The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using asfotase alfa in the context of national commissioning by NHS England. The Highly Specialised Technologies Evaluation Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this evaluation (see section 10) and the public. This document should be read along with the evidence base (the Committee papers).

The Evaluation Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the Committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of asfotase alfa in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Note that this document is not NICE’s final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Evaluation Committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final evaluation determination (FED).
- Subject to any appeal by consultees, the FED may be used as the basis for NICE’s guidance on using asfotase alfa in the context of national commissioning by NHS England.

For further details, see the Interim Process and Methods of the Highly Specialised Technologies Programme.

**The key dates for this evaluation are:**

Closing date for comments: 7 January 2016

Second Evaluation Committee meeting: 20 January 2016

Details of membership of the Evaluation Committee are given in section 9, and a list of the sources of evidence used in the preparation of this document is given in section 10.
1 Evaluation Committee’s preliminary recommendations

1.1 Asfotase alfa is not recommended, within its marketing authorisation, for long-term enzyme replacement therapy in paediatric-onset hypophosphatasia to treat the bone manifestations of the disease.

1.2 People whose treatment with asfotase alfa was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop. If applicable, this decision should be made jointly by the clinician and the child or young person, and their parents or carers.

2 The condition

2.1 Hypophosphatasia is a genetic disorder caused by mutations in the tissue non-specific alkaline phosphatase (TNSALP) gene, which reduce its activity. This causes disruption of mineralisation, a process in which calcium and phosphorous are deposited in developing bones and teeth. Several clinical forms of hypophosphatasia are currently recognised:

- perinatal-onset (onset before or at birth)
- infantile-onset (onset at 0–6 months)
- juvenile-onset (also referred to as childhood-onset; onset between 6 months and 18 years)
- adult-onset (onset at 18 years or older) and
- odonto-hypophosphatasia (only dental symptoms).

Paediatric-onset hypophosphatasia includes everyone with hypophosphatasia of perinatal-, infantile-, or juvenile-onset.
2.2 The signs and symptoms of hypophosphatasia vary widely and can appear anytime from before birth to adulthood. These include rickets, softening and weakening of the bones (osteomalacia), bone deformity and a greater incidence of fractures. Hypophosphatasia can also lead to chronic debilitating pain, muscle weakness, generalised seizures because of vitamin B6 deficiency, and renal and respiratory complications. The most severe forms of the condition tend to occur before birth and in early infancy. Infants who present with hypophosphatasia in the first 6 months of life have a high mortality rate. Approximately 50–100% of infants die within the first year of life, primarily because of respiratory failure. The forms of hypophosphatasia that appear later in childhood or in adults are associated with substantially lower mortality rates than those that appear in infancy, but are often debilitating and lead to bone deformities that may result in delayed walking, limb weaknesses, skeletal pain and non-traumatic fractures.

2.3 The prevalence of severe forms of hypophosphatasia is unknown in England. However, in Europe, the rate is estimated as 1 per 300,000 live births. Milder forms, in which signs and symptoms have a later onset, are more common and are estimated to be present in 1 per 6370 of the population. A clinical expert approximated that 7 people are diagnosed with perinatal- and infantile-onset hypophosphatasia each year in England. In 2011, there were 187 hospital admissions for hypophosphatasia in England.

3 The technology

3.1 Asfotase alfa (Strensiq, Alexion Pharma UK) is a targeted enzyme replacement therapy designed to restore the regulation of metabolic processes in the bones and teeth, and to reduce complications of dysregulated bone mineral metabolism. Asfotase alfa is administered by subcutaneous injection.
3.2 Asfotase alfa has a marketing authorisation in the UK ‘for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease’. Treatment should be started by a physician experienced in the management of metabolic or bone disorders. The recommended dosage of asfotase alfa is 2 mg/kg 3 times per week, or 1 mg/kg 6 times per week. For full details of the recommended dosage regimens of asfotase alfa, see the summary of product characteristics.

3.3 The summary of product characteristics lists the following very common adverse reactions for asfotase alfa: contusion, erythema, headache, injection site reactions, irritability, pain in extremity and pyrexia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.4 Asfotase alfa is available in vials of 40 mg/ml and 100 mg/ml. The cost of asfotase alfa is £58.80 per mg (excluding VAT; company’s evidence submission). The cost of a 52-week course of treatment assuming an average weight of 19.3 kg is £366,912 per patient (excluding VAT).

4 Evidence submissions

The Evaluation Committee (section 9) considered evidence submitted by the company of asfotase alfa, a review of this submission by the Evidence Review Group (ERG; section 10) and evidence submitted by clinical experts, patient experts and NHS England.

Nature of the condition

4.1 Patient experts and patient groups described how hypophosphatasia can have a profound impact on health-related quality of life.

- For people with perinatal- and infantile-onset hypophosphatasia, respiratory compromise and seizures have the greatest impact on health-related quality of life. Infants who survive have significant
ongoing morbidity and may still need invasive ventilation, further impairing health-related quality of life.

- Functional disability and pain were identified as the most burdensome aspects of juvenile-onset hypophosphatasia that affect health-related quality of life. They highlighted that many children with hypophosphatasia have difficulties with pain and mobility, and are therefore unable to participate in activities such as playing with friends or attending school. The emotional wellbeing of young people with hypophosphatasia may also be affected as they become more conscious of their condition (for example, experts noted that they may have anxiety or depression).

- Adults with paediatric-onset hypophosphatasia are often unable to work because of mobility problems and the need to have numerous surgical procedures during their lives.

- There is also a large burden on carers of people affected by hypophosphatasia, particularly carers of infants. There is a significant emotional impact on families because of the high risk of death associated with infantile-onset hypophosphatasia and the difficulty in parents accepting their child’s condition. Carers are likely to spend many days in hospital with their children, which reduces time with other family members and results in time away from work (or stopping work entirely). The daily lives of carers are affected because of seizures and the need to regularly monitor oxygen levels.

- Patient experts highlighted that because of the limited numbers of centres treating hypophosphatasia in England, long journeys for appointments or inpatient stays may be needed regularly, and in some circumstances may lead to families relocating.

4.2 For people with perinatal- and infantile-onset hypophosphatasia, treatments that can help prolong survival are of considerable importance; improving health-related quality of life is viewed as a secondary consideration by parents and healthcare professionals. A patient group
highlighted that the parents of 1 infant understood that, without asfotase alfa, their child was unlikely to survive to 9 months.

**Clinical evidence**

4.3 The company did a systematic literature review to identify studies evaluating the clinical effectiveness of asfotase alfa for treating paediatric-onset hypophosphatasia. It found 4 open-label phase II studies of asfotase alfa (2 of which had associated extension studies):

- ENB-002-08, a non-randomised 24-week single-arm study in 11 people of 36 months or younger with infantile-onset hypophosphatasia
- ENB-003-08, an extension study of ENB-002-08 that is evaluating 10 people for up to 5 years
- ENB-010-10, a non-randomised, dose-comparison study of asfotase alfa treatment for up to 48 months in 59 people of 5 years or younger with infantile-onset hypophosphatasia
- ENB-006-09, a randomised 24-week dose-comparison study in 13 people of 5–12 years with infantile- or juvenile-onset hypophosphatasia
- ENB-008-10, an extension study of ENB-006-09 that is evaluating 12 people for up to 5 years
- ENB-009-10, a randomised, 24-week concurrent control study in 19 people of 13–66 years with paediatric-onset hypophosphatasia.

Only ENB-002-08 and ENB-006-09 have finished. The company stated that patients included in the studies of asfotase alfa presented with clinical symptoms that were characteristic of their age at onset of hypophosphatasia and enrolment, and that a broad range of outcomes measures were collected across studies to reflect the symptoms of the disease in each age group.

4.4 The company also identified 3 retrospective non-interventional studies:
• ENB-011-10, a retrospective natural history study of infants with severe perinatal- and infantile-onset hypophosphatasia. Data on survival and the need for invasive ventilation were taken from medical records of children up to 5 years.

• ALX-HPP-502, a retrospective natural history study of children with juvenile-onset hypophosphatasia (5–15 years). The study focused on functional assessments of physical abilities, changes in growth (height and weight) and skeletal improvement (severity of rickets).

• ALX-HPP-502s, a single-centre substudy of ALX-HPP-502. Data for additional functional measures were taken from medical records and videos were obtained from a longitudinal natural history database to characterise gait.

4.5 The primary outcome of ENB-002-08 and ENB-010-10 was change in severity of rickets on skeletal radiographs from baseline to week 24, measured by the Radiographic Global Impression of Change (RGI-C) scale. The RGI-C is a 7-point rating scale that ranges from −3 (indicates severe worsening of hypophosphatasia-associated rickets) to +3 (indicates complete or near complete healing of hypophosphatasia-associated rickets). An RGI-C score of +2 or more is considered to be a response to treatment in people with hypophosphatasia. Secondary outcomes included height and weight Z-scores and the number of people needing respiratory support. The Z-score indicates how many standard deviations an infant’s height or weight is from the mean of the general population.

4.6 In ENB-002-08, treatment with asfotase alfa resulted in a mean and median change in RGI-C scores from baseline to week 24 of 1.67 and 2 respectively (p=0.0039). Most people had RGI-C score between 2 and 3 (7 out of 11; 63.6%). No patients had a RGI-C score of 3 by week 24 (‘complete or near complete healing’). However, by week 240 of ENB-003-08, 9 out of 9 people followed-up had a RGI-C score of 2 or more.
4.7 The company provided the results of an interim analysis of 28 people included in ENB-010-10. The company’s interim analysis suggested treatment with asfotase alfa resulted in a mean change in RGI-C score from baseline to week 24 of +1.7 (p<0.0001). The company stated that the results of the primary outcome for all of the 59 patients included in ENB-010-10, as presented in its evidence submission, were deemed academic in confidence and cannot be reported here. The results of the secondary outcomes in ENB-010-10 were deemed academic in confidence by the company and cannot be reported here.

4.8 The company submitted a pre-specified analysis of overall survival for asfotase alfa from people in ENB-002-08, ENB-003-08 and ENB-010-10 compared with an untreated historical control group (ENB-011-10). In this analysis, 4 out of 37 people (10.8%) in the asfotase alfa group had died, compared with 35 out of 48 people (72.9%) in the untreated group during the time period evaluated (p<0.0001). The company presented median survival by diagnosis date. The median number of days till death from birth in historical control by year of diagnosis increased over time. The values were deemed academic in confidence by the company and cannot be reported here.

4.9 In response to clarification, the company provided survival analyses adjusted for the following potential biases:

- differences in the year of diagnosis of the historical control population (see section 4.8)
- survival estimated from birth in historical control groups compared with from the start of treatment in people receiving asfotase alfa.

The company estimated an adjusted hazard ratio by excluding those diagnosed before 2000 and those who died before 38 weeks from the historical control group. The company stated that the adjusted hazard ratio was lower than the estimate for the unadjusted hazard ratio. The adjusted and unadjusted hazard ratios were deemed academic in
confidential by the company and cannot be reported here. The company presented the results of a further analysis that was requested by the Committee for Medicinal Products for Human Use. This additional analysis retrospectively matched infants from its historical control data with infants treated with asfotase alfa from its clinical studies (n=37; 29 were considered exact matches). The results of the company’s matched analysis were deemed academic in confidence by the company and cannot be reported here.

4.10 ENB-006-09 included 13 people randomised to asfotase alfa 2 mg/kg or 3 mg/kg 3 times a week for 24 weeks, and was the only study to include non-concurrent historical control patients selected from a natural history database (n=16). The primary outcome was change in the severity of rickets on skeletal radiographs from baseline to week 24, measured by RGI-C for asfotase alfa compared with the historical control. Treatment with asfotase alfa resulted in a median improvement compared with the historical control (p=0.0007). Median RGI-C scores for asfotase alfa and the historical control were 2.0 and 0.0 respectively. Nine out of 13 people receiving asfotase alfa had an RGI-C score of 2 or more (69%) compared with 1 out of 16 people in the historical control group (6.3%; p=0.0010). Improvements in the severity of rickets for asfotase alfa compared with the historical control were maintained until the data cut-off at week 96 of the extension study (ENB-008-10). The company also presented results by age of hypophosphatasia onset but these were deemed academic in confidence by the company and cannot be reported here.

4.11 The height, weight and body mass index Z-scores and 6 minute walk test (6MWT) distance results from ENB-006-09 and ENB-008-10 were deemed academic in confidence by the company and cannot be reported here.

4.12 The company submitted a comparative analysis of people receiving asfotase alfa from ENB-006-09 and ENB-009-10 with historical control patients from 3 sources (ALX-HPP-502, ALX-HPP-502s and
ENB-006-009/ENB-008-10) for rickets severity, growth and gait outcomes. The results of this comparative analysis were deemed academic in confidence by the company and cannot be reported here.

4.13 The results of a 6MWT at baseline and at 24 weeks were available for 13 people in the asfotase alfa group and 4 people in the historical control group of ENB-009-10. The 6MWT results from ENB-009-10 were deemed academic in confidence by the company and cannot be reported here.

4.14 The company noted that asfotase alfa is a lifetime therapy and stated that there is no evidence to guide the development of treatment continuation rules. A clinical expert suggested that, once a person’s bone health is improved, an individual treatment regimen for maintaining bone health could be investigated (for example, less frequent injections or lower doses).

4.15 Health-related quality of life data was measured at baseline and several time points using the Childhood Health Assessment Questionnaire (CHAQ; ENB-006-09 and ENB-008-10), Paediatric Outcome Data Collection Instrument (PODCI; ENB-006-09 and ENB-008-10) and the Lower Extremity Functional Scale (LEFS; ENB009-10). The health-related quality of life data were deemed academic in confidence by the company and cannot be reported here.

4.16 The company presented EuroQol-5 dimensions survey (EQ-5D) results from its European Patient Survey. The EQ-5D instrument was completed by 10 parents on behalf of their child, and by 25 adults with hypophosphatasia. The mean EQ-5D score for children receiving asfotase alfa was 0.76 (n=2) and 0.43 in children who did not receive asfotase alfa (n=8). The company highlighted that the EQ-5D scores were higher for children with normal walking ability (0.73, n=1) than for children with impaired walking ability (0.56, n=8) or who were dependent on walking aids (−0.24, n=1). All adults were untreated and had a mean EQ-5D score of 0.39. The company noted that the EQ-5D scores were only slightly
higher for adults with normal walking ability (0.51, n=6) than adults with impaired walking ability (0.48, n=14). The mean EQ-5D score for adults dependent on walking aids was −0.01 (n=5).

4.17 The company presented adverse event data for people receiving asfotase alfa (no data were presented for people who did not have treatment or historical controls). Median exposure to treatment with asfotase alfa was 1.90 patient years. In a pooled analysis of the interventional studies (excluding ENB 001 08), all people (n=102) had at least 1 adverse event. Most adverse events were considered unrelated to asfotase alfa treatment (2542 out of 3676) and of mild intensity (2758 out of 3676). Over 25% of the adverse events were classified as injection-site reactions or injection-associated reactions. Treatment was stopped by 4 people, who withdrew from the studies. A total of 274 non-fatal serious adverse events were reported by 48 people (47.1%). Most of these events were in people with infantile-onset hypophosphatasia (262 out of 274 events). Overall, 8 deaths were reported (1 of which was before treatment started).

**Value for money**

4.18 The company submitted a Markov state transition model that compared asfotase alfa with best supportive care. The company’s economic model had 6 states: 4 according to the level of severity defined by 6MWT distance, a state for people who needed invasive ventilation and death (including hypophosphatasia-related and age-related death). People who needed invasive ventilation moved to severity IV (that is, the most severe state). The company acknowledged that the 6MWT does not capture all the symptoms of hypophosphatasia (for example, craniosynostosis, severe pain, renal complications). However, the company stated that 6MWT distance was identified by its UK clinical experts as the outcome measure from its trials that most closely reflected the latent severity of disease. The company base-case analysis used a threshold of 17.8% to define a minimal clinically important difference between each severity level (that is, twice the minimal clinically important difference for the
6MWT distance in people with Duchenne muscular dystrophy, which the company stated provided the closest proxy available for people with paediatric-onset hypophosphatasia). The company used a 12-week cycle length, and half-cycle correction was applied to the first and last cycles. The company did the economic analysis from an NHS perspective and chose a lifetime time horizon. Costs and health effects were discounted at an annual rate of 1.5%.

4.19 Observations of the 6MWT were available from the trials for 28 people with either infantile- or juvenile-onset hypophosphatasia who received asfotase alfa and best supportive care (ENB-006-09, ENB-008-10 and ENB-009-10). The 28 people had at least 2 assessments of 6MWT distance, and their baseline age of hypophosphatasia onset ranged from 0 to 4.0 years (mean 1.3 years). For these 28 people, there were 250 observed transitions for people receiving asfotase alfa and 34 observed transitions for people receiving best supportive care. The company stated that between each 12-week visit, the average distance walked:

- improved by 11.6 m and 1.35 percentage points in per cent predicted in people receiving asfotase alfa and
- decreased by 13.6 m and 3.91 percentage points in per cent predicted in people receiving best supportive care.

Their baseline age at the first trial visit ranged from 5.9 years to 59.3 years (mean 26 years). To estimate the transition probabilities between each of the 6MWT severity levels in the economic model, the company used an ordered probit regression model that controlled for age and the days elapsed between healthcare visits. The distributions for the baseline level of severity were based on clinical trial data.

4.20 Hypophosphatasia-related deaths and invasive ventilation occurred in the company’s model at the same time at which they were seen in the trials (ENB-002-08, ENB-003-08, ENB-010-10 and ENB-011-10).
company’s base-case analysis used a mean starting age of 5.8 years (average age across the trials). Therefore, in the company’s base case, there was no risk of hypophosphatasia-related deaths or invasive ventilation because none of these events were seen in the trials in people 5 years and older. The company explored different starting ages and levels of severity in scenario analyses.

4.21 Drug costs for asfotase alfa were based on its list price and the recommended dosage in its summary of product characteristics. The company assumed that the list price for asfotase alfa reduced by 30% after 10 years because of a loss of data exclusivity. The company took unit cost data for monitoring and managing hypophosphatasia from NHS reference costs 2013–14, the Personal Social Services Research Unit and the Royal Manchester Children’s Hospital. Healthcare resource use estimates for managing each severity level were based on clinical expert opinion. Mean utility values included in the company’s economic model were approximated by 9 clinical experts who completed the EQ-5D-5L for vignettes for each severity level state. Annual costs and utility values for each 6MWT state are presented in table 1. The company excluded costs and disutility values associated with adverse reactions because it considered that asfotase alfa was well tolerated and most adverse reactions were mild to moderate in severity.

<table>
<thead>
<tr>
<th>Health state</th>
<th>Annual cost</th>
<th>Utility value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base case</strong></td>
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</tr>
<tr>
<td>Severity level I</td>
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<tr>
<td>Severity level II</td>
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</tr>
<tr>
<td>**Scenario analysis (when starting age is below 5.0 years)**¹</td>
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<td></td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>£267,824</td>
<td>−0.33</td>
</tr>
</tbody>
</table>

¹ No patients aged 5 years and older needed invasive ventilation in the asfotase alfa studies.
4.22 The company presented the results of its cost–consequence analysis for asfotase alfa compared with best supportive care. Total costs and incremental costs for asfotase alfa compared with best supportive care for all analyses were considered commercial in confidence by the company and therefore cannot be reported here. At a discount rate of 1.5%, asfotase alfa was estimated to produce an additional 25.04 quality-adjusted life years (QALYs) compared with best supportive care (37.53 total QALYs with asfotase alfa, 12.48 total QALYs with best supportive care).

4.23 The company explored parameter and structural uncertainty in its economic model in 1-way sensitivity analyses and scenario analyses. The 1-way sensitivity analysis suggested that the results were most sensitive to the discount rate used for costs and health effects, and changes to the utility values. The company presented a scenario analysis that varied the threshold defining the difference in 6MWT distance between each severity level state from 8.9% to 26.7% from a base case value of 17.8% (twice the minimal clinically important difference in Duchenne muscular dystrophy). This reduced the incremental QALYs in both scenarios from 25.0 in the base case to 17.9 and 19.6 respectively, but had little impact on the incremental cost.

4.24 The company presented the results of its probabilistic sensitivity analysis of asfotase alfa compared with best supportive care based on 500 simulations. Incremental costs were considered commercial in confidence by the company and cannot be presented here. Asfotase alfa treatment produced an additional 18.4 QALYs compared with best supportive care (34.2 total QALYs and 15.8 total QALYs respectively).

**Cost to the NHS and Personal Social Services**

4.25 The company explained that limited information was available for estimating the prevalence and incidence of hypophosphatasia in England. With no national statistics available, the company used the incidence
rates for paediatric-onset hypophosphatasia from the German Beck et al. (2003) study and applied it to the population in England in its base-case budget impact model. Beck et al. estimated that the incidence of hypophosphatasia was 0.8 per 1,000,000 in children younger than 1 year and 2.8 per 1,000,000 in children younger than 18 years. To estimate the prevalent population in England in people of 18 years or older, the company assumed a life expectancy of 81 years and applied the incidence for children younger than 18 years from Beck et al. Therefore, the company estimated that the number of people with paediatric-onset hypophosphatasia in England was 1.9, 149.4 and 553.5 in people younger than 1 year, between 1 year and 17 years, and 18 years or older respectively.

The company presented the results of a budget impact analysis over 5 years (see table 2). The company calculated the drug costs for asfotase alfa based on the average weight of people in these age groups included in the trials (5.4 kg, 19.3 kg and 76.5 kg respectively), and also assumed an 80% rate of adherence. The company considered that the rates of diagnosis of paediatric-onset hypophosphatasia would increase if asfotase alfa was used in the NHS, and that uptake of treatment would be higher in younger populations. The company’s estimates for the total number of patients treated with asfotase alfa was deemed commercial in confidence by the company and cannot be reported here. The number of deaths avoided over 5 years with asfotase alfa treatment was 38.5.

### Table 2 Results of the company’s budget impact analysis

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budget impact (including non-drug costs)</td>
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</tr>
</tbody>
</table>

**Abbreviations:** AA, asfotase alfa; BSC, best supportive care.

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**Evidence Review Group review**
Clinical evidence

4.27 The ERG did not believe any relevant studies were missed by the company’s searches.

4.28 The ERG stated that conclusions about the treatment effect may be confounded because some of the studies did not include a control group (limiting the robustness of the efficacy data). For the asfotase alfa studies without a control group, the ERG considered it reasonable to compare asfotase alfa with natural history data. However, the ERG considered that each of the comparative analyses was at high risk of bias in favour of asfotase alfa.

4.29 For the company’s comparative analysis of overall survival in people with infantile-onset hypophosphatasia, the ERG noted that the results were biased in favour of asfotase alfa for 2 reasons:

- **Year of diagnosis:** Despite no disease-modifying treatment, the company showed that the probability of survival for people with infantile-onset hypophosphatasia had improved over the years. Of the historical control group, 13 people were diagnosed before 1990, 14 between 1990 and 1999, and 21 after 2000, compared with all 11 people receiving asfotase alfa diagnosed after 2005.
- **Age at enrolment:** The historical control group probably included more people younger than 1 month and younger than 1 week (people with hypophosphatasia younger than 1 month are at higher risk of death than older people).

4.30 The ERG considered that the lower mean age and lower age at onset in the historical control group may bias the results of ENB-006-09 in favour of asfotase alfa. However, it considered that the patient populations were more comparable in this analysis than the populations included in the other 2 comparative analyses provided by the company.

4.31 The ERG agreed that people receiving asfotase alfa in the company’s comparative analysis of people with juvenile-onset hypophosphatasia
showed clear improvements in skeletal structure, growth and gait compared with the historical control and the pre-treatment group. The ERG commented that, without data on baseline characteristics, it was unclear whether the groups were comparable. Therefore, the precise benefit of asfotase alfa treatment was not clear.

4.32 The ERG stated that, although there is considerable follow-up in some of the asfotase alfa studies, it was only a fraction of the expected lifetime treatment as proposed by the company. The ERG explained that it cannot be assumed that treatment works equally well or even at all in everyone, and that the effectiveness of treatment may diminish over time. The ERG concluded that the long-term efficacy and safety of asfotase alfa was uncertain, and that stopping rules for asfotase alfa should be considered given the many differences between people with paediatric-onset hypophosphatasia.

Value for money

4.33 The ERG emphasised that the 6MWT does not capture all of the symptoms of hypophosphatasia, nor does it capture all of the important domains of health-related quality of life as measured by the EQ-5D, such as mental health and pain. The ERG considered that the company should have submitted separate models for people younger than 5 years, and for people 5 years or older because the symptoms of hypophosphatasia and the effect of asfotase alfa are different in these populations.

4.34 The ERG preferred that the costs and health effects were discounted at an annual rate of 3.5% rather than the 1.5% in the company’s base case. It explained that the evidence was not sufficiently clear around whether asfotase alfa restored people who would have died or who would have had a very severely impaired life to full or near full health, and that the long-term effects of treatment were uncertain. The ERG acknowledged that the company’s economic model indicated that more people would be in the least severe health states. However, the ERG was uncertain as to what extent this could be considered as ‘full health’ and whether the
treatment effect would be maintained for their lifetime. Therefore, the ERG concluded that a discount rate of 1.5% was not appropriate.

4.35 The ERG stated that the transition probabilities estimated by the company’s probit model for best supportive care were associated with considerable uncertainty because of the very limited number of 6MWT observations for people receiving best supportive care. It noted that the company’s chosen covariates in the probit model (age, time since previous visit) may not fully reflect the disease severity progression. Therefore, the ERG considered it would have been more appropriate for the company to estimate the transition probabilities with a single probit model controlled for treatment effect rather than with separate probit models for the asfotase alfa and best supportive care groups. The ERG was further concerned that the company’s chosen transition probabilities were from a population of people older than 5 years, and that the transition probabilities for younger patients relied on backwards extrapolation, which was not validated (particularly because credible reference 6MWT distances are not available for people younger than 3 years).

4.36 The ERG noted that it was not clear how the baseline age and severity levels were derived or whether they reflected a UK paediatric-onset hypophosphatasia population.

4.37 The ERG noted that the company’s unadjusted approach for estimating survival and need for invasive ventilation in the economic model may have been biased:

- The historical controls included people from the time of diagnosis, whereas clinical studies can only include people who survive to study enrolment.
- There were differences in the year of diagnosis.
- The survival curves were estimated from birth rather than from the start of treatment.
The ERG highlighted that the survival analyses provided by the company in response to a request for clarification showed that the company’s method of estimating survival in the economic model was potentially biased. The ERG concluded that the company should have attempted to match the populations between asfotase alfa and best supportive care and taken into account the age at enrolment and year of disease when estimating survival in its economic model.

4.38 The ERG considered that reducing the price for asfotase alfa after 10 years because of a loss of data exclusivity was not appropriate. The ERG also noted that the size of the discount was not reasonably justified by the company. The ERG noted that the company did not include costs associated with personal social services.

4.39 The ERG felt that it was a limitation that utility values were from clinical experts rather than from the clinical studies. It noted that the face validity of the utility values obtained by the experts for each of the health states seemed quite reasonable. However, the company’s vignettes assumed strong correlation among all dimensions of health, which may lead to underestimation of the true variation in health-related quality of life within each health state.

4.40 The ERG presented the results of an exploratory analysis that:

- estimated the transition probabilities using a single probit model for both asfotase alfa and best supportive care, and controlled for treatment effect (see section 4.35)
- approximated the survival and need for invasive ventilation in a matched population using a parametric model (the ERG explored 6 distributions and selected the Gompertz distribution as the best fit based on tests of internal and external validity)
- only used survival data from historical controls who were diagnosed after 2000
- excluded the price reduction for asfotase alfa after 10 years
• discounted the costs and health effects at an annual rate of 3.5%.

Total costs and incremental costs for asfotase alfa compared with best supportive care for all analyses were considered commercial in confidence by the company and therefore cannot be reported here. At a discount rate of 3.5%, the ERG estimated that asfotase alfa was expected to produce an additional 14.13 QALYs compared with best supportive care (21.59 total QALYs with asfotase alfa, 7.46 total QALYs with best supportive care).

4.41 The ERG did an additional exploratory analysis for younger people with paediatric-onset hypophosphatasia (starting age of 0). For this analysis, the ERG developed a new model structure with 2 health states: alive and dead. Patients who were alive could also have invasive ventilation. The ERG considered that an alternative model structure was appropriate given the differences in the symptoms of hypophosphatasia and the effect of asfotase alfa for this population compared with the company’s base-case population (mean age of 5.8 years). The ERG stated this was supported by the differences between rates for mortality and the need for invasive ventilation. This ERG exploratory model included people from birth and used a time horizon of approximately 5 years. Total costs and incremental costs for asfotase alfa compared with best supportive care for all analyses were considered commercial in confidence by the company and therefore cannot be reported here. At a discount rate of 3.5%, the ERG estimated that asfotase alfa was estimated to produce an additional 0.91 QALYs compared with best supportive care for younger people over the 5-year time horizon (2.46 total QALYs with asfotase alfa, 1.55 total QALYs with best supportive care). When combining this with the ERG’s estimate of cost and consequences beyond 5 years (obtained by applying the ERG’s preferred model assumptions to the company model), the ERG estimated a lifetime QALY gain of 13.92 when treating patients from birth. The ERG emphasised that its exploratory model for younger people was simple and based on the little evidence available. Therefore, the ERG stated that the results should be interpreted with caution.
Cost to NHS and personal social services

4.42 The ERG noted that several of the parameters used in the company’s budget impact model were the same as those in the cost–consequence model, and that the same limitations would apply to both models. It explored a scenario that estimated the budget impact using hypophosphatasia-related mortality data based on the ERG’s parametric survival analyses. The ERG’s estimates for the net budget impact over 5 years were deemed commercial in confidence by the company and cannot be reported here. The ERG estimated the number of deaths avoided over 5 years with asfotase alfa treatment was 21.4. The ERG included a scenario in which 100% adherence was considered.

4.43 Full details of all the evidence are in the submissions received for this evaluation, and in the ERG report, which are all available in the Committee papers.

5 Consideration of the evidence

The Evaluation Committee reviewed the data available on the benefits and costs of asfotase alfa, having considered evidence on the nature of paediatric-onset hypophosphatasia and the value placed on the benefits of asfotase alfa by people with the condition, those who represent them, and clinical experts. It also took into account the value for money that asfotase alfa represents and the effective use of resources for specialised commissioning.

Nature of the condition

5.1 The Committee discussed the nature of paediatric-onset hypophosphatasia. It understood that hypophosphatasia was a serious and heterogeneous, genetic condition associated with considerable morbidity that severely affects the quality of life of people with the condition, and their families. The Committee heard from the clinical experts that the signs and symptoms of paediatric-onset hypophosphatasia vary widely and can appear anytime from birth until
adulthood. The clinical experts considered that perinatal- and infantile-onset were more severe forms of paediatric-onset hypophosphatasia than juvenile-onset hypophosphatasia. They explained that perinatal- and infantile-onset hypophosphatasia are associated with significant mortality (up to 100%). They also explained that the severity of juvenile-onset hypophosphatasia was more variable in clinical practice because some people were asymptomatic and had normal functioning, but others had significant problems with pain, growth, mobility, bone strength and activities of daily living. The Committee heard from the patient experts that, for infants, treatment with asfotase alfa could enable them to have a good quality of life, go on to attend school and make friends, but without it they would not survive. A patient expert highlighted that their 12-year old child, who was diagnosed at 2 years, had pain and needed several medicines every day before getting out of bed. The patient expert emphasised that, on some days, their child feels so low that they do not want to get out of bed. Therefore, the condition has had a substantial impact on the family's emotional wellbeing as well as their child's. The Committee understood from the patient expert that, if treatment with asfotase alfa could make juvenile-onset hypophosphatasia more manageable and reduce the need for hospital admissions (for example, for fractures), it would provide benefits to people with the condition and their families. The Committee concluded that paediatric-onset hypophosphatasia is a serious, life-threatening and debilitating condition.

5.2 The Committee discussed the natural history of paediatric-onset hypophosphatasia. The Committee appreciated that the rate of mortality was extremely high in perinatal- and infantile-onset hypophosphatasia. The Committee agreed that natural history of perinatal- and infantile-onset hypophosphatasia over the first 2 years of life was well understood, and that real world experiences had highlighted the urgent need for an effective treatment option for these infants so that they survive into childhood. The Committee went on to consider the natural history of juvenile-onset hypophosphatasia. It heard from the clinical experts that
the natural history of juvenile-onset hypophosphatasia was less well understood, and that many patients had been lost to follow-up after 1 or 2 visits because of a lack of effective treatment. It further heard from the clinical experts that symptoms were highly variable among people with juvenile-onset hypophosphatasia, and could even vary significantly within the same patient over time. The Committee understood from the clinical experts that fractures and skeletal problems are common in later life but their occurrence and frequency were of a fluctuating nature. The Committee concluded that the natural history of paediatric-onset hypophosphatasia was well-defined for perinatal- or infantile-onset disease, but not entirely clear in juvenile-onset disease (and is particularly variable in people whose condition is not diagnosed until they are adults).

5.3 The Committee discussed the current treatment options and management of paediatric-onset hypophosphatasia. It was aware that there was no NICE, NHS England or national guidance for managing paediatric-onset hypophosphatasia. The Committee also understood from the patient expert statements that, as a result, the time taken to diagnose the condition can vary significantly. The Committee heard from the clinical experts that supportive care, which aims to monitor and alleviate symptoms to decrease morbidity, is the current mainstay of treatment. They explained that the goals of treatment for infants with perinatal- and infantile-onset hypophosphatasia were to manage craniosynostosis and prevent seizures, reduce the need for respiratory support (up to 90% of untreated infants need invasive ventilation) and prevent mortality. For people with juvenile-onset hypophosphatasia, the goals of treatment were to reduce and prevent pain, improve mobility and improve their ability to take part in activities of daily living. The Committee concluded that a treatment such as asfotase alfa, which addresses the cause of the condition, would be a valuable treatment option because there are currently no treatments available that specifically prevent or delay the progression of hypophosphatasia.
Impact of the new technology

5.4 The Committee acknowledged the patient experts’ view that asfotase alfa offered a lifeline for infants with paediatric-onset hypophosphatasia. The Committee heard from the clinical experts that, because asfotase alfa was the first therapy that specifically targets the underlying cause of hypophosphatasia, they considered it to be a step change in the management of paediatric-onset hypophosphatasia.

5.5 The Committee considered the robustness of the results from the company’s trials for asfotase alfa, noting that most of the company’s clinical trial evidence did not include a control group. The Committee understood from the Evidence Review Group (ERG) that, because some of the studies did not include a control group, the treatment effect may be confounded. It agreed that, in absence of a control group, it was reasonable in the circumstances for the company to compare with natural history data (that is, a historical control group). The Committee was aware that data on baseline characteristics were not available for some of the natural history data. It stated that evaluating single group studies and each of the comparative analyses available risked bias and was subject to considerable uncertainty. Therefore, the Committee considered that, given the heterogeneous nature of the condition and the trial designs used, the available clinical evidence did not provide either a robust estimate of the size of the benefit or a strong indication of the likely variation in the treatment effect.

5.6 The Committee discussed the results for overall survival in perinatal- and infantile-onset hypophosphatasia. The Committee noted that the ERG considered the company’s original unadjusted analysis of overall survival to be potentially biased in favour of asfotase alfa compared with the natural history data because of differences in the year of diagnosis and age at enrolment between the groups. The Committee was aware that the company had provided an analysis of overall survival that adjusted for these potential biases, which had reduced the size of the treatment
benefit. In contrast, a clinical expert highlighted to the Committee that the analyses of overall survival may also be biased in favour of the natural history group because 7 of the 12 sites in ENB-011-10 were in North America. The clinical expert explained that historically the influences of reimbursement in North America may have produced greater use of invasive ventilation in infants than was typical in England. However, the Committee was also told that more recently the use of invasive ventilation for infants has become more widespread in the UK. Therefore, the Committee agreed that it was more appropriate to use more recent data for the natural history group of infants (that is, those diagnosed in 2000 or after) and ensure baseline characteristics that influence prognosis are similar in the 2 groups (for example, age) when comparing overall survival data for asfotase alfa with best supportive care. The Committee acknowledged that, despite the potential issues with the natural history data, the estimated survival was still likely to be higher for asfotase alfa compared with the natural history data. The Committee concluded that asfotase alfa improved the probability of survival in perinatal- and infantile-onset hypophosphatasia compared with best supportive care.

5.7 The Committee discussed the other results of the asfotase alfa clinical trials for paediatric-onset hypophosphatasia. It commented that the trials of perinatal- and infantile-onset hypophosphatasia generally showed improvements with asfotase alfa treatment across several important outcomes such as the need for respiratory support, severity of rickets and growth. It also noted that improvements were generally seen with asfotase alfa in the company’s trials of juvenile-onset hypophosphatasia across several important outcomes such as growth, mobility and pain. The Committee concluded that, although there was considerable uncertainty around robustness and the precise size of the treatment benefit, the results of the trials generally suggested that asfotase alfa was associated with clinically meaningful improvements across a range of outcomes when compared with baseline.
5.8 The Committee discussed how asfotase alfa would potentially be used in infants with perinatal- and infantile-onset hypophosphatasia, including treatment continuation rules. It was aware that the company had proposed lifelong treatment for all patients (irrespective of age at diagnosis or clinical symptoms). The Committee heard from the clinical experts that, in principle, the decision to treat with asfotase alfa could be based on clinical judgement and dependent on the phenotype (that is, the overall clinical picture). However, the clinical experts agreed that, if available, they would give asfotase alfa to all infants with perinatal- and infantile-onset hypophosphatasia straight away. The clinical experts stated that they would only consider a dose reduction, or stopping treatment, once the child came off invasive ventilation and their condition had stabilised (generally supported by improved bone health because of better mineralisation). The Committee concluded that, on the basis of current evidence, it was not possible to define a treatment continuation rule for asfotase alfa in children with perinatal- and infantile-onset hypophosphatasia.

5.9 The Committee discussed how asfotase alfa would potentially be used in children and adults with juvenile-onset hypophosphatasia, including possible treatment continuation rules. The Committee was aware that juvenile-onset hypophosphatasia had a variable overall clinical picture and that some children had normal functioning. It heard from the clinical experts that the decision to start or continue treatment in children or adults could be based on the impact of the condition on their health-related quality of life (such as severity of pain, level of mobility and risk of fracture) and activities of daily living (such as going to school, playing with friends). Some clinicians would not treat all children and adults without significant morbidity. The clinical experts stated that, if the condition did not respond after 1 year of treatment (for example, no reduction in pain, or improvements in mobility and health-related quality of life), they would consider stopping asfotase alfa in clinical practice. The Committee heard from the patient experts that parents or carers of children with
hypophosphatasia would trust the judgement of the treating clinician on whether asfotase alfa could be reduced or stopped. A patient expert emphasised that this was only if their child had a good quality of life and was regularly tested. The Committee acknowledged from the clinical experts that some children and adults’ hypophosphatasia may need higher doses of asfotase alfa to achieve response, and that the trials were relatively short in duration so registries would be needed to monitor and subsequently guide decisions around whether the dosage could be reduced. The Committee accepted that, because it had not been formally studied, there was little information around the efficacy of giving a lower dosage of asfotase alfa in those people whose condition had a sustained response. The Committee concluded that the treatment need for children and adults with juvenile-onset hypophosphatasia varied and that criteria for starting and stopping treatment with asfotase alfa were not clearly defined.

**Cost to the NHS and personal social services**

5.10 The Committee discussed the results of the company’s budget impact model. It was aware that several of the parameters were the same as those in the company’s cost–consequence model, and therefore the same limitations applied (see ‘Value for money’ section). It noted that, at list price, the total cost per person per year of treatment with asfotase alfa is £366,912 (assuming an average weight of 19.3 kg and 100% adherence). However, the Committee highlighted that the dosage of asfotase alfa was based on a person’s weight. Therefore the treatment costs were significantly higher for young people and adults with paediatric-onset hypophosphatasia than for infants and children.

5.11 The Committee considered the assumptions in the company’s budget impact analysis. The Committee acknowledged that the company had assumed the rate of diagnosis of paediatric-onset hypophosphatasia would increase following the availability of asfotase alfa. This was supported by the clinical experts, who stated that clinical behaviour may
change with the availability of an active treatment. The Committee was aware that paediatric-onset hypophosphatasia may be diagnosed retrospectively in clinical practice. It understood from the clinical experts that it was therefore difficult to estimate the number of people with juvenile-onset hypophosphatasia in England, and consequently how many would be eligible for asfotase alfa treatment. Taking these factors into account, the Committee considered that the number of people identified in clinical practice with paediatric-onset hypophosphatasia was likely to rise. The Committee was also aware that the company had assumed that adherence to asfotase alfa was much lower than 100%. The Committee heard from the company that it had based its adherence rate on the upper limit of those rates reported for subcutaneous anti-TNF therapies. However, the clinical and patient experts both considered that the company’s assumption was not appropriate. The Committee heard from the company that parents of children with the condition will either administer asfotase alfa themselves, or ensure that the drug is taken by the person with the condition. The Committee agreed that the ERG’s scenario that assumed 100% adherence provided the more plausible estimate for the budget impact of asfotase alfa. The Committee concluded that the company’s assumption about adherence resulted in a significant underestimate of the budget impact.

5.12 Despite multiple requests from NICE, the company refused to make its estimates the number of people likely to be treated with asfotase alfa publically available. To allow consultees, commentators and the public to properly engage in the consultation process, the Institute prepared an illustration of the possible budget impact of asfotase alfa for treating paediatric-onset hypophosphatasia in England, using information available in the public domain. This was based on the list price and recommended dosage of asfotase alfa, and estimated the treatment cost for each of the 3 age groups identified by the company, which were 0–1 years, 1–17 years and 18+ years. The estimates were based on the average weight of people included in the trials (see sections 4.24–4.25).
The number of people with paediatric-onset hypophosphatasia in England was taken from the company’s analysis of Beck et al. (2003) and the Institute approximated different rates of uptake for asfotase alfa for each of the 3 age groups based on its interpretation of the views it heard from the clinical experts (see sections 5.8–5.9). The Institute’s illustrative analysis took the non-drug direct medical costs from the company’s submission, assumed 100% of people were diagnosed in clinical practice, assumed 100% adherence of asfotase alfa and did not take into account the impact on mortality. The number of people with paediatric-onset hypophosphatasia treated with asfotase alfa and budget impact estimates from the Institute’s illustrative analysis are presented in table 3.

Table 3 Summary of the Institute’s illustration of the possible budget impact of asfotase alfa for treating paediatric-onset hypophosphatasia

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uptake of asfotase alfa in people with paediatric-onset hypophosphatasia</strong>¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1 years</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>1–17 years</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>18+ years</td>
<td>5%</td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Total patients treated with asfotase alfa</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1 years</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>1–17 years</td>
<td>14.9</td>
<td>29.9</td>
<td>44.8</td>
<td>59.8</td>
<td>74.7</td>
</tr>
<tr>
<td>18+ years</td>
<td>27.7</td>
<td>55.4</td>
<td>83.0</td>
<td>110.7</td>
<td>138.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>45.5</td>
<td>87.1</td>
<td>129.7</td>
<td>172.4</td>
<td>215.0</td>
</tr>
<tr>
<td><strong>Budget impact (includes non-drug costs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA and BSC</td>
<td>£44.6m</td>
<td>£89.0m</td>
<td>£133.3m</td>
<td>£177.6m</td>
<td>£221.9m</td>
</tr>
<tr>
<td>Without AA</td>
<td>£2.1m</td>
<td>£1.9m</td>
<td>£1.8m</td>
<td>£1.7m</td>
<td>£1.5m</td>
</tr>
<tr>
<td>Net budget impact</td>
<td>£42.6m</td>
<td>£87.0m</td>
<td>£131.5m</td>
<td>£176.0m</td>
<td>£220.4m</td>
</tr>
</tbody>
</table>

Abbreviations: AA, asfotase alfa; BSC, best supportive care; BI, budget impact; m, million.

¹ The company’s estimates for total patients treated with asfotase alfa which at the moment is confidential and cannot be shared beyond those stakeholders who have signed a confidentiality agreement, was based on different assumptions for uptake and also considered the rate of diagnosis.

5.13 The Committee considered the cost of asfotase alfa in the context of costs incurred by the company for research, development and manufacturing. The Committee asked the company to explain the cost of treatment. It
heard from the company that the cost of asfotase alfa is driven by the need to recoup the high costs of research, development, manufacturing and marketing of a treatment to be used only by a small number of people, and reflect the long-term benefits associated with asfotase alfa treatment for a condition that severely affects a person’s health-related quality of life. The Committee acknowledged that developing orphan and ultra-orphan treatments was associated with challenges that were different from those for treatments with bigger patient populations. However, it was not convinced that the high cost per patient of asfotase alfa was justified compared with other treatments for rare conditions. The Committee was not persuaded that paediatric-onset hypophosphatasia was any rarer than other conditions for which NICE has evaluated highly specialised technologies, especially given its earlier concerns around increasing patient numbers because of greater diagnosis (see section 5.11). The Committee was not told of any clinical or safety needs during clinical development that might justify the development costs of asfotase alfa being greater than for other treatments for small populations. Furthermore, the Committee was not satisfied that there was an explanation of the relationship between the development costs of asfotase alfa and the price being proposed for the NHS. The Committee concluded that it had not been given enough justification for the high cost per person of asfotase alfa, or for the overall cost of asfotase alfa in terms of what could be expected to be reasonable in the context of a highly specialised service.

**Value for money**

5.14 The Committee discussed the company’s model structure for the cost–consequence and budget impact analyses. It was aware from the company and the ERG that the health states were based on the level of severity defined by 6-minute walk test (6MWT) distance. The Committee understood that the 6MWT did not capture all the symptoms of hypophosphatasia, or the important domains of the EuroQol-5 dimensions survey (EQ-5D) questionnaire (such as pain and mental health) although
clinicians may have taken these into account when providing utility values for the illustrative vignettes. The Committee heard from the clinical experts that the 6MWT was not used to assess mobility in clinical practice in England and was not persuaded that 6MWT distance was an appropriate outcome for all people with paediatric-onset hypophosphatasia (especially infants and young children). The Committee was uncertain about how credible the company’s minimal clinically important difference was for paediatric-onset hypophosphatasia, given that it was based on Duchenne muscular dystrophy. The Committee considered that there were important differences in the natural history between juvenile-onset hypophosphatasia and Duchenne muscular dystrophy (for example, life expectancy). However, the Committee acknowledged that the company’s clinical trial data suggested that the minimal clinically important difference for 6MWT distance was similar between the conditions, and noted that changing the threshold for a minimal clinically important difference in the economic model had a small impact on the results. The Committee concluded that it would have preferred the company’s model structure to capture all symptoms of hypophosphatasia, but accepted that using 6MWT distance to define health states was reasonable given the lack of evidence allowing for alternative structures.

5.15 The Committee discussed the use of the ordered probit regression model to estimate the transition probabilities. The Committee noted that the company used separate probit models for estimating transitions for asfotase alfa and for best supportive care and the ERG preferred a single probit model controlled for treatment effect. The Committee highlighted that using either approach estimated similar results in the company’s economic model. It understood from the company that each analysis provided nearly identical Markov traces. The Committee concluded that it preferred the ERG’s approach given the limited number of observations for best supportive care, but was prepared to accept the company’s results in its decision-making because the results were similar for the 2 different approaches.
5.16 The Committee discussed the population included in the company’s economic model. The Committee noted that the company’s base-case analysis included a population with a starting age of 5.8 years. The company’s base case therefore did not consider all costs and consequences for an important subpopulation of the marketing authorisation (that is, perinatal- and infantile-onset hypophosphatasia). However, it was aware that several scenario analyses were provided by the company that could help determine the costs and consequences of asfotase alfa compared with best supportive care for all patients. The Committee agreed with the ERG that separate model structures were generally appropriate for perinatal- and infantile-onset hypophosphatasia compared with juvenile-onset hypophosphatasia, given the important differences in costs and outcomes. However, the Committee also acknowledged that, given the lack of data, it was unsure whether the company could have provided a more robust approach. The Committee concluded that it would consider both the company’s model and the ERG’s exploratory model for the younger population in its decision-making.

5.17 The Committee discussed the most appropriate method for modelling overall survival and the need for invasive ventilation. The Committee noted that, in the company’s base case, risk of mortality and the need for invasive ventilation were not included because the starting age in the economic model was 5.8 years, and no one aged 5 years or older died or needed invasive ventilation in the asfotase alfa trials. However, the Committee was aware that asfotase alfa’s marketing authorisation in the UK (see section 3.2) included people younger than 5 years. This group was therefore within the remit issued to NICE by the Department of Health. The Committee recalled its earlier discussions around the natural history data and agreed that any potential for bias when comparing the effect of asfotase alfa with best supportive care should also be addressed in the economic modelling when possible (for example, year of diagnosis and differences between baseline populations that influence prognosis;
see section 5.6). The Committee was aware that the ERG’s exploratory analysis had attempted to address the potential bias associated with the natural history data. The Committee noted that the estimate of incremental life years reduced by 1 life year when using survival data from people in the historical control group who were diagnosed in 2000 or later compared with using survival data from all historical controls. The Committee concluded that using natural history data that attempted to adjust for the potential biases was appropriate in the economic modelling.

5.18 The Committee discussed the cost of asfotase alfa used in the company’s model. It noted that the company had assumed an arbitrary reduction in the price of asfotase alfa after 10 years because of a loss of data exclusivity. The Committee considered that there was no basis for making this assumption. The Committee stated that it had not considered price reductions because of a loss of data exclusivity in other evaluations, and that for the purposes of fairness and consistency, it would not start to do so now. It highlighted that the cost of several resources included in the company’s economic model could change over time. The Committee further noted that NICE’s guide to methods of technology appraisal (2013) stated that a reduced price should only be used when there is a nationally available price reduction. The Committee concluded that the costs associated with asfotase alfa treatment in the economic modelling had been underestimated by the company.

5.19 The Committee discussed other costs and healthcare resources used in the company’s model. The Committee noted the evidence submission from NHS England and the views of the clinical experts that suggested infants with paediatric-onset hypophosphatasia would need several months of intensive care and invasive ventilation. On this basis, the Committee was concerned that the costs of intensive care and invasive ventilation were not sufficiently captured in the company’s model. The Committee concluded that the costs associated with managing paediatric-onset hypophosphatasia had been underestimated by the company.
5.20 The Committee discussed the utility values used in the company’s model. The Committee heard from the patient experts that the health-related quality of life of a child with hypophosphatasia can be substantially lower than that of a child without hypophosphatasia of the same age. The Committee noted that the company’s mean utility value for the most severe 6MWT health state was 0.23, which represented a very low health-related quality of life. The Committee also acknowledged that the company had not included the health-related quality of life benefits for carers of people with the condition and that, if included, they were likely to increase the quality-adjusted life year (QALY) gain for asfotase alfa compared with best supportive care. The Committee concluded that the mean utility values used in the company’s model were reasonable estimates for the 6MWT health states.

5.21 The Committee discussed the most appropriate discount rate used for costs and health effects. The Committee understood from the company’s sensitivity analyses that the results of the company’s cost–consequence analysis were sensitive to the discount rate. It was aware that changing the discount rate from 1.5% to 3.5% resulted in approximately 14 to 25 incremental QALYs for asfotase alfa compared with best supportive care, respectively. The Committee commented that the relative change in incremental costs was similarly affected when changing the discount rate in the company’s economic model. Although not binding on the Highly Specialised Technologies evaluation programme, the Committee was aware from NICE’s guide to methods of technology appraisal (2013) that a non-reference case ‘discount rate of 1.5% for costs and benefits may be considered by the Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs’. The Committee acknowledged that asfotase alfa may restore some people (for example, infants) who would otherwise die or have a very severely impaired life to full or near full health. However, it
was not convinced on the balance of the clinical evidence, and the clinical expert and patient expert testimonies, that this was the case for all people with paediatric-onset hypophosphatasia (see sections 5.1, 5.2, 5.2 and 5.9). The Committee agreed that there was considerable uncertainty around whether the treatment effect would be maintained for the person’s lifetime, and that it would have been appropriate for the company to explore a scenario in which the treatment effect diminished over time. Therefore, the Committee was not sufficiently satisfied that the introduction of asfotase alfa did not commit the NHS to significant irrecoverable costs when considering the entire population included in the marketing authorisation. The Committee concluded it was more appropriate for the company to include a discount rate of 3.5% in its base-case analysis.

The Committee discussed the results of the company’s cost–consequence model. It noted that the company’s deterministic base case was associated with 25.04 incremental QALYs over the lifetime of the model. The total costs for asfotase alfa and incremental costs for asfotase alfa compared with best supportive care were considered commercial in confidence by the company and cannot be reported here. However, the Committee highlighted that the incremental costs for asfotase alfa compared with best supportive care were likely to be underestimated (see sections 5.17 and 5.18). The Committee stated that the company’s probabilistic sensitivity analysis suggested that the results were not very stable and were therefore associated with considerable uncertainty, particularly for the estimation of QALY gains (that is, 18.4 incremental QALYs in the probabilistic sensitivity analysis compared with 25.04 in the company’s deterministic base-case analysis). It was aware that the company had assumed the treatment effect was maintained for the person’s lifetime and that the ERG were concerned that the company’s vignettes did not capture the true variation around the health-related quality of life of patients between the 6MWT health states (see section 4.39). The Committee considered that these 2 factors were likely
to affect the size of the estimated QALY gain. The Committee concluded that it was persuaded that asfotase alfa provided a substantial QALY gain compared with best supportive care, but there was considerable uncertainty around the size of the benefit.

5.23 The Committee considered the overall value for money provided by asfotase alfa. It was aware that NHS England has a single budget for specialised services of £13 billion, which includes a budget of £156 million for high-cost drugs. The Committee considered the needs of people with paediatric-onset hypophosphatasia and their families compared with the needs of people with other rare diseases and conditions. It then discussed the overall value of asfotase alfa, taking into account both its health benefits (estimated to be between 14 and 25 additional QALYs) and associated costs in the context of other highly specialised technologies:

- It recalled that NICE’s guidance on eculizumab for treating atypical haemolytic uraemic syndrome stated that eculizumab produced similar incremental QALY gains when compared with standard care (estimated to be 25.22 by the company and 10.14 by the ERG). NICE estimated an annual cost per patient for eculizumab of £211,000 to £340,000.

The Committee was aware that the company manufactured both asfotase alfa and eculizumab. After consideration of the company’s model, the Committee was of the view that the average annual cost per patient and the incremental costs for asfotase alfa were substantially higher than those for eculizumab, but the estimated QALY gains were very similar. The Committee was also concerned that the number of patients eligible for treatment and the budget impact were likely to be underestimated by the company (see section 5.11). When queried by the Committee, the company was unable to explain why the average annual cost was higher for asfotase alfa compared with eculizumab, despite its similar QALY gain. Although the Committee had considered the evidence of improved outcomes from clinical trials and the patient testimonies, the Committee remained concerned that the size of the health benefits for asfotase alfa
compared with best supportive care were associated with considerable uncertainty, and were not great enough to justify its high cost. The Committee was also concerned that the cost of asfotase alfa depended on a person’s weight and was therefore more expensive for adults, who could have less potential to benefit from treatment than younger people (as suggested by the clinical experts). The Committee considered that, even based on more optimistic assumptions, the cost of asfotase alfa would be very high, and that it would be higher relative to treatment benefits than the Committee had previously regarded as acceptable. Without clear evidence explaining the reasons for the high cost of asfotase alfa at similar QALY gains compared with other highly specialised technologies that have been evaluated by NICE, the Committee was un convinced that asfotase alfa represented overall good value for money to the NHS.

5.24 The Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when evaluating asfotase alfa. The Committee noted NICE’s position statement about this, and accepted the conclusion ‘that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines’. The Committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this evaluation of asfotase alfa. It therefore concluded that the PPRS payment mechanism was irrelevant in considering the value for money offered by asfotase alfa.

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

5.25 The Committee considered the potential wider societal benefits of asfotase alfa treatment proposed by the company and the patient experts. It understood from the patient experts that because asfotase alfa improves the general health and functioning of people with paediatric-onset hypophosphatasia, it would enable children with the condition to be
educated and attend school. For adults with the condition and carers of people with the condition, it would enable them to work or at least work for longer (whether part-time or by reducing the need for early retirement).

The Committee also appreciated that asfotase alfa may reduce: the need to move house to be closer to specialist treatment centres; the need for home adaptations (for example, installation of oxygen or changes to help mobility); and the substantial expenses associated with constant travel for hospital appointments. The Committee was also aware that the company’s estimates for cost savings used a human capital approach and that the estimates for cost savings would have been lower if a friction cost approach had been used. On balance, the Committee agreed that there would be cost savings and benefits with asfotase alfa incurred outside the NHS and personal and social services, but it did not consider them to be qualitatively greater than those provided by other similar highly specialised technologies.

5.26 The Committee discussed the impact of asfotase alfa on the delivery of specialised services. It noted the submission received from NHS England indicating that it did not envisage the need for substantial training or education of staff, and that administration of asfotase alfa was straightforward. The Committee understood from the company that no additional infrastructure would be needed at the 3 specialist centres currently treating hypophosphatasia in England (Birmingham, Manchester and Sheffield), but that other centres in England do not have the necessary services or expertise to manage and treat hypophosphatasia. The Committee noted that NHS England had highlighted that several months of intensive care and invasive ventilation may be needed for infants until their condition stabilises. It heard from the clinical experts that because the survival of infants was expected to improve if asfotase alfa is made available in the NHS, they hoped the current capacity of intensive care units could cope with this increase in demand, but this was uncertain and would need to be monitored. The Committee concluded that based on the company’s estimates for the number of people in England likely to be
treated with asfotase alfa and reassurance from the clinical experts, it was satisfied that no additional staffing and infrastructure will be needed at the 3 specialist centres in England currently treating hypophosphatasia if asfotase alfa is made available (but with the concerns as noted above).

**Conclusion**

5.27 The Committee discussed the recommendation it could make for asfotase alfa for treating paediatric-onset hypophosphatasia. It appreciated that paediatric-onset hypophosphatasia is a serious, life-threatening and debilitating condition that has severe effects on the lives of people with the condition, as well as their families and carers. After considering all available evidence, and the opinions of the clinical and patient experts, the Committee recognised that asfotase alfa represents an important development in the treatment of paediatric-onset hypophosphatasia. The Committee agreed that the results of the trials generally suggested that asfotase alfa was associated with clinically meaningful improvements across a range of outcomes when compared with either pre-treatment measurements or with natural history data from patients who had received best supportive care. It acknowledged that asfotase alfa improved survival in infants with perinatal- and infantile-onset hypophosphatasia. However, the Committee believed that, given the designs of the trials and several issues with the natural history data, there was considerable uncertainty around the robustness of the results and the precise size of the benefit. The Committee was also concerned that the natural history of paediatric-onset hypophosphatasia in children and adults was not entirely clear. It was not convinced that the potential of benefit with asfotase alfa was the same for all people with juvenile-onset hypophosphatasia. This was supported by the clinical experts, who stated that they were not certain about how this population would be treated in clinical practice. The Committee encouraged further data to be collected in children and adults with paediatric-onset hypophosphatasia (on and off treatment). It also encouraged the company to consider generating starting and stopping rules for asfotase alfa that identify those people for whom treatment
should be a priority. The Committee considered that asfotase alfa has the potential to provide major benefits for some people with paediatric-onset hypophosphatasia, but not for all (as proposed by the company) because of the considerable uncertainty. The Committee thought that the company’s budget impact and cost–consequence model substantially underestimated the costs associated with asfotase alfa compared with best supportive care given the uncertainty around the model structure and several of the company’s assumptions. The Committee highlighted that it had not been given enough justification for the high cost per person of asfotase alfa, or for the overall cost of asfotase alfa in terms of what could be expected to be reasonable in the context of a highly specialised service. Overall, the Committee considered that asfotase alfa did not represent value for money for the NHS. Based on these considerations, the Committee concluded that it could not recommend asfotase alfa for treating paediatric-onset hypophosphatasia.

Summary of Evaluation Committee’s key conclusions

<table>
<thead>
<tr>
<th>Evaluation title: Asfotase alfa for treating paediatric-onset hypophosphatasia</th>
<th>Section</th>
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<tbody>
<tr>
<td>Key conclusion</td>
<td>1.1</td>
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<tr>
<td>Asfotase alfa is not recommended, within its marketing authorisation, for long-term enzyme replacement therapy in paediatric-onset hypophosphatasia to treat the bone manifestations of the disease. The Committee believed that, given the designs of the trials and several issues with the natural history data, there was considerable uncertainty around the robustness of the results and the precise size of the benefit. It was not convinced that the potential of benefit with asfotase alfa was the same for all people with juvenile-onset hypophosphatasia. The Committee encouraged further data to be collected in children and adults with paediatric-onset hypophosphatasia (on and off treatment), and the company to consider generating starting and stopping rules for asfotase alfa. The Committee thought that the company’s budget impact and cost–consequence model substantially underestimated the costs associated with asfotase alfa compared with best supportive care. The Committee highlighted that it had not been given enough justification for the high cost per person of asfotase alfa, or for the overall cost of asfotase alfa in terms of what could be expected to be reasonable in the context of a highly specialised service. Overall, the Committee considered that asfotase alfa did not represent value for money for the NHS.</td>
<td>5.27</td>
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### Current practice

| Nature of the condition, including availability of other treatment options | Paediatric-onset hypophosphatasia is a serious, life-threatening and debilitating condition that severely affects the quality of life of people with the condition, and their families. The signs and symptoms vary widely and can appear anytime from birth until adulthood.  
Natural history of paediatric-onset hypophosphatasia was well-defined for perinatal- or infantile-onset disease, but not entirely clear in juvenile-onset disease.  
A treatment such as asfotase alfa, which addresses the cause of the condition, would be a valuable treatment option because there are currently no treatments available that specifically prevent or delay the progression of hypophosphatasia. | 5.1  
| | **5.2**  
| | **5.3** |

### The technology

| Proposed benefits of the technology  
How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits? | Asfotase alfa is the first therapy that specifically targets the underlying cause of hypophosphatasia, so the clinical experts considered it to be a step change in the management of paediatric-onset hypophosphatasia. | 5.4 |

| Adverse reactions | Most adverse events were considered unrelated to asfotase alfa treatment and of mild intensity. | 4.17 |

### Clinical evidence

| Availability, nature and quality of evidence | Most of the company's clinical trial evidence did not include a control group. The Committee agreed that, in absence of a control group, it was reasonable in the circumstances for the company to compare with natural history data. | 5.5 |
| Uncertainties generated by the evidence | Given the heterogeneous nature of the condition and the trial designs used, the available clinical evidence did not provide either a robust estimate of the size of the benefit or a strong indication of the likely variation in the treatment effect. On the basis of current evidence, it was not possible to define a treatment continuation rule for asfotase alfa in children with perinatal- and infantile-onset hypophosphatasia. The treatment need for children and adults with juvenile-onset hypophosphatasia varied and criteria for starting and stopping treatment with asfotase alfa were not clearly defined. | 5.5  
5.8  
5.9 |
| Impact of the technology | Asfotase alfa improved the probability of survival in perinatal- and infantile-onset hypophosphatasia compared with best supportive care. Although there was considerable uncertainty around robustness and the precise size of the treatment benefit, the results of the trials generally suggested that asfotase alfa was associated with clinically meaningful improvements across a range of outcomes when compared with baseline. | 5.6  
5.7 |
| Cost evidence | The Committee discussed the company’s cost–consequence model and budget impact analysis. | 5.10–22 |
### Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis

<table>
<thead>
<tr>
<th>Uncertainties</th>
<th>The Committee identified the following uncertainties:</th>
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<tbody>
<tr>
<td></td>
<td>- Difficult to estimate the number of people with juvenile-onset hypophosphatasia in England, and consequently how many would be eligible for asfotase alfa treatment.</td>
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<td></td>
<td>- Agreed assumed 100% adherence provided the more plausible estimate for the budget impact.</td>
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<td></td>
<td>- Preferred the company’s model structure to capture all symptoms of hypophosphatasia, but accepted that using 6MWT distance to define health states was reasonable given the lack of evidence allowing for alternative structures.</td>
<td>5.14</td>
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<td></td>
<td>- Important differences in costs and outcomes for perinatal- and infantile-onset hypophosphatasia compared with juvenile-onset hypophosphatasia.</td>
<td>5.16</td>
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<td></td>
<td>- Using natural history data that attempted to adjust for the potential biases was appropriate in the economic modelling.</td>
<td>5.17</td>
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<td></td>
<td>- Costs in the economic modelling underestimated.</td>
<td>5.18–19</td>
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<td></td>
<td>- More appropriate for the company to include a discount rate of 3.5% in its base-case analysis.</td>
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<td></td>
<td>- Probabilistic sensitivity analysis suggested that the results were not very stable and were therefore associated with considerable uncertainty, particularly for the estimation of QALY gains.</td>
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<td></td>
<td>- Even based on more optimistic assumptions, the cost of asfotase alfa would be very high, and that it would be higher relative to treatment benefits than the Committee had previously regarded as acceptable.</td>
<td>5.23</td>
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<tr>
<td>Incorporation of health-related quality-of-life benefits and utility values</td>
<td>The Committee heard from the patient experts that the health-related quality of life of a child with hypophosphatasia can be substantially lower than that of a child without hypophosphatasia of the same age. The Committee concluded that the mean utility values used in the company’s model were reasonable estimates. The Committee acknowledged that the company had not included the health-related quality of life benefits for carers of people with the condition and that, if included, they were likely to increase the quality-adjusted life year (QALY) gain for asfotase alfa compared with best supportive care.</td>
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<tr>
<td>Cost to the NHS and PSS</td>
<td>The Committee concluded that company had significantly underestimated the budget impact. The Committee concluded that it had not been given enough justification for the high cost per person of asfotase alfa, or for the overall cost of asfotase alfa in terms of what could be expected to be reasonable in the context of a highly specialised service.</td>
<td>5.11, 5.13</td>
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<tr>
<td>Value for money</td>
<td>Without clear evidence explaining the reasons for the high cost of asfotase alfa at similar QALY gains compared with other highly specialised technologies that have been evaluated by NICE, the Committee was unconvinced that asfotase alfa represented overall good value for money to the NHS.</td>
<td>5.23</td>
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<tr>
<td>Impact beyond direct health benefits and on the delivery of the specialised service</td>
<td>Agreed that there would be cost savings and benefits with asfotase alfa incurred outside the NHS and personal and social services, but it did not consider them to be qualitatively greater than those provided by other similar highly specialised technologies. No additional staffing and infrastructure will be needed at the 3 specialist centres in England currently treating hypophosphatasia if asfotase alfa is made available.</td>
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### Additional factors taken into account

| Access schemes | Not applicable. | – |
| Equalities considerations and social value judgements | No equality issues were raised during the evaluation. | – |
6 Implementation

6.1 If asfotase alfa were to be recommended, section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 would require clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

6.2 NICE has not developed implementation tools. If asfotase alfa were to be recommended, NICE would work with NHS England to ensure implementation of the recommendations is monitored.

7 Related NICE guidance

There is no related guidance for this technology.

8 Proposed date for review of guidance

8.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson
Chair, Highly Specialised Technologies Evaluation Committee
November 2015
9 Evaluation Committee members and NICE project team

Evaluation Committee members

The Highly Specialised technologies Evaluation Committee is a standing advisory committee of NICE. Members are appointed for a 3-year term and a Chair and vice chair are also appointed for 3 years. A list of the Committee members who took part in the discussions for this evaluation appears below.

Committee members are asked to declare any interests in the technology to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each Evaluation Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Peter Jackson (chair)
Consultant Physician and Honorary Reader in Clinical Pharmacology

Ron Akehurst
Health Service Researcher, Strategic Director

Steve Brennan
Chief Finance Officer, NHS North Kirklees Clinical Commissioning Group

Trevor Cole
Clinician - Geneticist / Consultant in Clinical and Cancer Genetics/Honorary Reader in Medical Genetics

Sarah Davis
Senior Lecturer in Health Economics, the University of Sheffield

Jonathan Howell
Public Health Physician - Consultant in Public Health
Vincent Kirkbride  
Consultant Paediatrician, Sheffield NHS Foundation Trust  

Jeremy Manuel  
Lay Member  

Francis Pang  
Healthcare Industry – Vice President, Market Access  

Linn Phipps  
Lay Member  

Mark Sheehan  
Oxford BRC Ethics Fellow, The Ethox Centre, University of Oxford  

Sheela Upadhyaya  
Highly Specialised Programme of Care Lead (London Region), NHS England  

Anthony Wierzbicki  
Consultant in Metabolic Medicine/Chemical Pathology, Guy’s & St Thomas’ Hospitals, London  

**NICE project team**  
Each highly specialised technology evaluation is assigned to a team consisting of 1 or more technical personnel, a project manager and the Associate Director for the Highly Specialised Technologies Programme.  

Martyn Burke  
Technical Analyst  

Linda Landells  
Technical Adviser  

Leanne Wakefield  
Project Manager
10 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this evaluation was prepared by Kleijnen Systematic Reviews:


B. The following organisations accepted the invitation to participate in this evaluation as consultees and commentators. They were invited to comment on the draft scope and the evaluation consultation document. Organisations listed in I, II and III were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final evaluation determination.

I. Company:

- Alexion Pharma UK

II. Professional/specialist and patient/carer groups:

- Brittle Bone Society
- CLIMB – Children Living with Inherited Metabolic Diseases
- Birmingham Children’s Hospital
- Royal College of Nursing
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Physicians
- Sheffield Children’s NHS Foundation Trust - Metabolic Bone Disease Service
- Willink Unit, Royal Manchester Children’s Hospital, CMFT

III. Other consultees:

- Department of Health
- NHS England
IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Cochrane Cystic Fibrosis and Genetic Disorders Group
- MRC Clinical Trials Unit

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on asfotase alfa for treating paediatric-onset hypophosphatasia by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the evaluation consultation document.

- Prof Nick Bishop, nominated by Sheffield Children’s NHS Foundation Trust – clinical expert
- Prof Zulf Mughal, nominated by Royal Manchester Children’s Hospital – clinical expert
- Dr Nick Shaw, nominated by Royal College of Paediatrics and Child Health – clinical expert
- Helen Morris, nominated by CLIMB – patient expert
- Meryl Ockenden, nominated by CLIMB – patient expert
- Carole Shields, nominated by Sheffield Children’s NHS Foundation Trust – patient expert

D. The following individuals were nominated as NHS Commissioning experts by NHS England. They gave their expert/NHS commissioning personal view on asfotase alfa for treating paediatric-onset hypophosphatasia by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the evaluation consultation document.

- Edmund Jessop, selected by NHS England – NHS Commissioning expert
E. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Alexion Pharma UK