effectiveness model also formally incorporates patients' reported preference for oral therapy over infusion therapy in the base-case analysis via a utility increment of 0.12, which is applied in every cycle. This value was taken from a vignette study which was commissioned by the company [46]. The study included 100 patients from the general population who were enrolled based on their socio-demographic characteristics to approximate the UK general public. The mean age of participants was 35 years, and 66% were female. The authors developed five different health state descriptions which were validated by a clinician and piloted on six members of the general public. The first state described a scenario were an individual had GD1 but whose disease was under control through treatment, without making any reference to the type of treatment received. The second and third states posed the same scenario, however one stated that treatment would be administered orally, and another intravenously.

The study used EQ-5D, and elicited utility values from participants using the time trade off method. The CS supports these findings by referring to the ENCORE trial, where 92% of patients on eliglustat responded to a survey that found that 100% of these patients preferred oral treatment over the infusion therapy they had previously received. The utility increment is applied in every cycle of the analysis regardless of treatment duration, while the patient remains on treatment. The ERG has several issues with incorporating this value into the base case analysis.

It is likely that there will be improvements in quality of life attributed to patients taking an oral treatment instead of receiving an IV therapy. These improvements will stem from increased convenience attributed to not having to receive an IV infusion at home or in hospital every two weeks. However, it is not clear whether these benefits would yield quality of life gains due to improved health, or whether the differing method of administration would result in an improvement in general quality of life instead. Any benefits directly related to health have already been incorporated using data on the efficacy of the treatments, and by including an adverse event decrement associated with infusion related issues which may come as a result of ERT.

disutilities incorporated into the analysis. Back pain was assumed to have a disutility of -0.0187, joint pain -0.0012, abdominal pain -0.0006, URTI -0.0001, and dizziness -0.0004. Use of the 0.12 value means that patients over the time horizon of the cost-effectiveness model are willing to exchange 2.29 years of full health in order to have the increased convenience of taking an oral therapy over an equally efficacious ERT. If an extreme scenario is assumed in which patients experience '0' utility for the two hours they spend each fortnight receiving ERT and a utility of '1' otherwise, then the decrement each fortnight would be equal to '-0.006'. In this scenario you would have to experience a utility of '0' for 1.68 days as a result of ERT in order for the oral therapy increment to equal '0.12'. This value is implausibly large given that patients receive ERT for approximately two hours once every two weeks, and that 96% of these patients receive therapy at home.

Estimates presented in the literature and utilised in other NICE technology appraisal's which have been identified by the ERG cast further doubt on this value of 0.12. There is evidence to demonstrate that patients have a clear preference for oral over IV treatments when they are of a similar efficacy (Liu et al. 1997, [47] Twelves et al., 2005)[48] and that periods of stable disease on oral therapy are valued more highly than those on IV treatment [49]. However, a study by Liu et al. 1997 in patients with cancer found that although 92 of the 103 assessed patients stated a preference for oral therapy over IV, 70% were not willing to accept a lower response rate, and 74% were not willing to accept a shorter duration of response to maintain this preference.[47]

TA162 investigated erlotinib, an oral therapy for the treatment of non-small-cell lung cancer, versus chemotherapy[50]. This appraisal incorporated a utility decrement of '0.025' which was taken from a study conducted by Tabberer et al. 2006[49]. This study explored the impact of non-small-cell lung cancer on quality of life by eliciting utilities from a community sample of 154 people across the UK. Health states were valued using the EQ-5D, with the decrement calculated by taking the difference between the utility of patients with stable disease receiving IV therapy, and the utility of patients receiving an equally efficacious oral therapy. Hux et al. 2015[51] conducted a utility study in Canada on women suffering from symptomatic uterine fibroids. The study calculated a utility decrement of 0.02 when comparing treatment by injection to oral therapy. The study commissioned by the company which generated an increment of '0.12' stated that this 'level of burden is on par with that suggested of the use of subcutaneous insulin in diabetes'. The study that is referenced is one by Ericsson et al. 2013,[52] which evaluates the cost-utility of two types of insulin. The treatments differ both in terms of their treatment effectiveness, but also in the flexibility with which doses can be taken. The study therefore makes use of a disutility for inflexible dose timing of '0.015' which is taken from a time trade-off survey conducted by Evans et al. 2013.[53] Therefore, it is unclear why the study commissioned by the company claimed that the value of '0.12' was comparable to the value reported

Table 10: Cost and setting of administration of intravenous (IV) ERT

Administration Setting	Proportion	Annual cost	Source
Cost of nursing support	NA	£114*26.09=£2,974	PSSRU 2015. 10.1: Community nurse. Unit cost per hour of patient-related work, including qualifications. Assumed 2 hour infusion time (2 x £58)[60]
Home: independent administration	48%	£11,624=£199,976*0.073-£2,974	Assumption that homecare costs are 7.3% of list price of imiglucerase[61] minus cost of nursing support
Home: with nurse support	48%	£14,598 =£199,976*0.073	Assumption that homecare costs are 7.3% of list price of imiglucerase[61]
Day unit (haematology)	4%	£309.45* 26.09=£8,073.81	NHS Reference costs 2014-2015: Other haematological or Splenic Disorders with CC score 0-2 – Day Case
Key: PSSRU**,** Personal Social Services Research Unit.			

The cost of home administration of ERT was assumed to be 7.3% of the list price of imiglucerase.[61] This was assumed to cover the cost of providing delivery of the drug to the home, nursing costs and the provision of a refrigerator and administration pump: this cost was £559.52 per treatment. For patients not requiring nursing support the cost of administering ERT was assumed to be this figure minus the cost of nursing care: £445.53 per treatment. The cost of nursing care was based on the cost of a community nurse, with a 2 hour infusion time (data taken from the PSSRU). Costs of a hospital infusion was taken from NHS Reference costs "Other haematological or Splenic Disorders with CC score 0-2 – Day Case" and assumed to be £309.45 per hospital attendance.

The ERG considers the administrative costs for ERT delivered at home assumed by the company to be excessive and not reflective of actual costs likely to be incurred. The ERG does not consider it plausible that the costs of home administration are greater than the costs of administration in hospital. A number of studies have compared the cost-effectiveness of in home administration of IV therapies with in hospital administration of IV therapies and have consistently found the cost of in home administration of IV therapies to be lower than that of in hospital administration.[62-64]However, there is a paucity of publicly available data specifically to Gaucher disease patients in the UK regarding the relative costs of IV infusion at home compared with in hospital administration. NICE, were, however, able to supply the ERG with confidential data from the CMU on the rates charged by the by the 3 different homecare companies on the framework. This data suggest the costs of administration for home based ERT treatment are substantially less than those used in the company's base case model. This data, however, is present in a format that could be meaningfully incorporated into the company's model in the time available and therefore could note carry out analysis using this data. Instead the ERG present scenario analysis in which administration costs for home IV is assumed to be equal to

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

This section summarises the ERG's further exploration of the issues and uncertainties highlighted in the review and critique of the company's cost-consequence analysis and budget impact presented in section 5. This additional analysis addresses the following issues and uncertainties:

- Discontinuation rates associated with eliglustat and ERT treatment;
- Assumptions regarding the mortality of Gaucher patients;
- Assumptions regarding the HRQoL benefits associated with oral therapy.
- Assumptions made regarding the administrative costs of eliglustat and ERT;
- The dose of eliglustat and ERT treatment assumed in the model;
- Assumptions regarding the short-term effectiveness of eliglustat in treatment naïve patients;
- Assumptions regarding the prevalence of Type 1 Gaucher disease in England.

These are analyses are concluded with the presentation of alternative ERG base-case which the ERG believes is as at least as plausible the base-case presented by the company. All analyses in this section are based on the list prices of imiglucerase and velaglucerase. A confidential appendix replicates the analyses presented in this section using the prices for imiglucerase and velaglucerase currently faced by the NHS. To keep the analyses focused, the scenarios presented in this section assume a treatment stable population who are IM/EM metaboliser status. Full results are presented for all populations in the Appendix .

6.2 Additional ERG analyses

6.2.1 Discontinuation

The company base-case analysis assumes an annual discontinuation of 1.89% for all ERT naïve patients, and ERT stable patients who are treated with eliglustat for three years until they are considered being stable on treatment. In order to address the uncertainty surrounding the selected discontinuation rate in the company's analysis highlighted in Section 5.2.3.1, two scenarios were explored. The first assumed that there was no discontinuation in each patient group. The second used an annual discontinuation rate of 2.36% which was calculated from the rate in the 104 week extension period of the ENCORE trial. Five patients out of 106 who were enrolled onto eliglustat from the start of the trial discontinued therapy over the 104 week extension period, resulting in an annual discontinuation rate of 2.36%.The impacts of adjusting this assumption on incremental QALYs and costs are presented in **Error! Reference source not found.** and **Error! Reference source not found.**.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

Patient Access Scheme and Revised List Price implemented

9th Dec 2016

Patient access scheme evidence submission template

July 2015

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for highly specialised technologies. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a highly specialised technology evaluation, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical effectiveness and value for money of a technology, in the context of a highly specialised technology evaluation, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Highly Specialised Technologies Interim Evidence Submission Template' (https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/hst-interim-evidence-submission-template.doc) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the highly specialised technology evaluation process, please see NICE's 'Interim methods and process statement for highly specialised technologies' (https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/Highly-Specialised-Technologies-Interim-methods-and-process-statements.pdf). The 'Highly Specialised Technologies Interim Evidence Submission Template' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the highly specialised technology evaluation, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated.

If you are submitting the patient access scheme at the end of the evaluation process, you should update the economic model to reflect the assumptions that the HST Evaluation Committee considered to be most plausible. No other changes should be made to the model.

Note on versions:

A number of versions of this document have been submitted as part of this HST assessment. This document is *Revised List Price- 2nd version,* see table for full list of document versions.

Price	Date	Document
PAS + Revised list	9 Dec 16	Patient access scheme evidence submission template ■ PAS and Revised list price implemented. 9th Dec 16 Text entirely consistent with document below but corrected tables 12 and 13
PAS + Revised list	2 Dec 16	Patient access scheme evidence submission template ■ PAS and Revised list price implemented. 2nd Dec 16 Text entirely consistent with document below but renamed for clarity
Revised List Price	01-Dec-16	Patient access scheme evidence submission template ■ Revised list price – 2nd version Tables 12, 13, 16, 17 amended to be consistent with CE & BIM Model Date 01-Dec-16 Inconsistency with PASLU submission therefore Table 15 also amended. All amended text in green font
Revised List Price	17-Nov-16	Patient access scheme evidence submission template ■ Revised list price
PAS price	17-Nov-16	Patient access scheme evidence submission template ■PAS price - 2nd version
PAS price	24-Oct-16	Patient access scheme evidence submission template ■PAS price – 1st version
Initial List Price	06-Apr-16	Highly Specialised Technologies Evaluation Programme: Eliglustat for treating Gaucher disease type 1 Specification for manufacturer/sponsor submission of evidence

This document "PAS and Revised List Price- 2nd version" repeats the content of document ""Revised List Price", however, inconsistencies due to the version of the Budget Impact Model being used are corrected. Budget Impact

results in this document now align with the CE and BIM model dated 1 Dec 2016. As a result Tables, 12, 13, 16, 17 have new values.

In addition, an inconsistency was noted in the patient incidence estimate for 2019 compared to the PASLU submission. This value is corrected in Table 15 of this document and resultant new prevalence values are presented for years 2019, 2020 and 2021.

Amendments to the text in this document, compared with the text in, "Revised List Price" are presented in green font. Amendments to the text in this document, compared with the text in "PAS Price (2nd version)", are in red font.

The only place in this document that the PAS price is considered in relation to the list price (as opposed to an absolute value) is Question 4.3 in discussion of how the PAS is implemented in the economic model. This does not change in this version of the document. The model is submitted with the PAS price implemented. The base-case patient numbers in the CE and BIM dated 1 Dec 16 are consistent with those in the original manufacturer's submission. Details on how to input the revised budget impact model patient estimates are given on the worksheet Version Guide in the model dated 1 Dec 16. The worksheet also explains how to run the PAS and the revised list price in the economic model.

3 Details of the patient access scheme

Please give the name of the highly specialised technology and the disease area to which the patient access scheme applies.

Eliglustat (Cerdelga™) has a UK marketing authorisation for the following indication: “Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1), who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).”

Authorisation was granted by the EMA on 19 January 2015

The highly specialised technology (eliglustat) in the treatment of all licensed patients with GD1, is the disease area to which the patient access scheme applies.

Please outline the rationale for developing the patient access scheme.

The Patient Access Scheme (PAS) provides the NHS with a price that we hope to be competitive and represent value for payers.

Please describe the type of patient access scheme, as defined by the PPRS.

The patient access scheme proposed is fixed price (which will not vary with any change to the UK list price).

Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The patient access scheme applies to the full licensed population.

Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

There are no qualifying criteria for the PAS; all patients within the licensed indication will receive the PAS price on all packs consumed

What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

100% of patients identified for treatment with eliglustat on the NHS in England and Wales are eligible for this patient access scheme.

Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The PAS price will be an on-invoice price to the NHS. Sanofi will sell predominantly to Homecare providers (95% of vols) at List Price. The Homecare providers will sell to the NHS at PAS price and claim the rebate back from Sanofi on a monthly basis, in-line with our other products that use this route to market. The 5% of direct-to-NHS sales from Sanofi will be at PAS price, no rebate required.

Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

No additional data will be needed to implement this scheme hence no administrative impact on the NHS.

Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Not applicable – flows only relevant between Sanofi and Homecare provider

Please provide details of the duration of the scheme.

Indefinite – no end date.

Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

None

If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

The only relevant document is a letter that we make available to Hospital Pharmacists stating the PAS price of the product. This document has been successfully used by Sanofi with other PAS schemes. It is not a contract and does not require a signature from the NHS to get access to the price.

In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable, this is a Simple PAS as defined by the PPRS.

4 Value for money

If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the highly specialised technology evaluation (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence'. You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The revised list price for eliglustat is £342.23 per capsule (or £19,164.96 per 56-capsule pack).

The patient access scheme applies to eliglustat's full licensed GD1 population as described in the manufacturer's submission: poor metabolisers (PM), intermediate metabolisers (IM) and extensive metabolisers (EM). In line with the manufacturer's submission, eight analyses are used to estimate the relative efficacy and the cost consequences associated with eliglustat in the full, licensed population, with the revised list price applied. The following comparisons are made for both i) ERT stable and ii) treatment naïve patients:

- IM/EM, eliglustat compared with imiglucarase
- IM/EM, eliglustat compared with velaglucerase
- PM, eliglustat compared with imiglucarase
- PM, eliglustat compared with velaglucerase

If you are submitting the patient access scheme at the end of the highly specialised technology evaluation process, you should update the economic model to reflect the assumptions that the HST Evaluation Committee considered to be most plausible. No other changes should be made to the model.

We confirm that SanofiGenzyme have updated the model, that this is submitted to NICE with the only amendment being the implementation of the PAS price and the revised list price.

Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the HST Evaluation Committee considered most plausible

The PAS and the revised list price have been incorporated into the economic model with a simple updating of the relevant cost inputs. The simplest way of incorporating the PAS and the revised list price is to use the PAS functionality on the *Settings* worksheet. [redacted]

To input the revised list price the enclosed economic model should be set to: PAS = YES, percentage discount eliglustat = -21.2121% (note, this is a *negative* percent). This tracks through into the cells J19, J21 and J23 on worksheet 'Cost Inputs' with the revised list price of £342.23 per capsule.

The most plausible assumptions according to the HST Evaluation Committee are not yet known, therefore this application is run based on the manufacturers submitted base case.

Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The clinical effectiveness data are not affected by the proposed PAS or the revised list price therefore there is no change in the clinical data reported in the manufacturer's submission.

Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. .

Table 1 Costs associated with the implementation and operation of the patient access scheme (PAS)

	Calculation of cost	Reference source
Stock management		
Administration of claim forms		
Staff training		
Other costs…		
…		
…		
Total implementation/ operation costs		

Given the PAS proposed is a simple discount off the list price, no additional costs associated with the implementation of this PAS are anticipated.

Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the

intervention both with and without the patient access scheme.

Please give the reference source of these costs.

Table 2 Additional treatment-related costs for the intervention both with and without the patient access scheme (PAS)

	Intervention without PAS		Intervention with PAS		Reference source
	Unit cost (£)	**Total cost e.g. per cycle, per patient (£)**	**Unit cost (£)**	**Total cost e.g. per cycle, per patient (£)**	
Interventions					
Monitoring tests					
Diagnostic tests					
Appointments					
Other costs…					
…					
…					
Total treatment-related costs					

Given the PAS proposed is a simple discount off the list price, no additional treatment-related costs are anticipated to be incurred due to implementation of the patient access scheme.

Summary results

Base-case analysis

Please present in separate tables the economic results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

The tables below present the results for the intervention without and then with the patient access scheme. Table 1 to Table 4 are without the patient access scheme (with the revised list price), while

Table 5 to Table 8 are with the patient access scheme.

Table 1 Without PAS: summary results for the ERT stable poplation, IM and EM

	Eliglustat	Imiglucerase	Eliglustat	Velaglucerase
Intervention cost (£)	£4,978,055	£4,023,067	£5,042,966	£5,295,042
Other costs (£)	£66,358	£333,509	£66,358	£333,508
Total costs (£)	£5,044,413	£4,356,576	£5,109,324	£5,628,550
Difference in total costs (£)	**-**	**£687,837**	**-**	**-£519,226**
LYG (or other outcome)	37.52	37.52	37.52	37.52
LYG difference	**-**	**0**	**-**	**0**
QALYs (or other outcome)	16.81	14.52	16.8	14.52
QALY difference	**-**	**2.28**	**-**	**2.28**

LYG: life-year gained; QALY: quality-adjusted life-year

Table 2: Without PAS: Summary results for the ERT stable population, PM

	Eliglustat	Imiglucerase	Eliglustat	Velaglucerase
Intervention cost (£)	£2,591,678	£4,023,067	£2,656,590	£5,295,042
Other costs (£)	£66,359	£333,509	£66,358	£333,508
Total costs (£)	£2,658,037	£4,356,576	£2,722,948	£5,628,550
Difference in total costs (£)	**-**	**-£1,698,539**	**-**	**-£2,905,602**
LYG (or other outcome)	37.52	37.52	37.52	37.52
LYG difference	**-**	**0**	**-**	**0**
QALYs (or other outcome)	16.81	14.52	16.8	14.52

QALY difference		**2.28**		**2.28**

LYG: life-year gained; QALY: quality-adjusted life-year

Table 3 Without PAS: Summary results for the treatment naïve population, IM and EM

	Eliglustat	Imiglucerase	Eliglustat	Velaglucerase
Intervention cost (£)	£5,273,235	£4,330,992	£5,342,369	£5,540,195
Other costs (£)	£68,562	£338,554	£68,562	£338,554
Total costs (£)	£5,341,797	£4,669,546	£5,410,931	£5,878,749
Difference in total costs (£)	**-**	**£672,251**	**-**	**-£467,818**
LYG (or other outcome)	42.28	42.28	42.28	42.28
LYG difference	**-**	**0**	**-**	**0**
QALYs (or other outcome)	18.06	15.63	18.06	15.62
QALY difference	**-**	**2.43**	**-**	**2.45**

LYG: life-year gained; QALY: quality-adjusted life-year

Table 4 Without PAS: Summary results for the treatment naïve population, PM

	Eliglustat	Imiglucerase	Eliglustat	Velaglucerase
Intervention cost (£)	£2,745,949	£4,330,992	£2,815,083	£5,540,195
Other costs (£)	£68,562	£338,554	£68,562	£338,554
Total costs (£)	£2,814,511	£4,669,546	£2,883,645	£5,878,749
Difference in total costs (£)	**-**	**-£1,855,035**	**-**	**-£2,995,104**
LYG (or other outcome)	42.28	42.28	42.28	42.28
LYG difference	**-**	**0**	**-**	**0**
QALYs (or other outcome)	18.06	15.63	18.06	15.62
QALY difference	**-**	**2.43**	**-**	**2.45**

LYG: life-year gained; QALY: quality-adjusted life-year

Results with PAS implemented

Table 5 With PAS implemented: Summary results for the ERT stable, IM and EM

	Eliglustat	Imiglucerase	Eliglustat	Velaglucerase
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
LYG (or other outcome)	37.52	37.52	37.52	37.52
LYG difference	**-**	**0**	**-**	**0**
QALYs (or other outcome)	16.8	14.52	16.8	14.52
QALY difference		**2.28**		**2.28**

LYG: life-year gained; QALY: quality-adjusted life-year

Table 6 With PAS implemented: Summary results for the ERT stable, PM

	Eliglustat	Imiglucerase	Eliglustat	Velaglucerase
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
LYG (or other outcome)	37.52	37.52	37.52	37.52
LYG difference	**-**	**0**	**-**	**0**
QALYs (or other outcome)	16.8	14.52	16.8	14.52
QALY difference	**-**	**2.28**	**-**	**2.28**

LYG: life-year gained; QALY: quality-adjusted life-year

Table 7 With PAS implemented: Summary results for the treatment naïve population, IM and EM

	Eliglustat	Imiglucerase	Eliglustat	Velaglucerase
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
LYG (or other outcome)	42.28	42.28	42.28	42.28
LYG difference	**-**	**0**	**-**	**0**
QALYs (or other outcome)	18.06	15.63	18.06	15.62
QALY difference	**-**	**2.43**	**-**	**2.45**

LYG: life-year gained; QALY: quality-adjusted life-year

Table 8 With PAS implemented: Summary results for the treatment naïve population, PM

	Eliglustat	Imiglucerase	Eliglustat	Velaglucerase
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
LYG (or other outcome)	42.28	42.28	42.28	42.28
LYG difference	-	0	-	0
QALYs (or other outcome)	18.06	15.63	18.06	15.62
QALY difference	-	2.43	-	2.45

LYG: life-year gained; QALY: quality-adjusted life-year

Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

Table 9 presents the incremental results without the patient access scheme implemented, with the revised list price while Table 10 presents the incremental results with the patient access scheme implemented.

Table 9 Without PAS implemented: incremental results

		without PAS	
		Eliglustat vs Imiglucerase	**Eliglustat vs Velaglucerase**
Treatment stable	*Incremental QALYS*	*2.28*	*2.28*
IM/EM	Incremental cost	£687,837	-£519,226
PM	Incremental cost	-£1,698,539	-£2,905,602
Treatment naïve	*Incremental QALYS*	*2.43*	*2.45*
IM/EM	Incremental cost	£672,251	-£467,818
PM	Incremental cost	-£1,855,035	-£2,995,104

QALY: quality-adjusted life-year

[2] For outcome-based schemes, please see section 5.2.9

Table 10 With PAS implemented: incremental results

		With PAS	
		Eliglustat vs Imiglucerase	**Eliglustat vs Velaglucerase**
Treatment stable	*Incremental QALYS*	[redacted]	[redacted]
IM/EM	Incremental cost	[redacted]	[redacted]
PM	Incremental cost	[redacted]	[redacted]
Treatment naïve	*Incremental QALYS*	[redacted]	[redacted]
IM/EM	Incremental cost	[redacted]	[redacted]
PM	Incremental cost	[redacted]	[redacted]

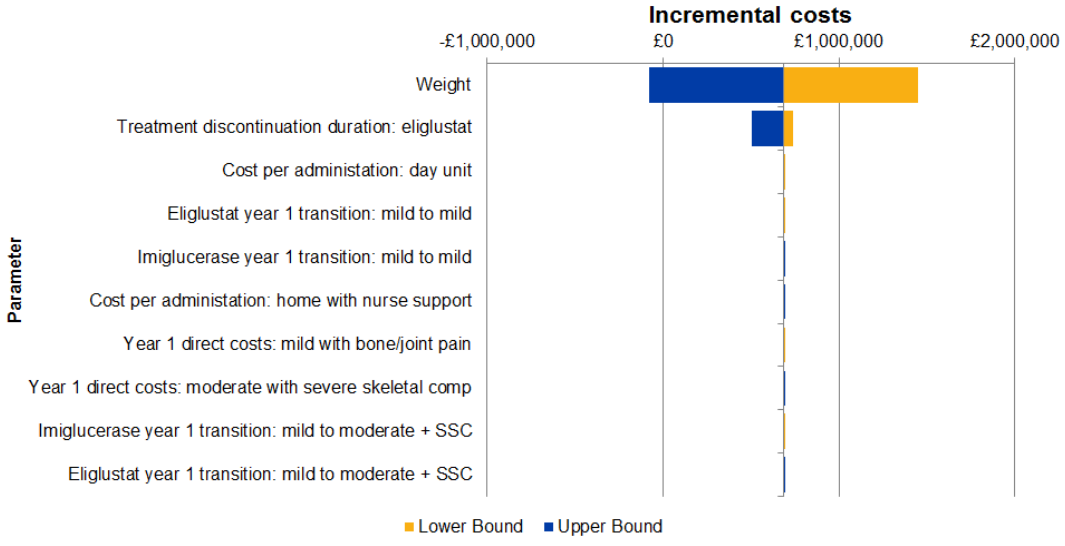
Sensitivity analyses

Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the highly specialised technology evaluation. Consider using tornado diagrams.

The results of the deterministic sensitivity analyses are presented below in tornado diagrams for each of the cost drivers and QALY drivers for each population, metaboliser status and comparator. Given that none of the drivers of the QALY results are related to cost of affected by the patient access scheme, the deterministic sensitivity analyses related to QALYs is unchanged from that presented in the manufacturer's submission dossier. They are repeated here for completeness.

With regards to cost drivers, the tornado diagrams based on the revised list price are presented alongside diagrams showing the impact of the implementation of the simple PAS [redacted]. Please note x-axis change between figures.

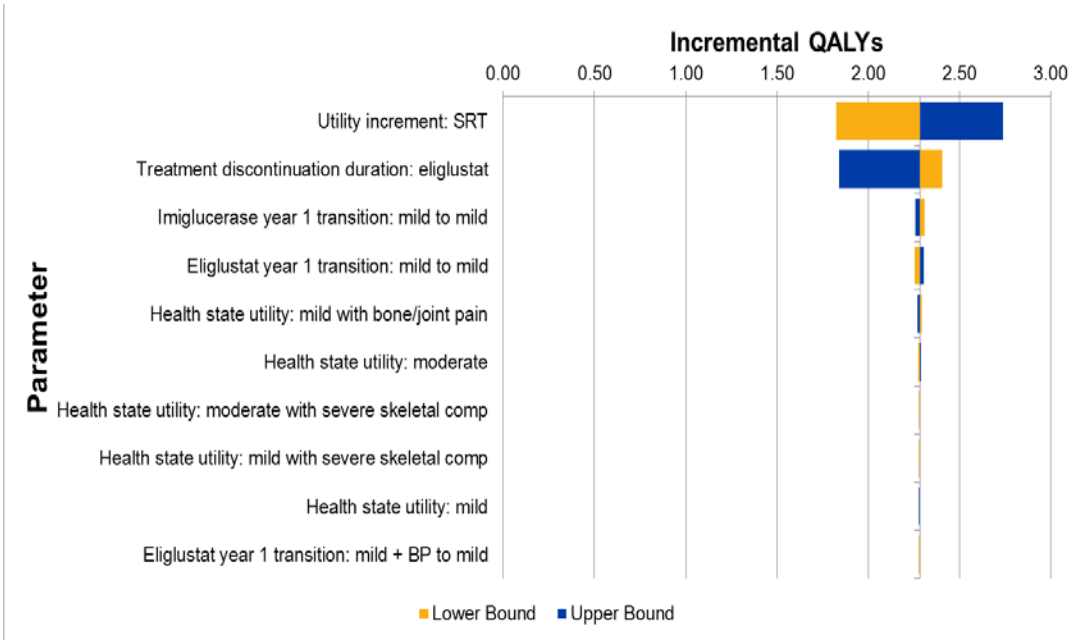
Figure 1: Revised List Price: Tornado diagram of incremental cost – ERT stable, versus imiglucerase, IM/EM patients



Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; SSC, severe skeletal complications.

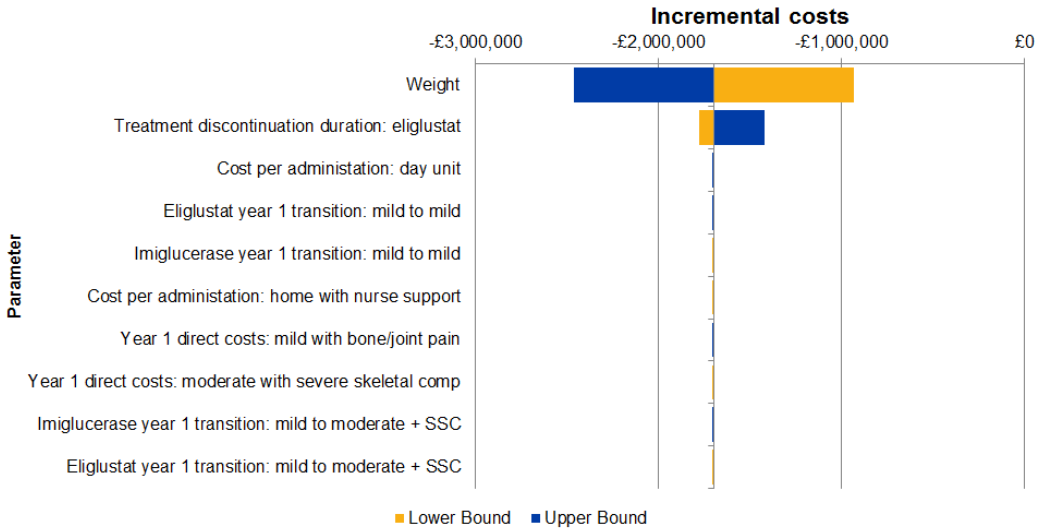
[redacted]

Figure 3: Tornado diagram of incremental QALYs – ERT stable, versus imiglucerase, IM/EM patients



Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

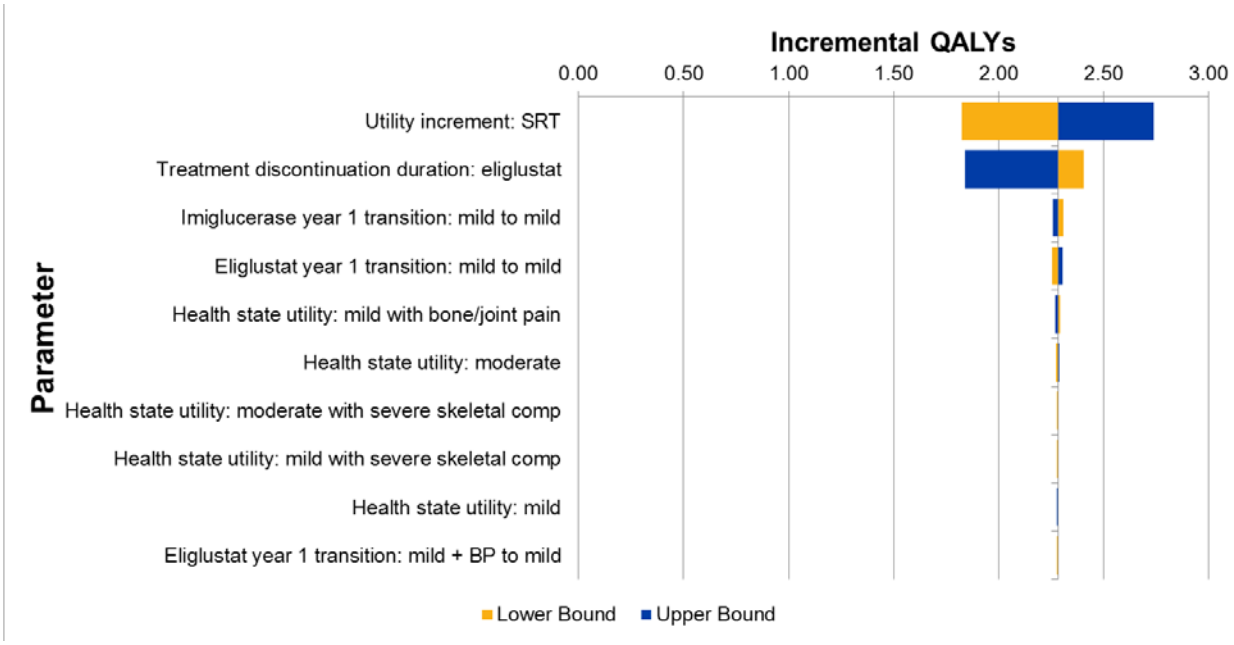
Figure 4: Revised List Price: Tornado diagram of incremental cost – ERT stable, versus imiglucerase, PM patients



Key: ERT, enzyme replacement therapy; PM, poor metaboliser; SSC, severe skeletal complications.

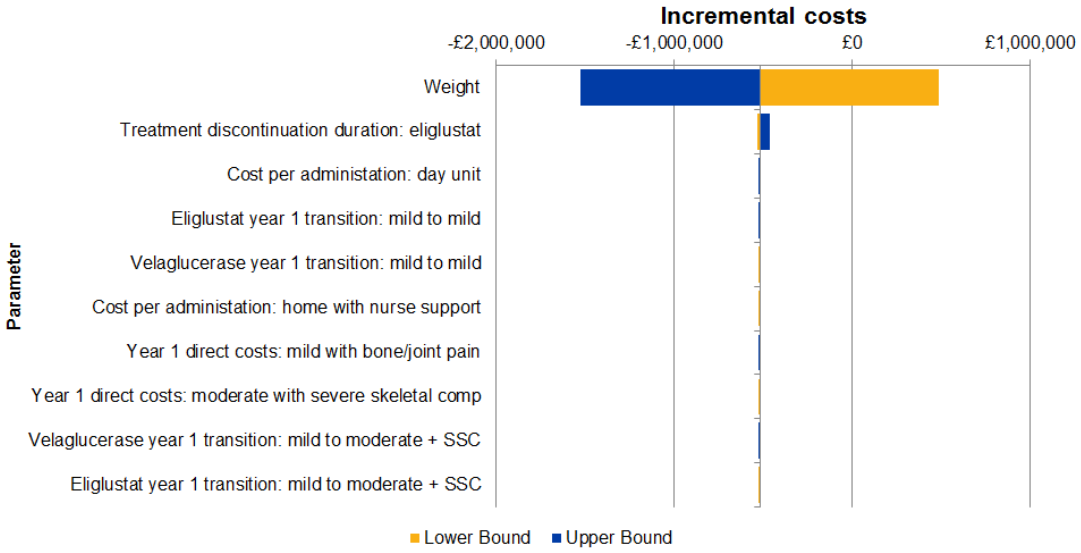
[redacted]

Figure 6: Tornado diagram of incremental QALYs – ERT stable, versus imiglucerase, PM patients



Key: ERT, enzyme replacement therapy; PM, poor metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

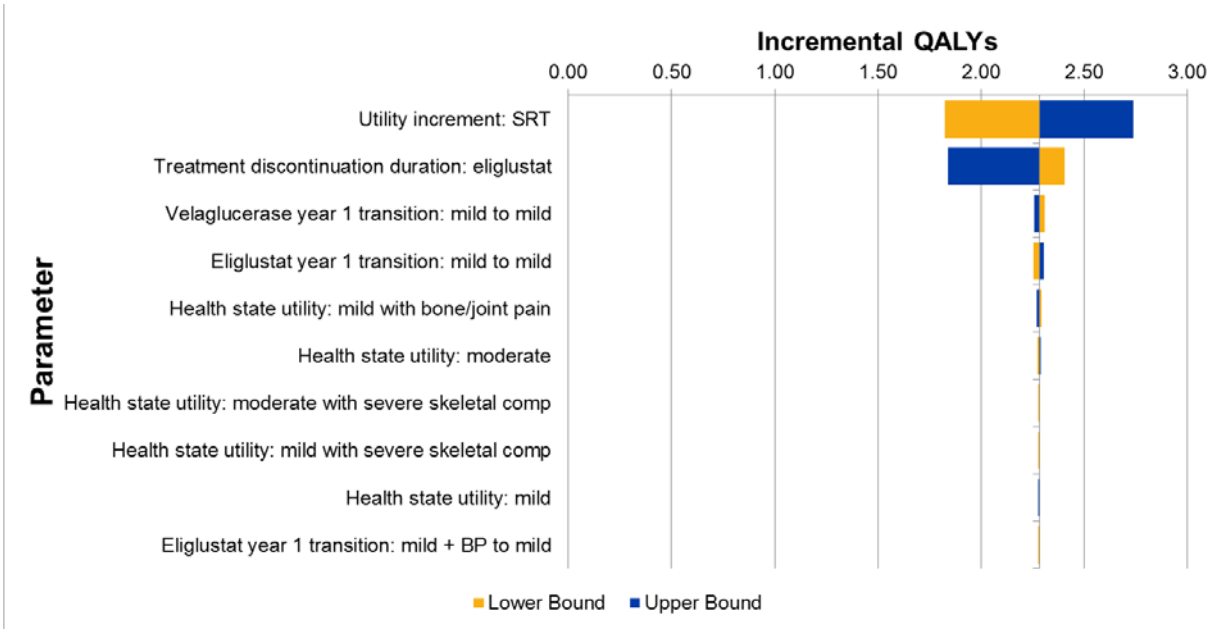
Figure 7: Revised List Price: Tornado diagram of incremental cost – ERT stable, versus velaglucerase, IM/EM patients



Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; SSC, severe skeletal complications.

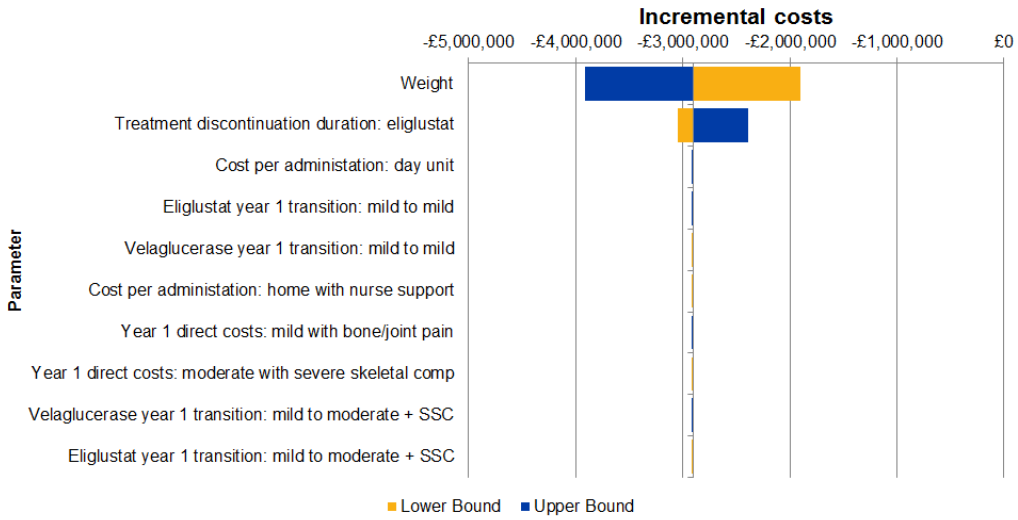
[redacted]

Figure 9: Tornado diagram of incremental QALYs – ERT stable, versus velaglucerase, IM/EM patients



Key: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

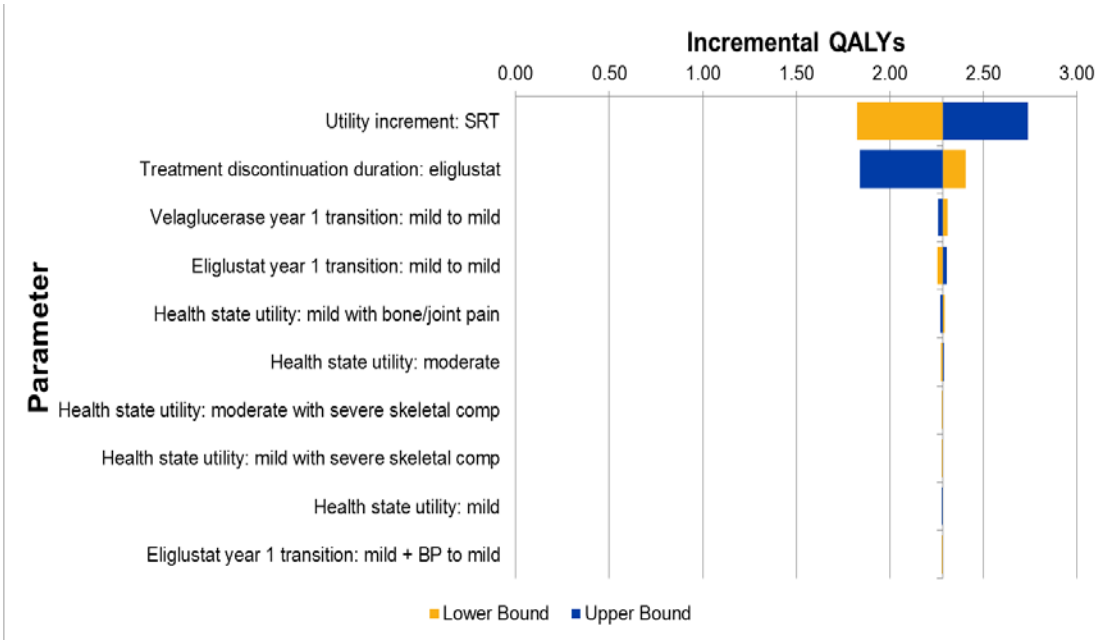
Figure 10: Revised List Price: Tornado diagram of incremental cost – ERT stable, versus velaglucerase, PM patients



Key: ERT, enzyme replacement therapy; PM, intermediate metaboliser; SSC, severe skeletal complications.

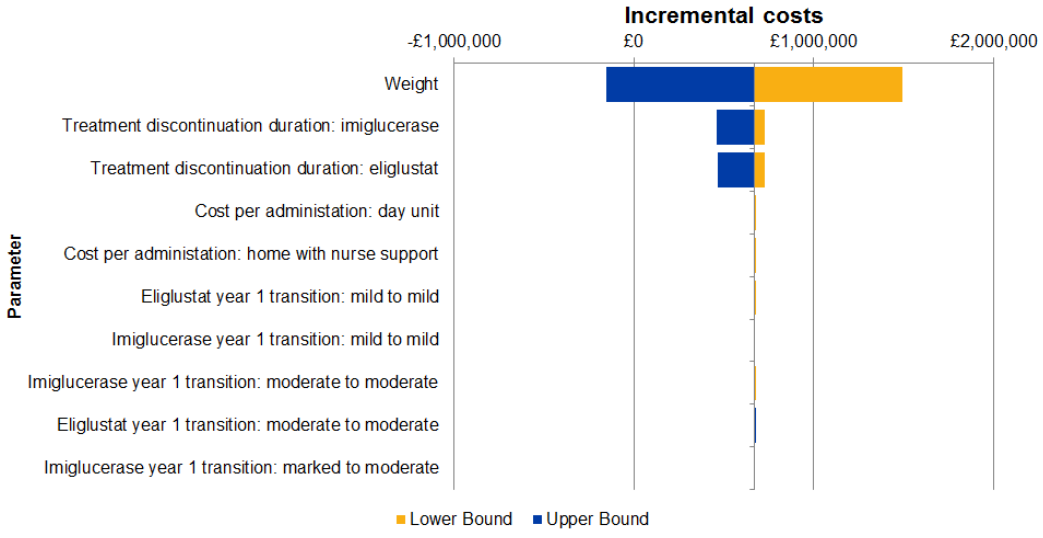
[redacted]

Figure 12: Tornado diagram of incremental QALYs – ERT stable, versus velaglucerase, PM patients



Key: ERT, enzyme replacement therapy; PM, poor metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

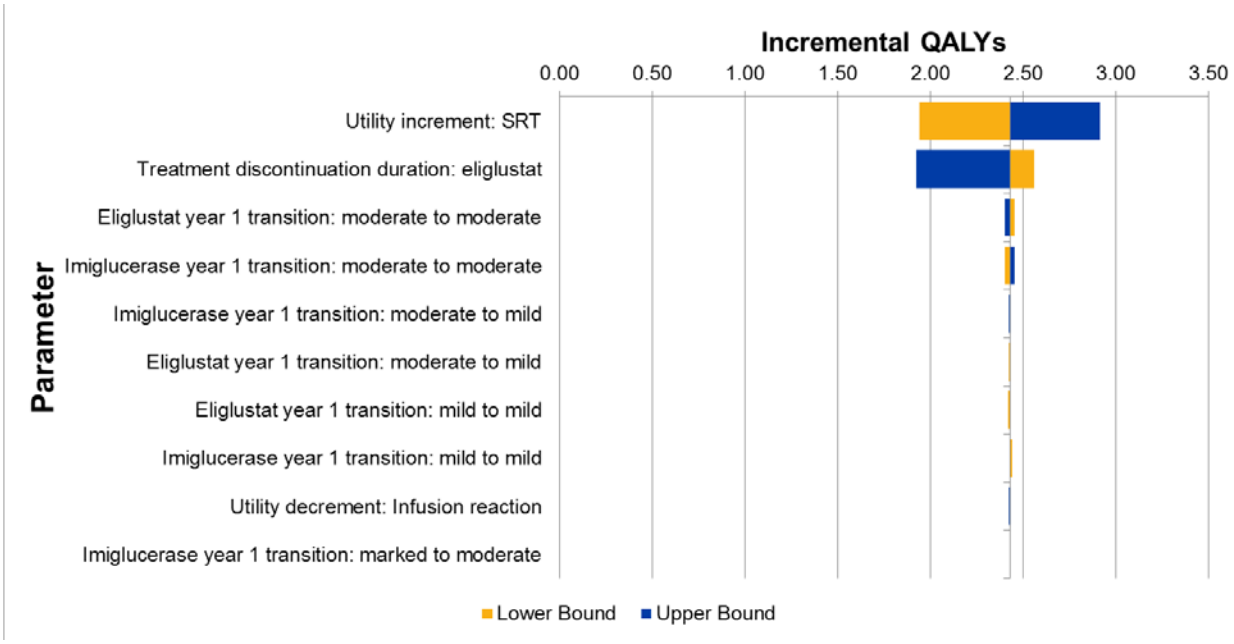
Figure 13: Revised List Price: Tornado diagram of incremental cost – treatment naïve, versus imiglucerase, IM/EM patients



Key: EM, extensive metaboliser; IM, intermediate metaboliser.

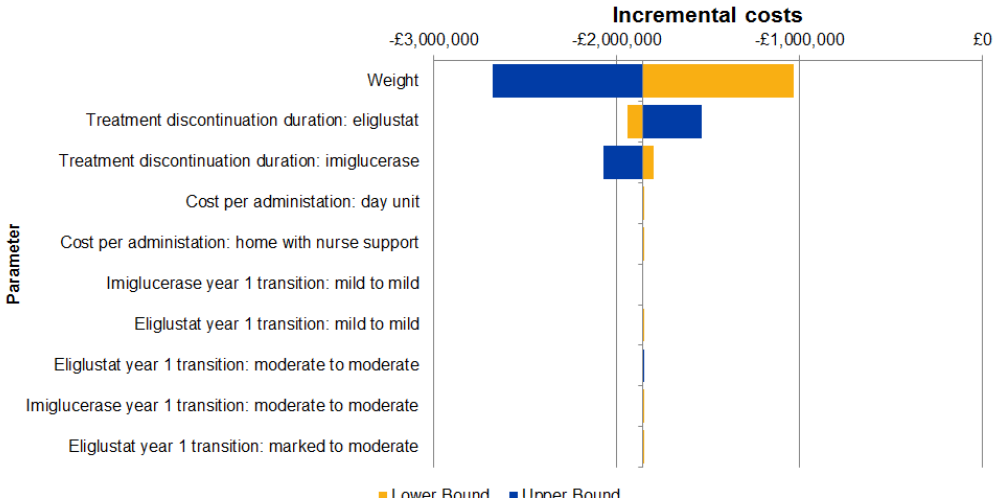
[redacted]

Figure 15: Tornado diagram of incremental QALYs – treatment naïve, versus imiglucerase, IM/EM patients



Key: EM, extensive metaboliser; IM, intermediate metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

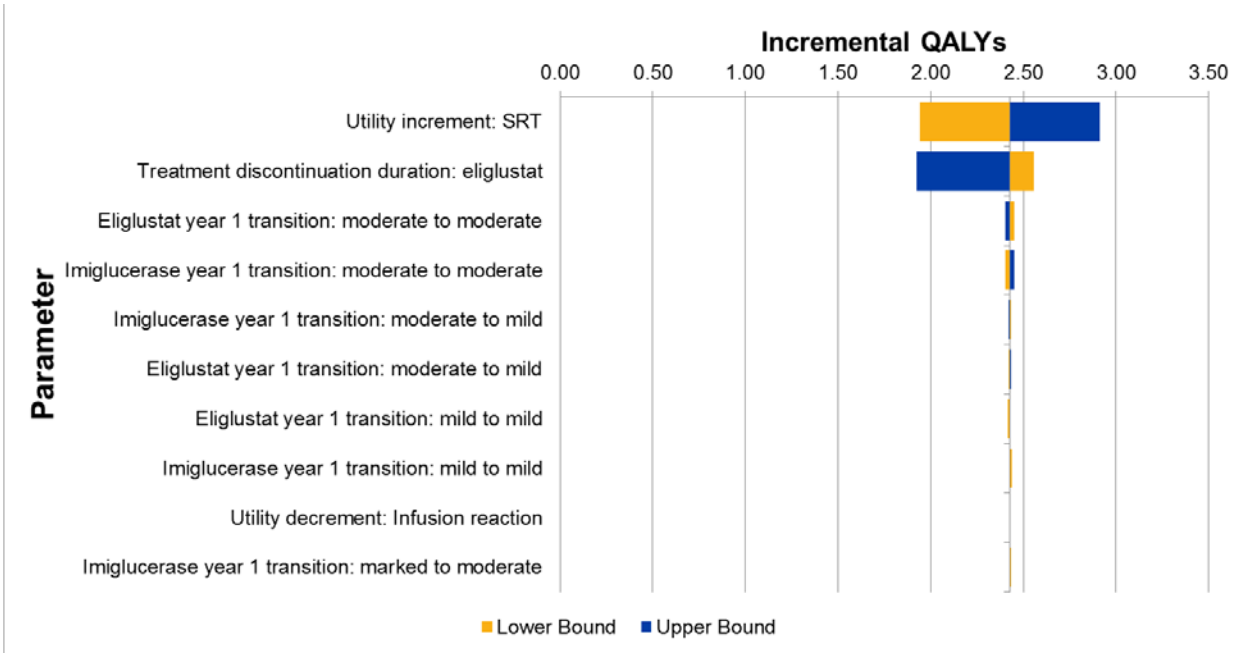
Figure 16: Revised List Price: Tornado diagram of incremental cost – treatment naïve, versus imiglucerase, PM patients



Key: PM, poor metaboliser.

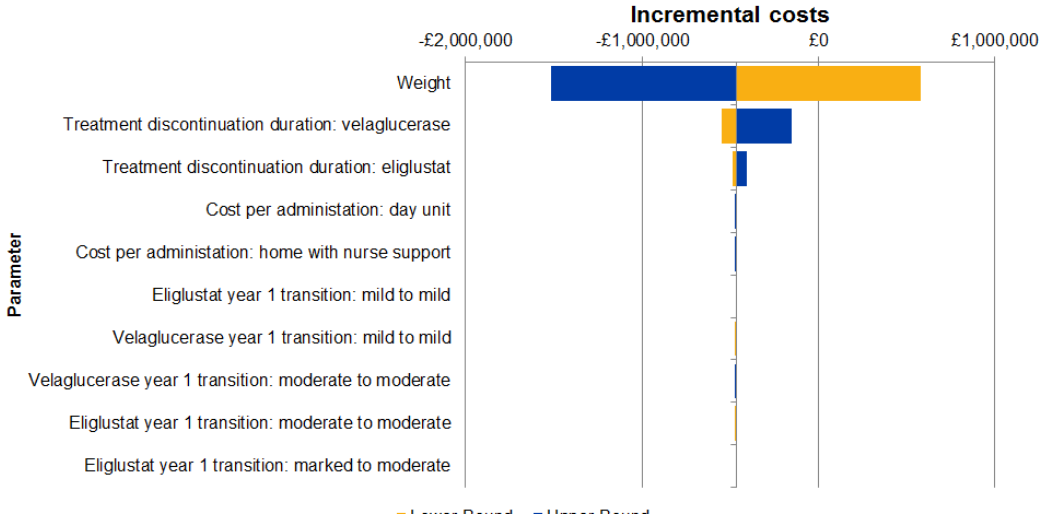
[redacted]

Figure 18: Tornado diagram of incremental QALYs – treatment naïve, versus imiglucerase, PM patients



Key: PM, poor metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

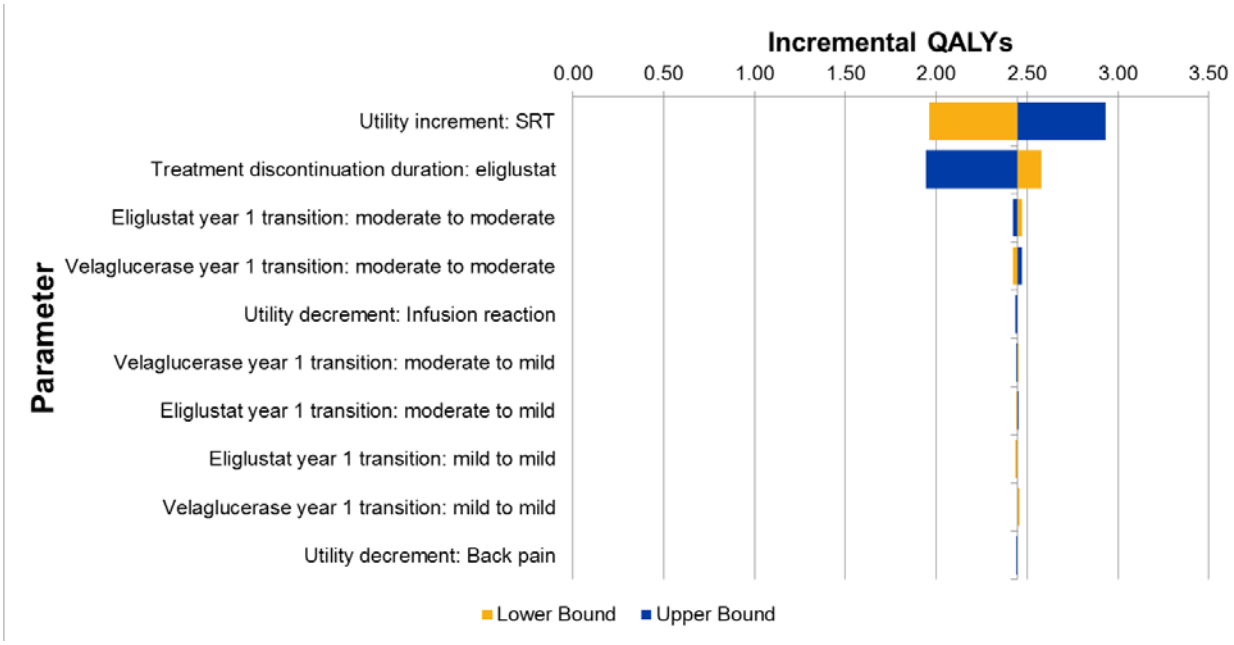
Figure 19: Revised List Price: Tornado diagram of incremental cost – treatment naïve, versus velaglucerase, IM/EM patients



Key: EM, extensive metaboliser; IM, intermediate metaboliser.

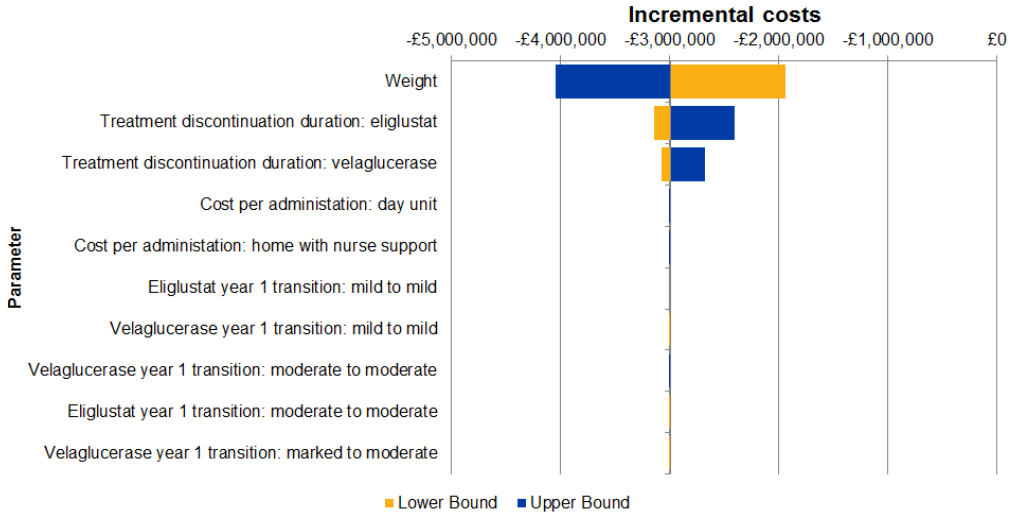
[redacted]

Figure 21: Tornado diagram of incremental QALYs – treatment naïve, versus velaglucerase, IM/EM patients



Key: EM, extensive metaboliser; IM, intermediate metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

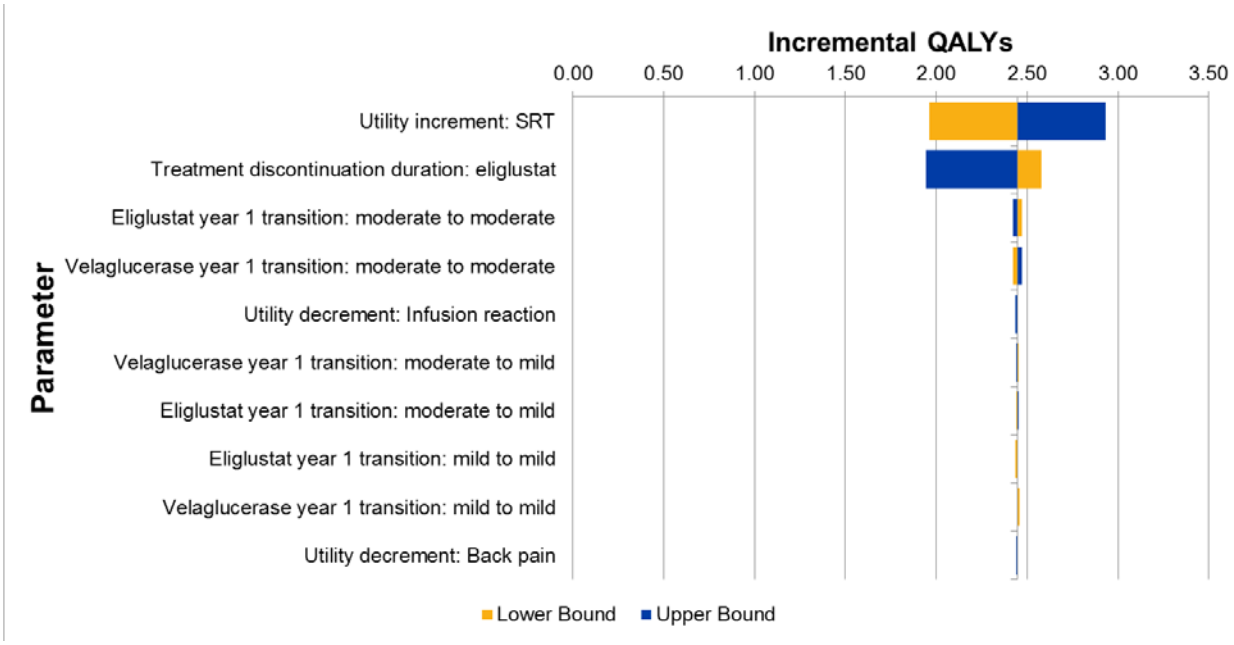
Figure 22: Revised List Price: Tornado diagram of incremental cost – treatment naïve, versus velaglucerase, PM patients



Key: PM, poor metaboliser.

[redacted]

Figure 24: Tornado diagram of incremental QALYs – treatment naïve, versus velaglucerase, PM patients



Key: PM, poor metaboliser; QALYs, quality-adjusted life years; SRT, substrate reduction therapy.

Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the highly specialised technology evaluation.

Table 11 presents the base case scenario analysis from manufacturer submission with additional columns estimating the impact of implementing the patient access scheme.

Table 11: Scenario analysis results: including PAS estimates

Parameter	Scenario	Technology	ERT stable population		With PAS: ERT stable population		Treatment naïve population		With PAS: Treatment naïve population	
			Cost	Inc. cost	PAS cost	Inc. cost	Cost	Inc. cost	PAS cost	Inc. cost
Base case results										
N/A		Eliglustat	£5,044,413		[redacted]	[redacted]	£5,341,797		[redacted]	[redacted]
		Imiglucerase	£4,356,576	£687,644	[redacted]	[redacted]	£4,669,546	£672,251	[redacted]	[redacted]
		Eliglustat	£5,109,324		[redacted]	[redacted]	£5,410,931		[redacted]	[redacted]
		Velaglucerase	£5,628,550	-£519,226	[redacted]	[redacted]	£5,878,749	-£467,818	[redacted]	[redacted]
Time horizon										
Time horizon of model (base case 70 years)	1 year (versus imiglucerase)	Eliglustat	£252,482		[redacted]	[redacted]	£252,222		[redacted]	[redacted]
		Imiglucerase	£216,600	£35,882	[redacted]	[redacted]	£217,423	£34,799	[redacted]	[redacted]
	1 year (versus velaglucerase)	Eliglustat	£253,665		[redacted]	[redacted]	£253,405		[redacted]	[redacted]
		Velaglucerase	£279,826	-£26,161	[redacted]	[redacted]	£278,282	-£24,877	[redacted]	[redacted]
Differential efficacy of eliglustat										
Application of different transition probabilities (Base case: trial based transitions for 1 year)	Equal efficacy using trial data (versus imiglucerase)	Eliglustat	£5,044,344		[redacted]	[redacted]	N/A	N/A	N/A	N/A
		Imiglucerase	£4,356,700	£687,644	[redacted]	[redacted]	N/A	N/A	N/A	N/A
	Equal efficacy using trial data (versus velaglucerase)	Eliglustat	£5,109,254		[redacted]	[redacted]	N/A	N/A	N/A	N/A
		Velaglucerase	£5,628,674	£519,420	[redacted]	[redacted]	N/A	N/A	N/A	N/A

Parameter	Scenario	Technology	ERT stable population		[redacted]		Treatment Naïve population		[redacted]	
			Cost	Inc. cost	PAS cost	Inc. cost	Cost	Inc. cost	PAS cost	Inc. cost
	Equal efficacy using registry data only (versus imiglucerase)	Eliglustat	£5,044,145		[redacted]	[redacted]	£5,341,914		[redacted]	[redacted]
		Imiglucerase	£4,356,501	£687,644	[redacted]	[redacted]	£4,669,664	£672,251	[redacted]	[redacted]
	Equal efficacy using registry data only (versus velaglucerase)	Eliglustat	£5,109,055		[redacted]	[redacted]	£5,411,049		[redacted]	
		Velaglucerase	£5,628,475	--£519,420	[redacted]	[redacted]	£5,878,867	-£467,818	[redacted]	[redacted]
Discontinuation										
Discontinuation rates for all treatments	Rates set to zero (versus imiglucerase)	Eliglustat	£5,044,344		[redacted]	[redacted]	£5,341,797		[redacted]	[redacted]
		Imiglucerase	£4,356,576	£687,644	[redacted]	[redacted]	£4,613,624	£672,251	[redacted]	[redacted]
	Rates set to zero (versus velaglucerase)	Eliglustat	£5,109,254		[redacted]	[redacted]	£5,410,931		[redacted]	[redacted]
		Velaglucerase	£5,628,550	-£519,420	[redacted]	[redacted]	£5,961,096	-£467,818	[redacted]	[redacted]
IV administration utility decrement										
Utility decrement associated with IV administration of ERT	No utility decrement (versus imiglucerase)	Eliglustat	£5,044,413		[redacted]	[redacted]	£5,341,797		[redacted]	[redacted]

If any of the criteria on which the patient access scheme depends are clinically variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the HST Evaluation Committee can determine which criteria are the most appropriate to use.

Not applicable with the patient access scheme proposed.

Impact of patient access scheme

For financially based schemes, please present the results of the value for money analyses showing the impact of the patient access scheme on the base-case and any scenario analyses. If you are submitting the patient access scheme at the end of the evaluation process, you must include the scenario with the assumptions that the HST Evaluation Committee considered to be most plausible.

The implementation of this simple PAS [redacted] would increase potential savings to the NHS due to both reduced administration costs and also through reduced therapy acquisition costs.

As eliglustat has launched in other countries, SanofiGenzyme has gained insight into the likely uptake of the eliglustat in the UK. Due to this, forecast patient numbers have been revised. Below is reported the budget impact, without and with the PAS implemented, for the original patient number estimates. We then repeat the budget impact analysis with the revised patient numbers, again without and with the patient access scheme implemented.

Table 12 is a repeat of Table 102 in the manufacturer's submission, with the revised list price, and presents the base-case budget impact for eliglustat, without the patient access scheme implemented. Table 13 reports the budget impact with the original patient numbers, with the PAS implemented.

Table 12: Revised list price: Without PAS Estimated budget impact 2017-2021

Cost category	Year				
	2017	2018	2019	2020	2021
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	£184,491	£312,562	£427,244	£560,347	£734,066

From model:eliglustat model with correct BIM 1 DEC 16

Table 13 With PAS implemented estimated budget impact 2017-2021

Cost category	Year				
	2017	2018	2019	2020	2021
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

From model:eliglustat model with correct BIM 1 DEC 16

The budget impact in Table 12 and Table 13, as in the manufacturer's base-case submission, are based on the patient numbers for eliglustat in Table 14.

Table 14 Estimated eliglustat patient numbers, 2017 to 2021, original base-case

	2017	2018	2019	2020	2021
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The revised forecast for eliglustat patient numbers is presented in Table 15 Note, the estimates for the first three years are in line with those submitted in the PASLU application. There is a correction in this version of the document to make it consistent with the numbers presented in the PASLU submission (noted in green font in table 15). The incidence estimate for 2019 has been changed, this impacts the total patient numbers for 2019, 2020 and 2021.

In order to implement the revised patient numbers in the economic model, (model version dated 1 Dec 2016) over type cells H95, I95, J95, K95, L95 in worksheet Budget Impact with the numbers in the Incidence row in Table 15.

Table 15: Revised estimated eliglustat patient numbers 2017 to 2021

	2017	2018	2019	2020	2021
Incidence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5 Based on these revised patient numbers, the budget impact without the PAS at the revised list price and with the PAS implemented are presented in Table 16 and Table 17.

Table 16 Revised list price: Without PAS, revised patient numbers, estimated budget impact 2017-2021

Cost category	Year				
	2017	2018	2019	2020	2021
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**£84,559**	**£199,622**	**£359,602**	**£501,906**	**£674,682**

From model:eliglustat model with correct BIM 1 DEC 16

Table 17 With PAS, with revised patient numbers, estimated budget impact 2017-2021

Cost category	Year				
	2017	2018	2019	2020	2021
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

From model:eliglustat model with correct BIM 1 DEC 16

These budget impact analyses demonstrate with a level of confidence that with the PAS implemented, eliglustat would offer the NHS a valuable therapy option in the treatment of Gaucher Disease Type 1.

Appendices

Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Appendix A Draft Letter to Chief Pharmacists

A template letter to Chief Pharmacists at the specialist treatment centres is provided below.

<<Chief Pharmacist>>
<<NHS Trust>>
<<Address 1>>
<<Address 2>>

<<Date>>

Notification of Patient Access Scheme

TA XXXX: Eliglustat (Cerdelga) for treating Gaucher Disease Type 1

Dear Chief Pharmacist

This is to notify you that NICE has approved eliglustat (Cerdelga) for use in the above indication.

Sanofi has agreed a Simple Patient Access Scheme which has been approved by NICE and the Department of Health.

The discount is confidential and commercially sensitive and therefore should only be disclosed to those personnel who you reasonably believe need to know the discounted price in order to effectively manage the purchasing and commissioning of this product including internal NHS benchmarking.

If you receive any requests from third-parties to disclose this confidential price (such as Freedom of Information requests) please inform Sanofi prior to disclosure.

Product: eliglustat (Cerdelga)
Strength: 100mg twice daily for CYP2D6 Intermediate and Extensive Metabolisers; 100mg once daily for CY2D6 Poor Metabolisers.

Product Code: [tbc]
NHS List Price*: £342.23 per 100mg capsule or £19,164.96 per 56 capsule pack.
Confidential Patient Access Scheme Price [redacted]
for a 56 capsule pack
*excluding VAT

If you have any questions regarding this Patient Access Scheme please do not hesitate to contact me

Yours,

Jessamy BAIRD
Director of Patient Access
UK & Ireland

Email: Jessamy.baird@sanofi.com
Tel.: +44 (0) 1483 55 4009

Appendix B: Details of outcome-based schemes

Not applicable

5.1.2 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

5.1.3 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

5.1.4 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

5.1.5 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

5.1.6 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

5.1.7 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Response

5.1.8 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

5.1.9 Please present the value for money results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.1.10 Please present in separate tables the results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

Eliglustat for treating type 1 Gaucher

ERG appraisal of patient access scheme and additional evidence provided following first committee meeting

Produced by Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE)

Date 16/12/16

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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Table of Tables

Section 1: Introduction

The ERG was requested by NICE to provide validity checks on the application of a patient access scheme (PAS) and additional evidence submitted by the company following the first committee meeting. Due to the limited resource available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission.

Following the first committee meeting the company provided the following:

1. Details of a revised list price for eliglustat, and cost-effectiveness results for the company's revised base-case incorporating the revised list price;
2. Details of PAS submission, and cost-effectiveness results for the company's revised base-case incorporating the PAS discount;
3. An amended version of the executable economic model;
4. Budget impact results from the amended version of the economic model;

The ERG's review of the documentation submitted by the company found that the documentation did **not** reflect the stated amendments to the model and we were unable to replicate the results presented in the provided documentation using the model provided. This was due to undocumented changes to the company's base-case model. The ERG notified NICE of these issues and highlighted the changes made to the company's original base-case model so as to enable the company either provide revised documentation or a revised executable model. The company responded by providing a revised PAS document and revised executable model. The ERG, however, noted that there were still a number of inconsistencies and again contact NICE to allow the company to make any necessary changes. IN response the company provided a third submission which included a revised PAS document and executable model. Unfortunately, the model still included a number of inconsistencies and was not identical to the model submitted by the company as part the original submission. At this juncture the ERG considered that the company were unable to provide the ERG with an appropriate executable model and associated documentation and therefore applied the stated revisions to the executable model to the executable model provided at the points for clarification stage. This model is one agreed by the company to represent their original base-case and produces results identical to those presented in the company's original submission assuming the original base-case assumptions and the original list price. The differences between the final model provide by the company and the one provided at the points for clarification stage are as follows:

- Cell H91 on the budget impact sheet has a value of 7 in the original submission and "0" in the provide model
- Stated value for cell K95 in amended model is 18, actual value used in provided model is 17.658;
- Stated value for cell L95 in amended model is 18, actual value used in provided model is 17.658.

The ERG cannot comment on the validity of the changes made in the company's new submission, because no documentation of these changes was provided in the company's PAS documentation. All results presented in this document are therefore based on the ERG's application of the stated changes to the model and are as faithful as possible to those intended by the company given the information provided.

Section 2: Application of revised list price and PAS discount

In this section, the ERG presents the following:

- Results of company's original base-case with revised the list price;
- Results of company's original base-case with the PAS discount applied;

The documentation provided by the company presents a revision to the list price for eliglustat and a new PAS. The PAS consists of a simple discount of xxx over the original list price and xxx over the new list price. Table 1 presents the original list price per pack, the revised list price per pack and price per pack with the new PAS discount applied.

Table 1 Price of Eliglustat with revised list price and new PAS discount

	Cost per 56-tablet blister pack (excluding VAT)	
	List price	**Discount over original list price**
Original List price	£15,811.04	0%
Revised List price	£19,164.96	-21.21%
Price with PAS applied	XXX	XXX

As stated above the ERG could not replicate the results provided by the company in the PAS documentation. The ERG has therefore applied the stated list price change and PAS discount to the original company base-case model provided to the ERG following corrections applied at the points for clarification stage. The results of the results of company's original base-case with revised the list price and new PAS discount are present in Tables 2 to 7.

Company's Base-Case New List Price

Table 2: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Total: 2.28	Total: £ 687,837
ERT stable PM	Total: 2.28	Total: -£ 1,698,539
ERT naïve IM/EM	Total: 2.43	Total: £ 672,251
ERT naïve PM	Total: 2.43	Total: -£ 1,855,035

Table 3: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Total: 2.28	Total: -£ 519,226
ERT stable PM	Total: 2.28	Total: -£ 2,905,602
ERT naïve IM/EM	Total: 2.43	Total: -£ 467,818
ERT naïve PM	Total: 2.43	Total: -£ 2,995,104

Table 4: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	£184,218	£304,543	£394,177	£493,482	£620,247
Cumulative Total	£184,218	£488,761	£882,938	£1,376,420	£1,996,667

Company's Base-Case PAS discount applied

Table 5: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	xxx	xxx
ERT stable PM	xxx	xxx
ERT naïve IM/EM	xxx	xxx
ERT naïve PM	xxx	xxx

Table 6: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	xxx	xxx
ERT stable PM	xxx	xxx
ERT naïve IM/EM	xxx	xxx
ERT naïve PM	xxx	xxx

Table 7: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Section 3: Amendments to the company base-case

In additional to the revised list price and PAS discount the company also provide an amended economic model with a modification to the budget impact model. This change reflected new information available to the company on the expected uptake of eliglustat by patients currently receiving Enzyme replacement therapy (ERT). The original and revised figures are present in Table 8.

Table 8 Revised estimated eliglustat patient numbers 2017 to 2021

	2017	2018	2019	2020	2021
Original Incidence	XXX	XXX	XXX	XXX	XXX
Revised Incidence	XXX	XXX	XXX	XXX	XXX

The ERG is not able to critique these values as we have no alternative sources of which to verify the company's data. The ERG, however, note that the revised figures are substantially lower than those provided in the original submission and it would be informative to hear from the company why they expect uptake of eliglustat to be much slower than previously predicted. These changes to the budget impact model have no impact on the cost consequence analysis results. Results for the company's revisited budget impact model are presented in Tables 5 and 6.

Company's Base-Case New List Price

Table 9: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	£84,559	£193,784	£331,078	£442,311	£571,487
Cumulative Total	£84,559	£278,342	£609,421	£1,051,731	£1,623,218

Company's Base-Case PAS discount applied

Table 10: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	XXX	XXX	XXX	XXX	XXX
Cumulative Total	XXX	XXX	XXX	XXX	XXX

Section 4: ERG scenario analysis

To allow the committee to consider the alternative scenarios present in the ERG's report this section presents results of all the scenario analysis carried out by the ERG in the ERG's original report with the new PAS discount applied. In an accompanying confidential appendix the ERG also present the

results of this analysis with PAS discounts for imiglucerase and velaglucerase applied. The ERG present results for the following scenarios:

- Alternative discontinuation rates for eliglustat and ERT treatments;
- Alternative assumptions regarding the mortality of Gaucher patients;
- Alternative assumptions regarding the HRQoL benefits associated with oral therapy.
- Alternative assumptions made regarding the administrative costs of eliglustat and ERT;
- Changes to the dose of eliglustat and ERT treatment assumed in the model;
- Alternative assumptions regarding the short-term effectiveness of eliglustat in treatment naïve patients;
- Alternative assumptions regarding the prevalence of Type 1 Gaucher disease in England.

These analyses are concluded with the presentation of alternative ERG base-case which the ERG believes is as at least as plausible the base-case presented by the company. Results of this analysis are presented in Tables 11 to 70 below.

Alternative discontinuation rates

Zero discontinuation for all treatments

Table 11: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	xxx	xxx
ERT stable PM	xxx	xxx
ERT naïve IM/EM	xxx	xxx
ERT naïve PM	xxx	xxx

Table 12: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	xxx	xxx
ERT stable PM	xxx	xxx
ERT naïve IM/EM	xxx	xxx
ERT naïve PM	xxx	xxx

Table 13: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 14: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Discontinuation for Eliglustat equal to 104 week ENCORE trial

Table 15: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	xxx	xxx
ERT stable PM	xxx	xxx
ERT naïve IM/EM	xxx	xxx
ERT naïve PM	xxx	xxx

Table 16: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	xxx	xxx
ERT stable PM	xxx	xxx
ERT naïve IM/EM	xxx	xxx
ERT naïve PM	xxx	xxx

Table 17: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 18: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Alternative mortality rates

Revised mortality applied to all GD1 patients

Table 19: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	xxx	xxx
ERT stable PM	xxx	xxx
ERT naïve IM/EM	xxx	xxx
ERT naïve PM	xxx	xxx

Table 20: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	xxx	xxx
ERT stable PM	xxx	xxx
ERT naïve IM/EM	xxx	xxx
ERT naïve PM	xxx	xxx

Table 21: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 22: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Revised mortality applied to 'Marked' and 'Severe' states

Table 23: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	xxx	xxx
ERT stable PM	xxx	xxx
ERT naïve IM/EM	xxx	xxx
ERT naïve PM	xxx	xxx

Table 24: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	xxx	xxx
ERT stable PM	xxx	xxx
ERT naïve IM/EM	xxx	xxx
ERT naïve PM	xxx	xxx

Table 25: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 26: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Zero Mortality for the calculation of budget impact results

Table 27: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 28: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

HRQoL: impact of increment for oral administration

Increment equal to '0.025'

Table 29: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Table 30: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Increment equal to '0.09'

Table 31: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Table 32: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Increment equal to '0.05'

Table 33: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Table 34: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Administration Costs

Alternative administration costs for ERT (home therapy cost equal to hospital cost)

Table 35: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental Cost
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Table 36: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental Cost
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Table 37: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 38: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Dispensary Costs for Eliglustat (£14.40 per month)

Table 39: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental Cost
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Table 40: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental Cost
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Table 41: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 42: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Alternative dosing for ERT patients

Vial wastage for ERT

Table 43: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental Cost
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Table 44: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental Cost
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Table 45: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 46: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

AWMSG Study Dosage and Weight inputs (32 U/kg and 75kg average weight)

Table 47: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental Cost
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Table 48: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental Cost
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Table 49: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 50: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Dosage of Eliglustat based on dose used in ENCORE trial (114mg)

Table 51: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental Cost
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Table 52: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental Cost
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Table 53: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

Cost category	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 54: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

Cost category	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

ERT dosing used in practice (25 U/kg)

Table 55: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental Cost
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Table 56: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental Cost
ERT stable IM/EM	xxx
ERT stable PM	xxx
ERT naïve IM/EM	xxx
ERT naïve PM	xxx

Table 57: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 58: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

Cost category	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Efficacy

ENCORE transition probabilities applied to first cycle in treatment naïve patients

Table 59: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT naïve IM/EM	xxx	xxx
ERT naïve PM	xxx	xxx

Table 60: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT naïve IM/EM	xxx	xxx
ERT naïve PM	xxx	xxx

Table 61: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 62: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Alternative Population Size assumption

248 Gaucher Patients – ERG estimate after correcting for company calculation error

Table 63: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 64: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

293 Gaucher Patients- Gaucher association population estimate

Table 65: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 66: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

ERG Base-Case Analysis

Table 67: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	xxx	xxx
ERT stable PM	xxx	xxx
ERT naïve IM/EM	xxx	xxx
ERT naïve PM	xxx	xxx

Table 68: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	xxx	xxx
ERT stable PM	xxx	xxx
ERT naïve IM/EM	xxx	xxx
ERT naïve PM	xxx	xxx

Table 69: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 70: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Section 5: Additional scenario analysis carried out by the ERG

This section presents an additional scenario analysis which corrects for the fact the budget impact model results presented in the company's submission assume that the population of Gaucher disease patients is made up entirely of intermediate metabolisers (IM) and extensive metabolisers (EM). This overestimates the budget impact of introducing eliglustat as the cost-effectiveness of eliglustat in poor metabolisers (PM) is quite different to that of the IM/EM sub-population due to the lower dose of eliglustat required in the PM population. This section presents a revised budget impact model that assumes that 4% of Eliglustat patients are PM. This figured is based on the proportion of PM in the ENGAGE trial. Results are presented for the following scenarios:

- Assuming the company's original base-case assumptions;
- Assuming the company's revised base-case assumptions concerning the number of patients switching from ERT to eliglustat;
- Assuming the ERG's base-case assumption with original figures for the number of patients switching to eliglustat;
- Assuming the ERG's base-case assumption with the revised figures for the number of patients switching to eliglustat.

The results of this analysis are present in Tables 71 to 74 below.

Company base-case

Table 71: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM/PM Patients weighted results)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 72: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM/PM Patients weighted results)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

ERG base-case

Table 73: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM/PM Patients weighted results)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Table 74: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM/PM Patients weighted results)

	2017	2018	2019	2020	2021
Total	xxx	xxx	xxx	xxx	xxx
Cumulative Total	xxx	xxx	xxx	xxx	xxx

Section 6: Conclusions

The introduction of the new PAS discount substantially lowers the acquisition costs associated with eliglustat and reduces the overall budget impact. Interpretation of these results should however, bear in mind that ERT is itself a highly cost-ineffective therapy in of itself and has an estimated ICER of £380,000 to £476,000 per QALY, based on a previous cost-effective analysis carried out as part of the NHS HTA programme.[1] Any consideration of the cost-effectiveness of eliglustat such therefore consider the fact that ERT is currently provided to Gaucher disease patients at a cost to the NHS which would be unacceptable for other more common diseases.

Section 7: References

1. Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, et al. The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review. Health Technol Assess 2006;10:1-136.

Eliglustat Results: Revised List Price

The tables below present the results of the ERGs analysis using the revised list price of eliglustat of £342.23 (A price increase of 21.2121%). The table numbers (67-74) correspond with those reported in the ERGs response to the company's PAS document.

ERG Base-Case Analysis

Table 1: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Total: 1.05	Total: £ 2,638,293
ERT stable PM	Total: 1.05	Total: -£ 6,825
ERT naïve IM/EM	Total: 1.04	Total: £ 2,605,712
ERT naïve PM	Total: 1.04	Total: -£ 49,688

Table 2: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	Total: 1.05	Total: £ 1,849,412
ERT stable PM	Total: 1.05	Total: -£ 795,706
ERT naïve IM/EM	Total: 1.06	Total: £ 1,900,060
ERT naïve PM	Total: 1.06	Total: -£ 755,340

Table 3: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	**£5,058,551**	**£8,172,429**	**£10,130,622**	**£12,088,535**	**£14,048,638**
Cumulative Total	**£5,058,551**	**£13,230,980**	**£23,361,602**	**£35,450,137**	**£49,498,775**

Table 4: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	**£2,321,945**	**£5,058,377**	**£7,688,503**	**£9,682,106**	**£11,677,472**
Cumulative Total	**£2,321,945**	**£7,380,322**	**£15,068,824**	**£24,750,930**	**£36,428,402**

Company base-case

Table 5: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM/PM Patients weighted results)

	2017	2018	2019	2020	2021
Total	**-£50,939**	**-£71,693**	**-£64,912**	**-£47,810**	**-£4,509**
Cumulative Total	**-£50,939**	**-£122,632**	**-£187,544**	**-£235,354**	**-£239,862**

Table 6: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM/PM Patients weighted results)

	2017	2018	2019	2020	2021
Total	**-£23,382**	**-£39,205**	**-£19,232**	**£6,107**	**£49,822**
Cumulative Total	**-£23,382**	**-£62,586**	**-£81,818**	**-£75,712**	**-£25,889**

ERG base-case

Table 7: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM/PM Patients weighted results)

	2017	2018	2019	2020	2021
Total	**£4,818,908**	**£7,785,194**	**£9,650,430**	**£11,515,367**	**£13,382,472**
Cumulative Total	**£4,818,908**	**£12,604,102**	**£22,254,532**	**£33,769,899**	**£47,152,371**

Table 8: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM/PM Patients weighted results)

	2017	2018	2019	2020	2021
Total	**£2,211,946**	**£4,818,731**	**£7,324,191**	**£9,223,107**	**£11,123,765**
Cumulative Total	**£2,211,946**	**£7,030,676**	**£14,354,867**	**£23,577,974**	**£34,701,739**

Eliglustat for Treating Type 1 Gaucher Disease

Expert engagement meeting

31 February 2017

Discussion point 1

- The company has updated the likely uptake of the eliglustat in the UK, based on experiences in other countries. Do these numbers reflect expectations in clinical practice in England?

Forecast for eliglustat patient numbers					
	2017	2018	2019	2020	2021
Original	xxx	xxx	xxx	xxx	xxx
Revised	xxx	xxx	xxx	xxx	xxx

- Note: UK Gaucher Association submission noted 293 Type 1, 2 and 3 Gaucher disease patients in the UK (adults and children); = 193 adults with type 1 GD in England.

Discussion point 2

- The dose of ERT assumed in the model is a driver of economic results
- The committee heard previously that:
  - practice is to titrate the dose of ERT and use the lowest effective dose
  - patients generally start on 30 U/kg, followed by close monitoring for the first 12 months, with further dose reductions depending on response
  - some people with newly diagnosed type Gaucher disease occasionally have very severe disease and may need a higher starting dose
- Are there any additional comments on this issue?

Discussion point 3

- In the recent evaluation for migalastat for Fabry disease, the committee noted that the main comparator, ERT (agalsidase alfa and agalsidase beta), has not been evaluated for treating Fabry disease – adding uncertainty
- Imiglucerase and velaglucerase have also not been evaluated by NICE for type 1 Gaucher disease.
- Are there any comments on this?

Eliglustat for treating type 1 Gaucher disease [ID709]

Expert Engagement Meeting – Discussion notes

Discussion paper: Confirmed

Date and Time: Tuesday 31 January 2017, 1pm – 2pm

In attendance:

Dr Peter Jackson	Chair, HST Committee
Sheela Upadhyaya	Associate Director, National Institute for Health and Care Excellence
Jenna Dilkes	Project Manager, National Institute for Health and Care Excellence
Heidi Livingstone	Public Involvement Advisor, National Institute for Health and Care Excellence
Mark Sheehan	Lay member, HST commitee
Dr Derralynn Hughes	Senior lecturer in haematology and consultant haematologist, Royal Free London
Tanya Collin-Histed	CEO, UK Gauchers Association

Notes

Welcome

1. The Chair welcomed all attendees.

2. Apologies were received from Dr Timothy Cox, Niamh Finnegan, Chantal de Carlo and Baljit Dhillon.

3. The Chair asked all attendees to declare any relevant interests

3.1. Dr Peter Jackson, Mark Sheehan, Sheela Upadhyaya, Heidi Livingstone and Jenna Dilkes all declared that they knew of no conflicts of interest.

3.2. Dr Derralynn Hughes was the co-Principal Investigator for eliglustat at the Royal Free Hospital and received grants and honoraria for speaking engagements from Genzyme, Shire and Amicus.

3.3. Tanya Collin-Histed declared that the UK Gauchers Association receive unrestricted grants from Genzyme, Amicus and Shire.

4. **Discussion point 1– uptake in the first 5 years.**

4.1. The experts thought that the uptake would be higher than in the second forecast in years one and two, with possibly some people waiting to see what happened in years one and two before moving to eliglustat themselves.

4.2. All agreed that the numbers would then drop in years 4 and 5

4.3. It was agreed, however, that the [redacted]igure of the second forecast was more accurate than the [redacted] of the first forecast.

4.4. The Gaucher Association asked 39 patients whether they might consider moving to eliglustat and 37 of them would.

4.5. There are about 6 or 7 new patients diagnosed each year.

5. **Discussion point 2 – how ERT is currently used.**

5.1. The clinical expert agreed that both up and down titration occur

5.2. The majority of patients will start on 30U/kg but the most severe 10% of the population would need a higher starting dose of either 45 or 60 U/kg to get the disease under control before dropping down.

5.3. An increase in the dose is based on clinical end points and assessment. Usually somebody would be on a particular dose for a year before titrating it up or down.

5.4. Those patients who start on a dose of 30 U/kg might end up long term on a dose of 15-30U/kg (one exceptional case dropped down to 4)

5.5. Those patients starting on either 45 or 60 U/kg may stay on a higher dose for approximately 2-3 years but eventually might end up on a dose somewhere between 30-60U/kg when under control.

5.6. Patients, centres and NHS England developed standard operating procedures in 2015 about how people are treated and titrated.

5.7. The Standard Operating Procedure (SOP) has been agreed with all clinicians at all highly specialised centres and all centres use the SOP.

6. **Discussion point 3 - ERT**

6.1. There was agreement that there should be a rigorous evaluation of treatments both novel and already commissioned for ultra orphan diseases but less certainty that the current methodologies could provide an acceptable degree of rigour.

6.2. The clinical expert said that ERT works very well in Gaucher, whereas the effectiveness is less certain in Fabry and there was a strong feeling that the clinical effectiveness of ERT for Gaucher was not a priority for an evaluation process.

6.3. Many patients with Gaucher on ERT are able to work and lead a normal family life – the treatment is that effective.

6.4. Imiglucerase has been in use for Gaucher since 1998.

6.5. SMC have recommended imiglucerase for Gaucher

Point 1 ; Forecast.
There are to my knowledge many type 1 adult patients who have expressed an interest in the drug and reports of safety and efficacy are favourable, now with >10 years international experience. There are about 510 patient years of safety data. I would judge the take up values as revised to be if anything conservatively low if we are talking about reimbursement for the whole of 2017 as one calendar year.

Quality of life data are now available from the Switch Study I have done and these are very encouraging in this patient-reported area. I would estimate that the total population would within 3 years soon be 45% of adults with >180 eligible on age and indication. More will follow but those with multiple other medications (generally older) will need caution.We should not forget that the drug has been authorized now for at least two years so people know of the acceptability in this community. Oral therapy largely obviates the low self-esteem associated with regular 'medicalizing' intravenous infusions of enzyme (see also below).

Point 2; Economic driver
This is substantially correct but with two provisos:

(a) it cannot be a direct concern as a treating physician to discuss health care economics: the ethical duty is to the patient and to argue for the best treatment in relation to life quality and efficacy and importantly a factual point

(b) oral therapy has other tangible economic advantages – travel costs; healthcare delivery costs of enzyme for systemic infusions to the home; nursing time; on call time; refrigerators; on-call safety monitoring of the same; infusion time and apparatus and related paraphernalia in the home or indeed the outpatient clinic – many third party providers (private).

Point 3 NICE evaluation and future real-world assessments
While attractive for economists and apparently justified objectives for evaluation, the healthcare economic models for ultra-orphan (not orphan) agents are imperfectly developed. I contend that the arbitrariness of the current utilitarian calculus has unacceptable bias as a result of the extreme rarity and disease diversity. Unlike the other lysosomal diseases, enzyme therapy for Gaucher disease (one agent only – imiglucerase) was the subject of a preliminary examination (2005-6) of the tractability of such methodology; this process was not pursued but went as far as a citizen's panel (strong positive vote).

I will perhaps add that the evidence for fundamental efficacy (and safety) for the two approved enzyme therapies in Europe and now for eliglustat is striking: the capacity to reverse many aspects of the disease is not equalled. For the therapeutic outcomes, Gaucher disease is quite unlike the other lysosomal diseases with high-cost therapies cited. Moreover, it is substantially less frequent than the X-linked Fabry disease.

As the CI of GAUCHERITE [Gaucher Investigative Therapy Evaluation] - a current National, MRC – funded Stratified Medicine Programme, ongoing since 2013 with 211 Gaucher patients enrolled so far, I can report that we have collected deep phenotyping data in all aspects of the disease from all eight specialist centres. this is the only rare disease to be the subject of a Stratified Medicine programme of Investigation. These data with major investigative strands (osseous and neurological) prospective in the cohort as well as cross-sectional and retrospective (mortality data up to 25 years also will be entered) should be able to assist future evaluations in the real word alongside our Cochrane review which is just now undergoing intensive revision.

Our Ref: 17-0210.1

Specialised Commissioning
Skipton House
80 London Road
London
SE1 6LH

Jenna Dilkes
National Institute for Health and Care Excellence
Level 1A, City Tower, Piccadilly Plaza
Manchester M1 4BT
Sent via email Jenna.Dilkes@nice.org.uk

10th February 2017

Dear Ms Dilkes

Eliglustat – response to questions of NHS England

1. Expected uptake of eliglustat

All estimates of uptake are largely guesswork. We believe that initial uptake will be 20 – 25% of eligible patients (about 30 – 40 patients), rising over time to 40 – 60% of eligible patients (about 60 – 90 patients). More precise estimates are not possible.

The actual uptake in 2017 will be a part-year effect depend on whether and when eliglustat is recommended for commissioning by the NHS.

2. Precedent set by migalastat ECD

Although the general theme of the response by NHS England to NICE's ECD on migalastat applies also to eliglustat, we believe it does not have quite the same force because:

1. Gaucher disease is more acute than Fabry disease and so the effectiveness of enzyme replacement therapy (ERT) is more obvious;
2. Again because of the acute nature of the condition, clinicians are able to dose titrate ERT for Gaucher disease, using the lowest dose which effectively controls disease activity in individual patients. This is not possible in Fabry disease. Hence ERT is used more cost effectively in Gaucher disease than in Fabry disease; and
3. Far more patients receive ERT for Fabry disease (over 400) than for Gaucher disease (about 250), and the number for Fabry is rising steadily without evidence of any plateau. Hence the spend and the financial pressure are both greater for Fabry disease than for Gaucher disease.

I hope this information is helpful to you.

Yours sincerely

[redacted]
[redacted] **of Specialised Commissioning**
NHS England