NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

Appraisal Consultation Document

1st Committee meeting

The following documents are made available to the Committee:

The **final scope and final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission summary** from **Shire Pharmaceuticals, a Takeda company**

2. **Company clarification:**
   a. NICE clarification letter to company
   b. Company clarification response

3. **Patient group, professional group and NHS organisation submission** from:
   a. HAE UK
   b. British Association of Dermatologists
   c. Royal College of Pathologists
   d. Royal College of Physicians

4. **Expert personal perspectives** from:
   a. Rachel Annals – patient expert, nominated by HAE UK

5. **Evidence Review Group report** prepared by Aberdeen HTA Group

6. **Evidence Review Group report – factual accuracy check**

7. **Evidence Review Group – erratum**

8. **Summary of clinical expert responses to NICE technical team**

Post-technical engagement documents

9. **Technical engagement response from Shire Pharmaceuticals, a Takeda company**

10. **Technical engagement responses from experts:**
    a. Sinisa Savic, Consultant Immunologist – clinical expert, nominated by Shire Pharmaceuticals

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b. Laura Szutowicz, Chief Executive Officer – patient expert, nominated by HAE UK
c. Rachel Annals – patient expert, nominated by HAE UK

11. Technical engagement responses from consultees and commentators:
a. Royal College of Pathologists
b. United Kingdom Primary Immunology Network

*A **'no comment'** response was received from the Department of Health & Social Care*

12. Evidence Review Group critique of company response to technical engagement prepared by Aberdeen HTA Group

13. Technical Report

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

Document B

Company evidence submission

10 December 2018

File name	Version	Contains confidential information	Date
		Yes/no	

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Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

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Tables and figures

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Abbreviations

A&E	accident and emergency
ACE	angiotensin-converting enzyme
ADA	antidrug antibody
AE	adverse event
AE-QoL	Angioedema Quality of Life instrument
AESI	adverse event of special interest
ALT	alanine transaminase
AST	aspartate transaminase
BMI	body mass index
C1-INH	C1 esterase inhibitor
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CrI	Credible interval
CSR	clinical study report
DSU	Decision Support Unit
EAACI	European Academy of Allergy and Clinical Immunology
EDC	electronic data capture
EMA	European Medicines Agency
EQ-5D-5L	5-level EQ-5D
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	generalised estimating equation
GLM	generalised linear model
HAARP	HAE Attack Assessment and Reporting Procedures
HADS	Hospital Anxiety and Depression Scale
HAE	HAE with normal C1-INH
HAE nC1-INH	HAE with normal C1-INH
HAE-BOIS-Europe	Hereditary Angioedema Burden of Illness Study in Europe
HAE-QoL	Hereditary Angioedema Quality of Life questionnaire
HMWK	high-molecular-weight kininogen
HRQL	health-related quality of life
HTA	health technology assessment
IOS	Icatibant Outcomes Survey

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ITC	indirect treatment comparison
ITT	intent-to-treat
IV	intravenous
IWRS	Interactive Web-based Randomisation System
KM	Kaplan–Meier
LS	least squares
LTP	long-term prophylaxis
LY	life year
MCID	minimal clinically important difference
MCMC	Markov Chain Monte Carlo
MCS	mental component summary
MIMS	Monthly Index of Medical Specialities
nC1-INH	normal C1-INH
NHS	National Health Service
NMA	network meta-analysis
PCS	physical component summary
PD	pharmacodynamic
PK	pharmacokinetic
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
q2w	every 2 weeks
q4w	every 4 weeks
QALY	quality-adjusted life year
QoL	quality of life
RCT	randomised controlled trial
SC	subcutaneous
SE	standard error
SF-12	12-item short form health survey
SF-36	36-item short form health survey
SLR	systematic literature review
SPC	summary of product characteristics
Sweha-Reg	Swedish population-based registry of hereditary angioedema
TEAE	treatment-emergent adverse event
TSD	Technical Support Document
TTO	time-trade-off
WAO	World Allergy Organization

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WPAI	Work Productivity and Activity Impairment questionnaire

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B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission focuses on part of the population covered by the technology's anticipated marketing authorisation, specifically people aged 12 years and older, with HAE Type I or II who have at least one angioedema attack every 4 weeks.

The proposed population is narrower than the marketing authorisation because the evidence base on lanadelumab is limited to this population.

The decision problem is presented in Table 1.

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Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 12 years and older with HAE	People aged 12 years and older with HAE Type I or II who have at least one angioedema attack every 4 weeks	The submission is focused on the population of the key trial, HELP-03; patients with HAE Type I and Type II, and those having at least one angioedema attack every 4 weeks
Intervention	Lanadelumab	Lanadelumab	N/A
Comparator(s)	Established clinical management for preventing recurrent attacks of hereditary angioedema without lanadelumab (including but not limited to C1-INHs, attenuated androgens and anti-fibrinolytics)	Plasma-derived C1-INHs (Cinryze IV and Berinert IV)	Oral prophylactic treatments (attenuated androgens and anti-fibrinolytics) are not considered comparators given that lanadelumab would be used for patients who are not controlled with or who are not suitable for oral prophylactic treatment.
Outcomes	The outcome measures to be considered include: • Frequency of angioedema attacks • Severity of angioedema attacks • Need for acute treatment • Mortality • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Frequency of angioedema attacks (attack rate during treatment period [Day 0 to Day 182]; between Day 14 and Day 182; and between Day 70 and Day 182) • Severity of angioedema attacks • Need for acute treatment • Time to first attack after Day 0, Day 14, Day 28, and Day 70 • High morbidity attacks in treatment period (severe, hospitalised, haemodynamically significant or laryngeal)	Several efficacy outcomes have been presented in addition to those in the scope as several secondary, exploratory and post-hoc outcomes were reported in the HELP-03 trial that provide additional insight into the efficacy of lanadelumab.

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		• Proportion of responders with a ≥50% reduction in attack rate • Proportion of responders with a 100% reduction in attack rate • Mean attack-free days (Day 0 to Day 182; Day 0 to Day 28; Day 0 to Day 84; Day 70 to Day 182) • Mortality • Adverse effects of treatment • Health-related quality of life	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	Adhering to the reference case, the cost-effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year.	NA
	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	Adhering to the reference case, a lifetime horizon is used.	NA
	Costs will be considered from an NHS and Personal Social Services perspective.	The reference case has been adhered to.	NA
	The availability of any PAS for the intervention or comparator technologies will be taken into account.	A confidential PAS has been applied.	It is anticipated that the confidential PAS that has been applied to lanadelumab will be approved in time for the appraisal committee meeting.
Key: IV, intravenous; N/A, not applicable; PAS, patient access scheme.			

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B.1.2. Description of the technology being appraised

Appendix C includes the summary of product characteristics or information for use, and the European public assessment report, scientific discussion or drafts.

A description of lanadelumab is presented in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Lanadelumab (brand name: Takhzyro™; alternative identifier: DX-2930; ATC code: B06AC05)
Mechanism of action	Fully human monoclonal antibody (immunoglobulin G1/ κ-light chain) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.[1] Lanadelumab provides sustained inhibition of plasma kallikrein-induced proteolysis of high-molecular-weight kininogen (HMWK), which produces cleaved HMWK (cHMWK) and bradykinin, a potent vasodilator that increases vascular permeability resulting in HAE attacks and associated swelling and pain. Patients with HAE due to C1-INH deficiency or dysfunction have increased plasma kallikrein activity, both during and in between HAE attacks. In inhibiting active plasma kallikrein proteolytic activity and subsequently limiting bradykinin generation, lanadelumab directly addresses the mechanism of HAE attacks.[1] Furthermore, lanadelumab is highly selective and binds active kallikrein without binding similar proteins (e.g. other serine proteases the pre-kallikrein zymogen, factor X1a and tissue kallikrein 1 gene).[1]
Marketing authorisation/CE mark status	The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) granted a positive opinion on 18 October 2018 with marketing authorisation expected in December 2018.[1-3] Lanadelumab was designated as an orphan medicinal product on 9 October 2015 and reviewed under EMA's accelerated assessment programme.[4]
Indications and any restriction(s) as described in the summary of product characteristics (SPC)	The indication is:[1] Lanadelumab is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.
Method of administration and dosage	Lanadelumab is administered by subcutaneous (SC) injection, by the patient themselves or by a caregiver, only after training on SC injection technique by a healthcare professional.[1] The injection should be restricted to the recommended injection sites: the abdomen, the thighs, and the upper outer arms; rotation of the injection site is recommended.[1] The recommended starting dose is 300mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose

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	reduction of 300mg lanadelumab every 4 weeks may be considered, especially in patients with low weight.
Additional tests or investigations	In case of a severe hypersensitivity reaction, discontinue lanadelumab and institute appropriate treatment. No other tests or investigations are required.[1]
List price and average cost of a course of treatment	[redacted]. Expected cost of treatment is [redacted] in the first year, followed by an annual cost of [redacted] thereafter, based on the PAS price.
Patient access scheme (if applicable)	A confidential PAS has been submitted and is expected to be approved prior to the first appraisal committee meeting. This arrangement provides lanadelumab to NHS patients at a [redacted] discount to list price.
Key: C1-INH, C1 esterase inhibitor; CHMP, Committee for Medicinal Products for Human Use; CHO, Chinese hamster ovary; EMA, European Medicines Agency; HAE, hereditary angioedema; PAS, patient access scheme; SC, subcutaneous.	

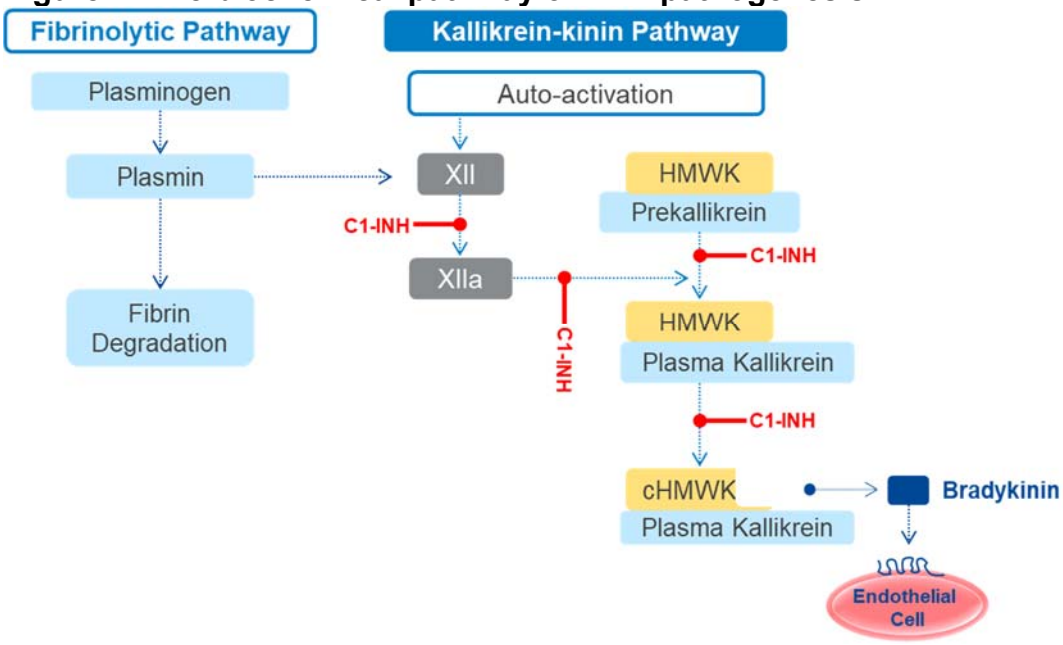
B.1.3. Health condition and position of the technology in the treatment pathway

Disease overview

Brief overview of disease

Hereditary angioedema (HAE) is a very rare genetic disorder resulting from inherited or spontaneous mutations in the biochemical pathway, known as the contact system (Figure 1).[5-7]

Figure 1: The biochemical pathway of HAE pathogenesis



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Key: XII, factor XII; XIIa, factor XIIa; HAE, hereditary angioedema, HMWK: high-molecular-weight kininogen, cHMWK: cleaved high-molecular-weight kininogen.**Source:** Figure adapted from Zuraw *et al*., 2005.[8]

Plasmin triggers factor XIIa to activate the kallikrein-kinin system by converting pre-kallikrein to kallikrein, which in turn converts high-molecular-weight kininogen (HMWK) to bradykinin, a stimulator of vasodilation and enhanced vascular permeability.[5-7] Inhibitors such as C1 esterase inhibitor (C1-INH) prevent over-activity of the kallikrein-kinin system.[5-7]

However, in HAE, mutations in the *SERPING1* gene, which encodes C1-INH, leads to dysregulation in the kallikrein-kinin system resulting in over-production of kallikrein and, thus, bradykinin.[6, 9] Excessive bradykinin production leads to increased vascular permeability, resulting in fluid leakage that causes the pain and swelling characteristic of HAE.[6, 9]

There are three types of HAE:[10, 11]

- Type I and Type II are due to a known genetic mutation and account for almost all HAE cases
  - Type I is defined by low levels of a normal protein C1-INH in the plasma, resulting in diminished functional activity, and accounts for ~85% of all HAE cases
  - Type II is defined by normal levels of a dysfunctional protein C1-INH in the plasma and account for ~15% of all HAE cases

HAE with normal C1-INH (HAE nC1-INH; also known as Type III HAE) is associated with normal C1-INH protein quantity and function and is extremely rare.[12] The focus of this submission relates to Type I and Type II HAE only; Type III HAE/nC1-INH will not be discussed further.

Epidemiology of HAE

HAE is a very rare condition, affecting between 1/50,000 and 1/100,000 of the population in the UK.[13] In the international Icatibant Outcomes Survey (IOS) of patients with Type I or Type II HAE, 73 patients were included from the UK.[14] These UK patients had a mean age of 42.9 years (non-UK: 45.1 years), were 39.7% male

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(non-UK: 40.6%), and had a delay of 9.5 years between first symptom and diagnosis (non-UK: 10.5 years).

Patients with HAE experience unpredictable attacks at several locations; [15, 16] of these, attacks of the larynx are particularly dangerous as these can restrict the airway and can be life-threatening.[8, 17, 18] There are limited data on mortality in the UK, but the Office of National Statistics reported that five patients died from angioedema (hereditary and acquired) in 2017 in England and Wales.[19] In a 2011 German real-world study of 728 patients from 182 families with HAE, 214 died, of which 70 died from asphyxiation relating to a laryngeal attack (i.e. 9.6% of all patients in the cohort).[17] Deaths due to asphyxiation resulting from HAE were assumed if: the person belonged to a family with known HAE (i.e. at least one family member had a proven deficiency of functionally active C1-INH and low C4 in plasma); the patient had recurrent skin swellings and abdominal attacks; the death was sudden and unexpected; and no concomitant disease was known that could explain the sudden death. Of the 70 asphyxiation deaths reported, 90% were in undiagnosed patients.[17] In Italy, a survey of approximately 1,000 patients with HAE Type I or II who were followed between 1973 and 2013, reported five deaths from asphyxiation due to laryngeal attacks in patients who received on-demand therapy.[20]

Aetiology of HAE

HAE (Type I and Type II) is an autosomal dominant condition caused by one of more than ~450 known genetic mutations in the *SERPING1* gene, which encodes the C1-INH protein.[6] As described earlier, the C1-INH protein is a serine protease inhibitor (SERPIN) and the major inhibitor of contact system proteases (plasma kallikrein and coagulation factor XIIa), as well as a minor inhibitor of the fibrinolytic protease plasmin.[6]

Most attacks occur spontaneously, without an obvious trigger, although some have a recognisable external trigger such as[6, 11, 21, 22]:

- Physical exertion
- Stress and trauma (e.g. emotional stress/anxiety medical procedures, fatigue, dental work, infections)

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- Weather changes
- Hormonal changes (e.g. oral contraceptive use, menstruation, pregnancy)
- Medications (e.g. angiotensin-converting enzyme [ACE] inhibitors, aspirin, non-steroidal anti-inflammatory drugs [NSAIDs], cyclooxygenase-1 [COX-1] inhibitors, antibiotics)
- Intubation during general anaesthesia
- Diet (e.g., shellfish, nuts, milk, eggs)

According to a study of 92 patients with HAE in Hungary, in which trigger factors of 3,176 attacks were analysed, only 30% had an identifiable trigger.[22] Of those, mental stress was the most common (21%), followed by menstruation (18% in the female population), physical exertion (17%), weather changes (15%), infection (11%), trauma (11%), fatigue (6%) and pregnancy (4% in the female population).

Diagnosis of HAE

In the UK, the British Society for Allergy and Clinical Immunology (BSACI) guidelines recommend that a diagnosis of HAE involves taking a detailed history, including the frequency, circumstances of onset, triggers, timing, pattern of recurrence and duration of attacks.[23] The history should also include a description of the nature, site and duration of individual lesions and whether they itch or are painful. A positive family history should also be obtained before HAE diagnosis can be confirmed.[23] Specific laboratory tests are used to differentiate HAE from other forms of angioedema; a low serum C4 level (even between attacks) coupled with a low functional C1-INH level indicate a diagnosis of either Type I or Type II HAE.[23]

For optimal treatment, HAE should be diagnosed early, given the substantially poorer survival from laryngeal attacks in undiagnosed HAE patients compared with diagnosed HAE patients (mean age at death: 40.8 versus 72 years, respectively).[17]

However, despite improved education, awareness and therapeutics, patients are still experiencing delayed diagnosis. Of the 73 UK patients in the IOS study, the mean age of diagnosis was reported as 21.5 years, a substantial delay from the mean age of 11.3 years, at initial symptom presentation.[14]

Clinical characteristics

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HAE attacks involve painful, non-pruritic, non-inflammatory swelling, which can occur in several locations across the body.[5, 15, 16] Other associated symptoms vary according to specific attack locations. Attacks are generally categorised into three main types[15, 16]:

- Laryngeal, which can result in restriction of the airways and are the main cause of death in patients with HAE
- Abdominal attacks, which are associated with excruciating pain and are very debilitating
- Peripheral attacks, in particular attacks of:
  - Hands and feet, which can severely impact patient functioning
  - The face, which may lead to disfigurement and consequently impact patient well-being, including anxiety and depression

All attack types, even if not life-threatening, have a substantial impact on the patient's quality of life (QoL) and functioning, as described in full below.

Several studies have investigated the clinical characteristics of HAE attacks in UK patients. In a UK audit of 376 patients with HAE, peripheral attacks were most common (58% of all attacks; annual attack rate: 8 per patient), followed by abdominal attacks (38%; annual attack rate: 5 per patient), with laryngeal attacks being the least common (4%; annual attack rate: 0.5 per patient).[15] In the IOS study involving 73 patients from the UK, 854 HAE attacks were reported between February 2008 and July 2016.[14] The median number of treated and untreated attacks per UK patient was 3.0 and 2.0, respectively, and untreated attacks had a median duration of 72 hours. Given that swelling and other symptoms of HAE attacks can worsen gradually but relentlessly over 12 to 36 hours, sometimes spreading to other sites, reducing the duration of attack as well as the frequency of attacks will both be important in improving patients' lives.[24, 25]

Also, in the IOS study, before treatment, almost two thirds of attacks (65.5% [non-UK: 53.3%]) were severe (seriously interfering with daily activities and with or without other treatment) or very severe (seriously interfering with daily activities and other treatment required); 26.1% (non-UK: 37.2%) were moderate (moderately interfering

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with daily activities and no other treatment required), and 8.5% (non-UK: 9.5%) were mild or very mild (mild or very mild interference with daily activities).[14]

Impact of HAE on patient and carers

In addition to swelling, HAE attacks may be accompanied by a range of symptoms, depending on the attack location[16, 26]:

- Abdomen – abdominal pain, vomiting, diarrhoea, and abdominal cramping. Cases of hypovolemic shock resulting from fluid loss, plasma extravasation, and vasodilation have been reported in severe attacks
- Larynx, uvula, tongue or oesophagus – tightness of throat, dysphagia, dyspnoea, pain swallowing, voice changes, hoarseness, aphonia, stridor, globus sensation (feeling of a lump in the throat), and fear of asphyxiation. In severe attacks, laryngeal swelling can lead to asphyxiation and death
- Brain/head – severe headache, feeling of pressure behind the eyes, vomiting, visual disturbances, impaired balance, and disorientation
- Chest – tightness and pressure in the chest, dyspnoea, and chest pain
- Joint and muscle pain – pain and swelling of the shoulder and hip joints, and muscles of the neck, back, and arms
- Kidneys – renal pain and renal colic
- Urinary bladder/urethra – strangury, urinary stammering, retention of urine in the bladder, anuria, bladder spasms, and pain at micturition

HAE symptoms themselves, coupled with the ongoing fear of an attack, have a substantial impact on patient QoL. In the UK audit study of patients with HAE, patients were asked to rate the impact of HAE on their QoL.[15] Of the 223 adults questioned, 37% rated the impact as moderate or severe, whilst of the 29 parents who rated the impact on behalf of their children, 14% rated the impact as moderate, although none reported it severe.[15] Since then, a range of generic and HAE-specific QoL tools have been used to assess the impact of HAE on the patient.[27] Several studies have reported the impact on overall QoL by means of the generic EQ-5D® and SF-12® instruments:

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- A US study in 457 patients demonstrated that patients with HAE had significantly poorer QoL across all items of the SF-12 questionnaire ($p<0.001$), with a mean physical component summary (PCS) score of 43.7 (compared with 49.6 in the normal population) and a mean mental component summary (MCS) score of 42.6 (49.4 in the normal population).[28]
- A study of 21 adult patients with HAE in Canada also reported the detrimental impact of HAE on the SF-36®.[29] When the different domains were compared with heathy Canadians, patients with HAE had significantly impaired general health scores ($p=0.0063$), and overall mean PCS and MCS scores were 49.1 (versus 51.4 for healthy Canadians) and 50.3 (versus 52.6 for healthy Canadians).[29, 30]
- In a US study of 445 patients with HAE, patients with a greater attack frequency experienced worse QoL compared with those with a lower attack frequency. Both PCS and MCS scores were substantially higher in patients who had no attacks versus patients who had ≥13 attacks in the previous 6 months (PCS: 54.5 versus 42.3; MCS: 51.0 versus 42.8).[31]
- Utility values have also been estimated for HAE patients, using the EQ-5D instrument.
  - In a retrospective study of 103 patients with HAE in the Sweha-Reg census in Sweden, patients reported a utility score of 0.825 for the moment in time at which they were interviewed ("today score") and a mean score of 0.512 during an attack.[32] With increasing attack severity, the utility value during attacks decreased, and the difference between the utility today and during attacks was larger. A significant difference between the utility "today score" and the score during their latest attack was observed for all levels of severity but was greatest for severe attacks (-0.486; $p<0.0001$), followed by moderate (-0.369; $p<0.0001$), and mild attacks (-0.07; $p<0.05$).[32]
  - Based on findings from 111 patients with HAE from the Hereditary Angioedema Burden of Illness Study in Europe (HAE-BOIS-Europe) survey across Germany, Spain and Denmark, the detrimental impacts of HAE overall and of HAE attacks on patient utility were apparent.[33] Utility was 0.72 between HAE attacks and 0.44 during an acute attack, but substantially decreased with increasing attack pain (0.61 for no pain/mild pain, 0.47 for moderate pain, and 0.08 for severe pain).

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Disease-specific instruments have now been developed for use in patients with HAE, and studies using these have reported substantial impacts on QoL. The Angioedema Quality of Life instrument (AE-QoL)[34] has shown detriments in QoL and a Swedish study of 64 patients, with the main impacted areas being fears/shame and fatigue/mood.[35] Another disease-specific instrument, the Hereditary Angioedema Quality of Life questionnaire (HAE-QoL), was recently developed.[36] In a survey of 445 patients with HAE in the US, the HAE-QoL reported detriments in all domains measured, with generally greater negative impact as the frequency of HAE attacks increased.[31] QoL scores were also dependent on the location of the most recent attack, with lowest QoL observed for patients whose last attack involved the throat, and highest for those whose last attack was at the extremities only.[31]

Depression and anxiety are particular issues in patients with HAE, resulting from fear of attacks because of their unpredictable nature (severity, location and triggers are often unknown), pain, disfigurement, and the impact of attacks on daily activities. Depression and anxiety persist between attacks, as well as during them. In a European study of 186 HAE patients assessed with the Hospital Anxiety and Depression Scale (HADS), 38% of patients were found to have clinically meaningful anxiety and 14% had clinically meaningful depression, neither of which were limited to during attacks themselves.[37] In the aforementioned US survey of 445 HAE patients, half (49.9%) reported anxiety and 24.0% reported depression; anxiety/depression severity increased with increasing HAE attacks frequency.[31]

Physical functioning is greatly impacted in patients with HAE, especially during attacks themselves, and this has a subsequent effect on the patients' daily activities and ability to work. Data from 116 patients with HAE in a UK study reported that annually, each patient lost a mean of 9 days from work/school or where activities of daily living could be performed.[15] In another UK study, an audit of 73 UK patients within the IOS reported that 63.3% of patients missed work or education before the study, and 54.9% during the study.[14] Similar results were reported on the WPAI in the previously mentioned US study of 445 patients; work productivity loss was 25.4% and activity impairment was 31.8%.[31] Furthermore, work/activity impairment was reported to worsen with increased attack frequency and severity of anxiety and depression.[31] In the HAE-BOIS-Europe study, the impact of HAE on employment

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and daily activities was assessed.[38] The median amount of time lost on daily activities during an episode varied by site, from 2–4 hours for an abdominal attack to a substantial 12–24 hours for attacks at more than one site.[38] Of the 72 patients in the study reporting work/school absenteeism data, 56% reported missing time from work/school during the last attack, with a higher pain severity of the last attack being significantly associated with a greater productivity loss. Overall, each patient was estimated to miss 20 days of work/school per year due to HAE, and patients who reported severe pain during the recent attack had the highest absenteeism of approximately 28 days per year.[38] Patients with HAE may experience long-term impacts on their education and careers; a large proportion of patients questioned in the HAE-BOIS-Europe study felt that HAE had hindered their educational (42%) or career advancement (36%), or prevented them from applying for certain jobs (40%).[38]

In addition to the impact of the disease itself, patients with HAE also experience a burden in terms of treatment administration. Current long-term prophylaxis of HAE in the UK involves daily dosing of an oral treatment (e.g. danazol, oxandrolone), or intravenous (IV) administration of a C1-INH from a minimum of twice a week to a maximum of 4 times/week. Studies have reported on the issues associated with IV preparations in HAE; 62% of patients with HAE who used a peripheral vein to administer treatment reported difficulties in finding a usable vein, or getting the infusion to work properly.[39] In a survey on treatment preference, 50% of HAE patients who responded preferred a non-invasive administration method (i.e. oral, SC, or non-IV).[40] Furthermore, a higher frequency of administration is not only inconvenient for patients (and potentially carers), but is also associated with a higher frequency of injection-related side effects (e.g. rash/erythema, infusion site pain).[41]

As well as the significant impacts on patients themselves, carers and families of patients with HAE are also greatly affected by the condition. Of the 164 patients in the HAE-BOIS-Europe study, 86 (52%) reported having assistance from a caregiver during the last attack, and this proportion increased with increasing pain severity (69% of those with severe pain, 64% of those with moderate pain, and 26% of those with no/mild pain [$p<0.001$]).[38] Caregivers of those with severe pain also missed more work/leisure time during the last attack (2.1 days) than caregivers of patients

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with moderate pain (1 day) or no/mild pain (1.2 days) (p=0.015). In qualitative interviews with 30 patients participating in the HAE-BOIS-Europe study from Spain, Germany and Denmark, patients reported five key themes characterising the impact of HAE on QoL, of which caregiver impacts was one.[42] Patients perceived that attacks have a substantial impact on their caregivers, including an emotional burden of needing to be prepared to take the patient for treatment or administer the injection, as needed, as well as taking on additional responsibilities in the home while the patient is ill. Patients also indicated that caregivers had to miss work at times to accompany them to the hospital during severe attacks.[42] Caregivers also experience an ongoing burden in between attacks. In a Spanish study involving a focus group and in-depth interviews of 16 family caregivers of patients with HAE, caregivers spoke of their anguish, despair and bewilderment at the lack of specific HAE symptoms and the unpredictability of the attacks, as well as how the initial delay in diagnosis generated fear, anxiety, uncertainty, ignorance, isolation and incomprehension.[43]

Clinical pathway of care

Aside from avoiding triggers of HAE attacks, there are three main treatment strategies for patients with HAE:[6, 8, 23]

- Treatment of acute attacks
- Prophylactic treatment of acute attacks
  - Short-term prophylaxis of attacks before known triggers (e.g. dental work, surgery)
  - Long-term prophylaxis (LTP) of attacks to reduce the need for acute treatment.

Please note that this appraisal will cover only LTP of attacks in Type I and Type II HAE. The appraisal will not cover acute treatment or short-term prophylaxis of any HAE type, or LTP of HAE nC1-INH attacks.

Despite the existence of acute treatments, the IOS study revealed that of 854 attacks reported in 73 patients in the UK between February 2008 and July 2016, two thirds (568 attacks) were reported as untreated (although it should be noted that because IOS is an icatibant registry, data for attacks treated with acute C1-INH were not

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recorded).[14] The median annual number of untreated attacks per UK patient in the IOS study was 2.0, and the median duration of untreated attacks was substantially longer than treated attacks (72 versus 9.0 hours).[14] The issue of undertreatment of acute attacks only highlights further the importance of LTP in patients with HAE. Furthermore, the current National Health Service (NHS) Outcomes Framework issued by the Department of Health highlights the NHS commitment to preventing people from dying prematurely (Domain 1) and enhancing quality of life for people with long-term conditions (Domain 2).[44]

UK and global guidelines, and UK policy on the management of HAE are presented in Appendix L. Guidance from NHS England for the management of long-term prophylaxis of HAE, issued in 2016, recommends oral prophylaxis (androgens or anti-fibrinolytics) should be the first-line treatment for individuals at risk of attack. LTP with C1-INH is only considered as an option for patients meeting either of the following strict criteria, coupled with being under the care of a specialist team and involving a discussion on treatment eligibility between at least three consultant immunologists:[18]

- Patients who fail, or are intolerant of, oral prophylaxis and continue to experience two or more clinically significant attacks per week over a period of at least 56 days, requiring acute treatment with C1-INH or icatibant
- Patients who are contraindicated for oral prophylaxis (e.g. pregnant women)

In accordance with this guidance is the 2015 UK consensus statement, which states that attenuated androgens are considered effective as LTP for most people.[45] [redacted].[46] In accordance with the NHS England guidance, the UK consensus statement also indicated that C1-INH prophylaxis may be required when control of acute attacks is not otherwise possible by other means.[45] The consensus statement recognises poor evidence for the efficacy of anti-fibrinolytics (e.g. tranexamic acid) but that these may be useful in a minority of patients. However, in children, tranexamic acid is the drug of choice for prophylaxis, as the use of attenuated androgens should be avoided in pre-adolescent children.[45] It should be noted that

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the guidance from the World Allergy Organization (WAO) and European Academy of Allergy and Clinical Immunology (EAACI) issued in 2018 recommends C1-INH as first-line therapy and oral attenuated androgens as second-line LTP[6], while the UK guidance recommends the opposite.

In line with current UK guidance, the treatments for LTP are:

- Oral prophylaxis treatments:
  - Attenuated androgens (e.g. danazol and oxandrolone). These treatments do not have a marketing authorisation in the UK for HAE
  - Anti-fibrinolytics (e.g. tranexamic acid) may be used as oral prophylaxis in a minority of patients (including in children, for whom it is the recommended first choice[11, 45, 47]), although these are not recommended by the global WAO/EAACI guidelines
- Plasma-derived IV C1-INHs:
  - Cinryze® IV
  - Berinert® IV (licensed for acute treatment and short-term prophylaxis but not LTP)

  Please note that although Berinert® 2000/3000 subcutaneous (SC) is licensed in the UK, it is not commercially available in the UK. For the same reason it had not been included in the scope. Cinryze SC is not licensed or available in the UK.

- Recombinant C1-INH:

  - Ruconest® is a non-plasma-based C1-INH, produced by recombinant DNA technology in the milk of transgenic rabbits. It has a licence for acute use only and [redacted].[46]

Given that lanadelumab is expected to be used as an option in patients with HAE who are not adequately controlled with oral prophylaxis or for when oral prophylaxis is not suitable, the relevant comparator for lanadelumab is prophylactic treatment with plasma-derived IV C1-INHs (Cinryze IV and Berinert IV).

Key differences between lanadelumab and the plasma-derived C1-INHs (Cinryze IV and Berinert IV) are presented in Table 3.

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Table 3: Differentiation between lanadelumab and potential comparators

	Lanadelumab[1, 3]	Plasma-derived IV C1-INHs	
		Cinryze IV[41]	Berinert IV[48]
EMA licence terms	Indication wording: • "Lanadelumab is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older."	Indications: • "Treatment and pre-procedure prevention of angioedema attacks in adults, adolescents and children (2 years old and above) with hereditary angioedema (HAE). • Routine prevention of angioedema attacks in adults, adolescents and children (6 years old and above) with severe and recurrent attacks of hereditary angioedema (HAE), who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment."	Indications: • "Hereditary angioedema Type I and II (HAE) • Treatment and pre-procedure prevention of acute episodes."
NICE recommendations	Currently under appraisal	Not appraised by NICE. C1-INH recommended by NHS England for LTP treatment[18]	Not appraised by NICE. C1-INH recommended by NHS England for LTP treatment,[18] although Berinert does not have a license for LTP
Dosing and administration	SC injection The recommended starting dose is 300mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction of 300mg lanadelumab every 4 weeks	IV injection Adults and adolescents (aged ≥12 years): 1000IU of Cinryze every 3 or 4 days is the recommended starting dose for routine prevention against angioedema attacks; the dosing interval may need to be adjusted	IV infusion or injection No approved dose for LTP as Berinert is not approved in this indication. Dosing for short-term prophylaxis:

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	Lanadelumab[1, 3]	Plasma-derived IV C1-INHs	
		Cinryze IV[41]	Berinert IV[48]
	may be considered, especially in patients with low weight.	according to the individual response. The continued need for regular prophylaxis with Cinryze should be reviewed on a regular basis.	• Adults: 1000IU, <6 hours prior to a medical, dental, or surgical procedure • Paediatrics: 15 to 30IU per kilogram body weight (15–30IU/kg body weight), <6 hours prior to a medical, dental, or surgical procedure For LTP, assume use of [redacted][46, 49]
Precautions for use/ contraindications	Contraindication: • Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 of the SPC (disodium phosphate dihydrate; citric acid monohydrate; histidine; sodium chloride; polysorbate 80; water for injections) Special warnings and precautions for use: • In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. • Hypersensitivity reactions have been observed. In case of a severe hypersensitivity reaction, administration of lanadelumab must be stopped immediately and	• Thrombotic events have been reported in neonatal and infant patients undergoing cardiac bypass procedures while receiving high doses of another C1-INH (up to 500units/kg) to prevent capillary leak syndrome. • Standard measures to prevent infections resulting from the use of human blood-/plasma-derived products include: selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived Cinryze.	• In patients with known tendency towards allergies, antihistamines and corticosteroids should be administered prophylactically. If allergic or anaphylactic-type reactions occur, Berinert must be stopped immediately (e.g. discontinue injection/infusion) and an appropriate treatment initiated. • Unlicensed use or treatment of Capillary Leak Syndrome (CLS) with Berinert is not advised. • Berinert contains up to 486mg sodium (~21mmol) per 100ml solution. To be taken into consideration by patients on a controlled sodium diet. • There are limited data on Berinert use in home- or self-administration. Potential risks are related to the administration itself and the

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	Lanadelumab[1, 3]	Plasma-derived IV C1-INHs	
		Cinryze IV[41]	Berinert IV[48]
	appropriate treatment must be initiated. • Lanadelumab is not intended for treatment of acute HAE attacks. In case of a breakthrough HAE attack, individualised treatment should be initiated with an approved rescue medication. • There are no available clinical data on the use of lanadelumab in HAE patients with normal C1-INH activity. • Lanadelumab can increase activated partial thromboplastin time (aPTT) due to an interaction of lanadelumab with the aPTT assay. The reagents used in the aPTT laboratory test initiate intrinsic coagulation through the activation of plasma kallikrein in the contact system. Inhibition of plasma kallikrein by lanadelumab can increase aPTT in this assay. None of the increases in aPTT in patients treated with lanadelumab were associated with abnormal bleeding adverse events. There were no differences in international normalised ratio (INR) between treatment groups.	• Every time Cinryze is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product. • Hypersensitivity reactions may occur, and can have symptoms similar to angioedema attacks. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur after administration, patients should alert their physician. In case of anaphylactic reactions or shock, administer emergency medical treatment. • There are limited data on Cinryze use in home- or self-administration. Potential risks are related to the administration itself and the handling of AEs, particularly hypersensitivity. • Each vial of Cinryze contains ~11.5mg sodium and should be	handling of AEs, particularly hypersensitivity. • Standard measures to prevent infections resulting from the use of human blood-/plasma-derived products include: selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived Berinert. • Every time Berinert is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

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	Lanadelumab[1, 3]	Plasma-derived IV C1-INHs	
		Cinryze IV[41]	Berinert IV[48]
	• This medicinal product contains less than 1mmol sodium (23mg) per vial, that is to say essentially 'sodium-free'. Side effects listed in the CHMP positive opinion: • The most common side effects are injection site reactions (including pain, erythema and bruising). Of these, 97% were of mild intensity.	considered when treating patients on a controlled sodium diet.	
Monitoring needs	No additional monitoring required over and above usual clinical practice	• Patients with known risk factors for thrombotic events (including indwelling catheters) should be monitored closely • The use of home treatment (if used) should be reviewed by the treating physician at intervals • Check that patients are not receiving a controlled sodium diet	• Patients with laryngeal oedema require particularly careful monitoring with emergency treatment in stand-by • The use of home treatment should be reviewed by the treating physician at intervals • Check patients are not receiving a controlled sodium diet
Key: aPTT, activated partial thromboplastin time; AE, adverse event; C1-INH, C1 esterase inhibitor; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; HAE, hereditary angioedema; IV, intravenous; LTP, long-term prophylaxis; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SC, subcutaneous; SPC, summary of product characteristics.			

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Current plasma-derived C1-INHs (Cinryze IV and Berinert IV) have several limitations:

- Firstly, these treatments do not prevent all attacks. Data for LTP of Berinert IV are sparse, but data for 47 patients with HAE have been obtained from the Berinert Patient Registry in the US, Germany, Denmark and Switzerland. The study found 31.9% had no attacks within the first 7 days after infusion with Berinert IV, while the remainder had at least one attack within 7 days of infusion.[50] Cinryze has been more widely studied. In the randomised, placebo-controlled, 24-week-crossover CHANGE trial of 22 patients, the normalised attack rate was 6.26 for patients receiving Cinryze prophylaxis, compared with 12.73 for those receiving placebo.[51] Furthermore, in an open-label extension study of the CHANGE trial involving 146 patients with HAE receiving prophylaxis with Cinryze over 2.6 years, only 34.9% reported no attacks during the study, and of the patients with attacks, 87.7% reported ≤1 attacks per month and 12.3% reported ≥1 attacks per month during the study.[52] Further data from Cinryze studies are presented within the systematic literature review (SLR) report.[53]
- Additionally, plasma-derived C1-INHs are associated with the potential for thromboembolic events and infections, as described in their SPCs.[41, 48]
- Berinert and Cinryze are both IV products. Several issues exist with IV preparations in HAE, including finding a usable vein, getting the infusion to work properly, issues accessing veins, exhausted veins, occlusion, thrombosis, and infections.[39] In a study of 50 patients with HAE receiving IV C1-INH treatment as on-demand or prophylaxis, 62% of those who used a peripheral vein to administer treatment reported having difficulty finding a usable vein or getting the infusion to work properly at least some of the time.[39] In another study of 150 patients with HAE, of those who responded 50% preferred a non-invasive method of administration, such as oral (24%), SC (18%), or non-IV (8%) routes.[40]
- Finally, plasma-derived IV C1-INHs have a greater frequency of administration (every 2–4 days), as reported in Table 3. A less frequent administration would likely improve patient convenience and minimise injection-related side effects (e.g. injection site rash/erythema, infusion site pain[41]). Indeed, a reduction in dose frequency has previously shown a significant association with improved

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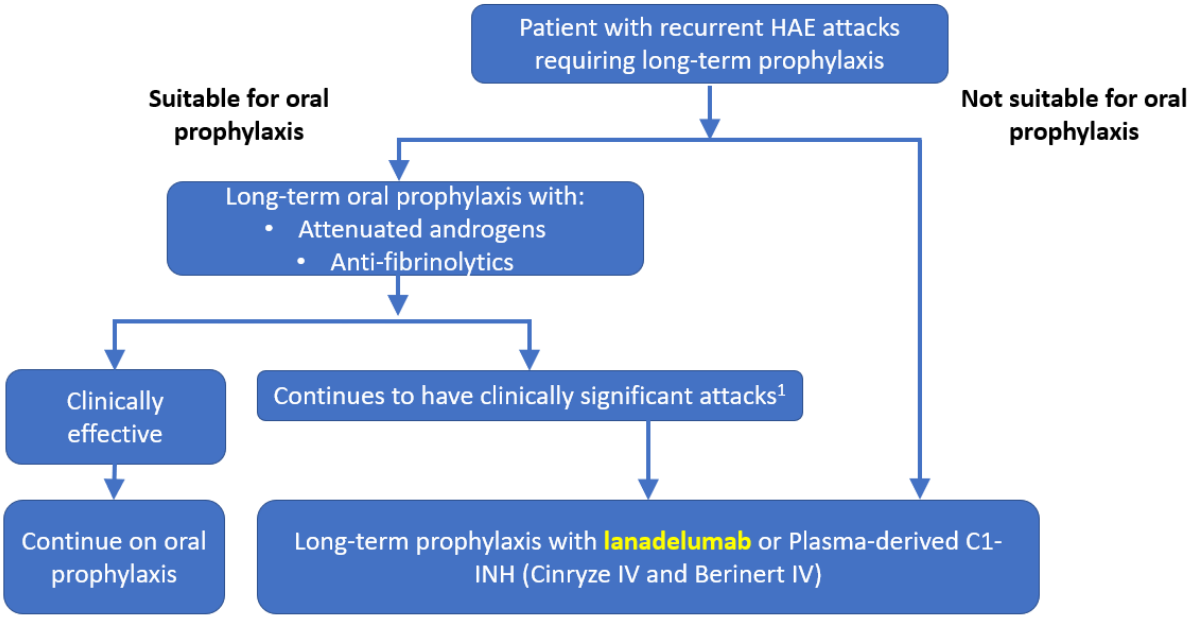
adherence and compliance, as well as reduced healthcare costs, in a range of disease areas.[54-57]

Based on the points above, it is clear that there remains a high unmet need for an effective and well-tolerated treatment that improves the potential for attack-free status, involves a convenient and less invasive mode of administration and requires a lower frequency of administration.

Figure 2 presents the current clinical pathway in the UK for LTP management of HAE, including the proposed place for lanadelumab.[18] Lanadelumab, in line with the EMA license, is proposed as an option for LTP in patients aged 12 years and older who are experiencing at least one HAE attack per month despite oral prophylaxis (androgens or anti-fibrinolytics), or for whom oral prophylaxis is not suitable (Figure 2).

Figure 2: Current clinical pathway for LTP management of HAE in the UK and proposed positioning of lanadelumab



Key: C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; IV, intravenous.
Notes: [1]A clinically significant attack is defined as one that i) is potentially life threatening because it affects the head or neck or ii) causes pain or disability such that the patient cannot continue their normal activities.[18]

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B.1.4. Equality considerations

No equity or equality issues are anticipated for the appraisal of lanadelumab. However, the following points were discussed at the NICE scoping meeting for consideration in the appraisal[58]:

- Attenuated androgens can affect a woman's fertility because of the risk of virilisation to the female foetus. As such, these are not prescribed to adolescents or women who have not completed their family. The marketing authorisation for danazol states that 'Women of childbearing age should be advised to use an effective, non-hormonal method of contraception'. Therefore, consideration should be given to the treatment options available to women who have completed their family to ensure that any recommendations as a result of this appraisal do not directly or indirectly discriminate on the basis of gender. Lanadelumab does not impact on a woman's ability to have a family.
- The three currently available C1-INHs included in the scope are derived from either human plasma (Cinryze IV and Berinert IV) or rabbit DNA (Ruconest), with which some religious groups may be unwilling to be treated. As such, consideration should be given to treatment options available for people who are unwilling to receive human or animal products, to ensure that any recommendations do not directly or indirectly discriminate on the basis of religion. Lanadelumab is not based on human or animal products.

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B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised. A systematic literature review (SLR) was performed in June 2017 and subsequently updated in July 2018, to identify published clinical trial data on the efficacy and safety of long-term prophylaxis therapies, including lanadelumab in patients aged 12 years and older with HAE. Full details are presented in the SLR report.[53] The updated SLR identified ten randomised control trials (RCTs) that evaluated either lanadelumab or other relevant long-term prophylaxis therapies in this treatment setting. These included:

- Two lanadelumab studies (Phase 1b study [DX-2930-02] and Phase III HELP-03)
- One plasma-derived C1-INH IV (Cinryze) study
- Four plasma-derived C1-INH SC (two Cinryze, two Haegarda) studies
- One non-plasma-derived C1-INH IV (Ruconest) study
- Two androgen (one danazol and one methyl testosterone) studies

However, as described in Section B.1.3, current UK guidelines recommend oral prophylaxis (androgens or anti-fibrinolytics) as first-line treatment for individuals at risk of attack, and long-term prophylactic C1-INH IV injections are considered as an option for patients who fail, or are intolerant of, oral prophylaxis.[18] As such:

- The two androgen (danazol and methyl testosterone) studies were excluded from the submission as they are not considered relevant comparators for this submission.
- The four plasma-derived C1-INH SC (two Cinryze, two Haegarda) studies were excluded from the submission, as no plasma-derived C1-INH SC therapies are currently approved in the UK for long-term prophylactic treatment, therefore, they are not considered relevant comparators.

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- The one non-plasma-derived C1-INH IV (Ruconest) study was excluded from the submission as [redacted][46]; therefore is not considered a relevant comparator. Moreover, it was a phase II study with a very short follow-up (4 weeks).

The two lanadelumab studies (Phase 1b study and Phase III HELP-03 RCT) identified in the SLR directly compared the efficacy and safety of lanadelumab versus placebo. Furthermore, the unpublished, ongoing, open-label, long-term extension study (HELP-04), also provides evidence for the use of lanadelumab. Data from these three studies will form the basis of this submission and are presented throughout the following sections.

Evidence from the one plasma-derived C1-INH IV study identified in the SLR, has been used to the inform the indirect treatment comparison (ITC) presented in Section B.2.9.

Non-RCT evidence identified in the SLR were not used for comparative effectiveness.

B.2.2. List of relevant clinical effectiveness evidence

The pivotal, regulatory evidence to support lanadelumab for the treatment of HAE is the Phase III HELP-03 study and the open-label HELP extension study (HELP-04), and these studies are the focus of this submission.

Summaries of the HELP-03 study and the long-term extension HELP-04 study are presented in Table 4 and Table 5, respectively, and further details of the design of these studies are provided in Section B.2.3. One further lanadelumab study was identified in the SLR described in Section B.2.1. This was the Phase Ib study, DX-2930-02. A summary of the Phase Ib lanadelumab study DX-2930-02 is presented in Table 6, and a brief summary of its results is provided in Appendix P.

Table 4: Clinical effectiveness evidence – HELP-03

Study	HELP-03: NCT02586805[59, 60]
Study design	HELP-03 was a Phase III, multicentre, randomised, double-blind, placebo-controlled trial.

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<table>
<tr><td>Population</td><td colspan="5">People aged 12 years and older with hereditary angioedema Types I or II who have at least one angioedema attack in 4 weeks in the run-in period</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Lanadelumab 300mg q4w (n=29)
Lanadelumab 300mg q2w (n=27)
Lanadelumab 150mg q4w (n=28)</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Placebo (n=41)</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">HELP-03 presents the pivotal, regulatory and clinical evidence in support of lanadelumab in the population directly relevant to the decision problem.</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• Frequency of angioedema attacks (attack rate during treatment period [Day 0 to Day 182]; between Day 14 and Day 182; and between Day 70 and Day 182)
• Severity of angioedema attacks (number of patients with moderate or severe attacks during treatment period)
• Need for acute treatment
• Mortality
• Adverse effects of treatment
• Health-related quality of life</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• Time to first attack after Day 0 and Day 70
• High morbidity attacks in treatment period (severe, hospitalised, hemodynamically significant or laryngeal)
• Proportion of responders with a ≥50% reduction in attack rate
• Proportion of responders with a 100% reduction in attack rate
• Mean attack-free days (Day 0 to Day 182; Day 0 to Day 28; Day 0 to Day 84; Day 70 to Day 182)</td></tr>
<tr><td colspan="6">Key: q2w, every 2 weeks; q4w, every 4 weeks
Source: HELP-03 CSR[59]; Banerji et al., 2018[60]</td></tr>
</table>

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Table 5: Clinical effectiveness evidence – HELP-04

Study	HELP-04: NCT02741596[61, 62]				
Study design	HELP-04 is an ongoing Phase III, multicentre, open-label, long-term safety and efficacy study.				
Population	**HELP-03 rollover patients:** Patients who completed the 26-week treatment period in HELP-03 and enrolled in the open-label extension study HELP-04 **Non-rollover patients:** Patients aged 12 years and older with HAE Types I or II who had a historical baseline attack rate of at least one attack per 12 weeks				
Intervention(s)	**HELP-03 rollover patients (n=109):** 300mg dose at Day 0 followed by 300mg q2w following first HAE attack. **Non-rollover patients (n=103):** 300mg dose at day 0 then 300mg q2w for the entire study.				
Comparator(s)	N/A				
Indicate if trial supports application for marketing authorisation	Yes		**Indicate if trial used in the economic model**	Yes	
	No	✓		No	✓
Rationale for use/non-use in the model	As HELP-04 is currently an ongoing study, it was therefore not used in the model.				
Reported outcomes specified in the decision problem	N/A				
All other reported outcomes	• Long-term safety of lanadelumab • Long-term efficacy of in preventing HAE attacks over 132 weeks				
Key: HAE, hereditary angioedema; N/A, not applicable; q2w, every 2 weeks; q4w, every 4 weeks. **Source:** NCT02741596[61]; Riedl et al. 2017;[62] Riedl et al., 2018[63]					

Table 6: Clinical effectiveness evidence – DX-2930-02

Study	DX-2930-02: NCT02093923[64]				
Study design	DX-2930-02 was a Phase Ib, multicentre, randomised, double-blind, placebo-controlled, multiple-ascending-dose study.				
Population	People aged 12 years and older with hereditary angioedema Types I or II who had two or more attacks of angioedema per year, with at least one attack in the previous 6 months				
Intervention(s)	Lanadelumab 30mg q2w (n=4) Lanadelumab 100mg q2w (n=4) Lanadelumab 300mg q2w (n=5) Lanadelumab 400mg q2w (n=11)				
Comparator(s)	Placebo (n=13)				
	Yes			Yes	

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Indicate if trial supports application for marketing authorisation	No	✓	**Indicate if trial used in the economic model**	No	✓
Rationale for use/non-use in the model	DX-2930-02, a Phase Ib study, was not used in the model as results from the Phase III HELP-03 study superseded it.				
Reported outcomes specified in the decision problem	N/A				
All other reported outcomes	• HAE attack rate per week • Safety				
Key: q2w, every 2 weeks **Source:** Banerji et al. 2017[64]					

The HELP-04 study is currently ongoing and was therefore not used to populate the economic model, but details of the study are included in Sections B.2.2 to B.2.6. The results of this study support the long-term safety and efficacy of lanadelumab.

The results from DX-2930-02 were not included in the economic model because results from the pivotal Phase 3 HELP-03 study superseded them, but details of the study are included in Section B.2.2. The results of this study support the results observed in the HELP-03 study.

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

Design of the HELP-03 study and the open-label extension study HELP-04

A summary of the methodology used in the Phase III clinical trial HELP-03 and the open-label extension study HELP-04 is presented in Table 7.

Trial design

The HELP-03 study was a Phase III, multicentre, randomised, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of lanadelumab in the LTP of acute attacks in patients with Type I or Type II HAE. As depicted in Figure 3, the HELP-03 study consisted of a 2-week screening period, a 4-week run-in period, a 26-week double-blind treatment period, and either an open-label extension study or an 8-week follow-up period.

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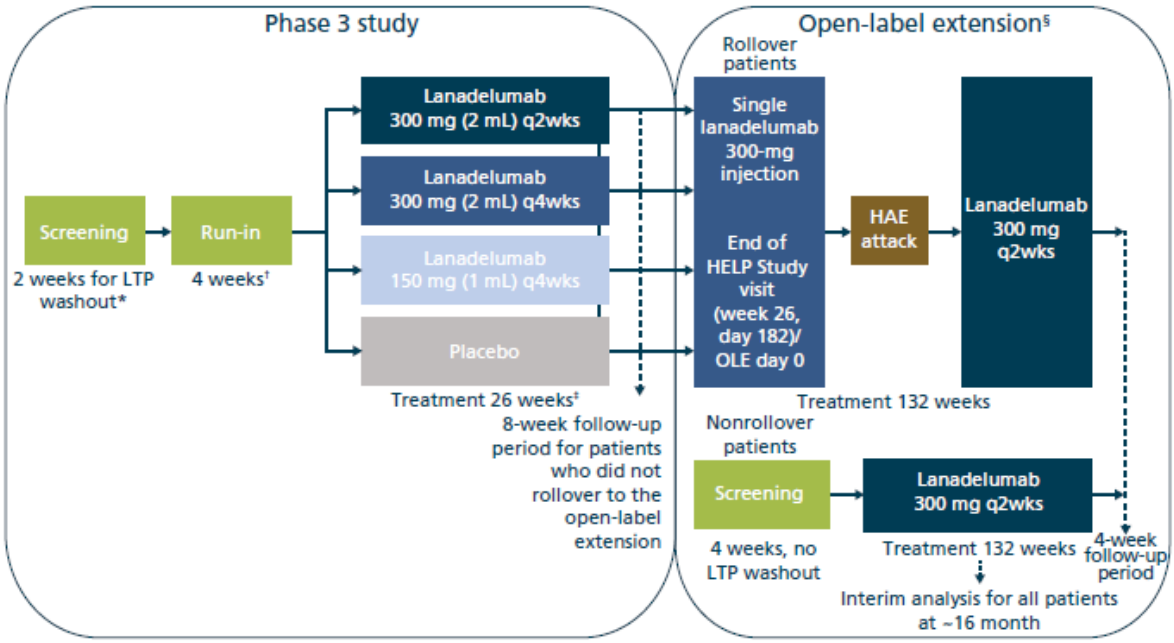
Figure 3: HELP-03 and the open-label extension study HELP-04 study design



Key: HAE, hereditary angioedema; LTP, long-term prophylaxis; q2wks, every 2 weeks; q4wks, every 4 weeks.
Notes: *, LTP washout only for patients ≥18 years of age; †, Run-in period could be shortened if the patient experienced ≥3 attacks before completion of 4 weeks; run-in period could be extended to 8 weeks if the patient did not experience any attacks during 4 weeks; ‡, Treatments administered as 2 separate 1-mL injections in the upper arm q2wks to maintain the blind; §, NCT02741596.
Source: Riedl *et al.* 2018[63]

Following screening and prior to the start of the run-in period, patients who were on LTP therapy for HAE were required to undergo a minimum 2-week washout period. However, the LTP washout period was only permitted if doing so would not place the patient at any undue safety risk and the patient was at least 18 years of age.

Screened patients who were either not on LTP therapy for HAE or who had completed the required washout period entered a run-in period of 4 weeks to determine the baseline HAE attack rate. Only patients meeting a minimum baseline rate of at least one investigator-confirmed HAE attack per 4 weeks were eligible for enrolment and randomisation. Patients who experienced three or more investigator-confirmed attacks before the end of the 4 weeks were allowed to exit the run-in period early and proceed to enrolment and randomisation. Patients who did not meet the minimum baseline attack rate had their run-in period extended for a further 4 weeks. In order to proceed to enrolment and randomisation, these patients were required to have a minimum of two investigator-confirmed attacks during this

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extension period. Patients who did not meet the minimum attack rate during the run-in period or were otherwise determined to be ineligible due to screening assessments were considered screen failures. These patients were not allowed to rescreen for the study at a later stage.

Randomisation

After verification of eligibility (see Table 7 for further details), patients were randomised 2:1 to receive repeated SC administrations of lanadelumab or placebo in a double-blind fashion via an Interactive Web-based Randomisation System (IWRS). Patients who were randomised to lanadelumab were assigned in a 1:1:1 ratio to one of three dose regimens:

- 300mg every 2 weeks (q2w)
- 300mg every 4 weeks (q4w)
- 150mg q4w

Randomisation into all treatment groups was stratified by the baseline attack rate observed during the run-in period into the following groups:

- One or two attacks per 4 weeks
- Two or three attacks per 4 weeks
- More than three attacks per 4 weeks

Following randomisation, each patient entered a treatment period consisting of 13 doses of blinded investigational product, for a period of 26 weeks from the date of first dose on Day 0 through 2 weeks after the final dose.

Enrolment into the open-label extension study (HELP-04)

All patients who completed the 26-week treatment period in HELP-03 were given the option to enrol in the open-label extension study HELP-04 or to enter an 8-week safety follow-up. Patients who consented to participate in HELP-04 (rollover patients) received their first open-label dose following the completion of all double-blind assessments scheduled on Day 182. Rollover patients received their first dose of lanadelumab 300mg on Day 0 then entered a “dose-and-wait” phase, where they would not receive another dose until their first attack. They received lanadelumab

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300mg q2w thereafter. In contrast, patients who elected not to participate in HELP-04 underwent safety and additional evaluations during an 8-week follow-up period. These patients were instructed to inform the site of any HAE attack experienced for up to 30 days after the final follow-up visit on Day 238.

In addition, non-rollover patients who did not participate in the HELP-03 study but who may or may not have been receiving prophylactic therapy were enrolled in the open-label extension study HELP-04. Non-rollover patients received open-label lanadelumab 300mg on Day 0 followed by 300mg q2w until the end of the study regardless of the first attack, for a total of 26 doses.

Definition and rationale of endpoints

The primary efficacy endpoint of the HELP-03 study comparing each active treatment group (lanadelumab) to the placebo group was the number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182). Lanadelumab has been developed for the LTP of attacks in HAE Type I and II (Figure 2). Therefore, the prevention of HAE attacks as an endpoint was appropriate, and the number of investigator-confirmed HAE attacks was a direct way of measuring efficacy. However, as patients can self-administer acute attack medication in real-world clinical practice, not all HAE attacks will be diagnosed by medical professionals.[65] Therefore, a sensitivity analysis on the primary efficacy endpoint was conducted that included all patient-reported HAE attacks instead of limiting the analysis to those attacks that were investigator-confirmed (see Section B.2.6 and Appendix M). This will be discussed further in Section B.2.13.

In the HELP-03 study, to be confirmed as an HAE attack the event must have had symptoms or signs consistent with an attack in at least one of the following locations:

- Peripheral angioedema: cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region
- Abdominal angioedema: abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhoea
- Laryngeal angioedema: stridor, dyspnoea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx

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Despite the presence of these symptoms, the investigator may have clinically determined that the event did not represent an HAE attack if there were features that strongly refuted such a diagnosis – for example, if the reported event was accompanied by symptoms that were not consistent with an HAE attack (e.g. urticaria), the reported event persisted well beyond the typical time course of an HAE attack, or there was a likely alternate aetiology for the event (e.g. the patient's abdominal symptoms are attributable to a viral gastroenteritis outbreak in the household). Furthermore, to be counted as a unique attack, distinct from the previous attack, the new symptoms had to occur at least 24 hours after resolution of the prior attack's symptoms. The definition of a HAE attack used in the HELP-03 study is in line with what is used in clinical practice (Section B.1.3). This will be discussed further in Section B.2.13.

In the HELP-03 study, the generic 5-level EQ-5D (EQ-5D-5L) and disease-specific AE-QoL tools were used to assess changes in patient QoL. The AE-QoL tool was developed and validated as the first symptom-specific patient-reported-outcome tool to assess QoL impairment in any type of recurrent angioedema patients over time, including assessing changes due to treatment.[66] The AE-QoL consists of 17 items that address four dimensions – functioning, fatigue/mood, fears/shame, and food – and is sensitive to change, with a minimal clinically important difference of six points.[34] Given its demonstrated validity for use in HAE, and that at the time of study this was the only disease-specific QoL tool available, the AE-QoL was selected as the most appropriate tool for measuring changes in QoL in HAE patients. This will be discussed further in Section B.2.13.

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Table 7: Summary of methodology of HELP-03 and HELP-04

Trial number (acronym)	NCT02586805 (HELP-03)	NCT02741596 (HELP-04)
Location	The study was conducted at 41 centres in six countries: Canada, Germany, Italy, Jordan, the UK, and the US.	This study is being conducted in 43 sites across six countries: Canada, Germany, Italy, Jordan, the UK, and the US.
Trial design	HELP-03 was a Phase III, multicentre, randomised, double-blind, placebo-controlled study conducted to evaluate the efficacy and safety of lanadelumab in preventing acute angioedema attacks in patients with Type I or Type II HAE.	HELP-04 is an ongoing Phase III, multicentre, open-label, long-term safety and efficacy study to evaluate lanadelumab in preventing acute (on-demand) angioedema attacks in patients with Type I and Type II HAE.
Eligibility criteria for participants	**Inclusion criteria:** • Males and females 12 years of age or older at the time of screening • Documented diagnosis of HAE (Type I or II) based upon all of the following: – Documented clinical history consistent with HAE (SC or mucosal, nonpruritic swelling episodes without accompanying urticaria) – Diagnostic testing results obtained during screening that confirmed HAE Type I or II: C1-INH functional level <40% of the normal level. Patients with functional C1-INH level 40–50% of the normal level may have enrolled if they also had a C4 level below the normal range. Patients may have begun participating in the run-in period before these diagnostic results were available. Patients may have retested if results were incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use – At least one of the following: age at reported onset of first angioedema symptoms ≤30 years, a family history consistent with HAE Type I or II, or C1q within normal range	**Inclusion criteria** Rollover patients: • All patients enrolled in the HELP-03 study were eligible for rollover into the open-label extension study HELP-04 (Figure 3). Non-rollover patients: • Male or female patients who are ≥12 years of age at the time of screening • Patients must have documented confirmation of type I/II HAE. Confirmation requires all of the following: – A clinical history consistent with HAE – Diagnostic testing results that confirm HAE (C1-INH functional level <40% of normal. Patients with functional C1-INH at 40–50% of normal may be enrolled if they also have a C4 level below the normal range)

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	• Experienced a baseline rate of at least one investigator-confirmed HAE attack per 4 weeks as confirmed during the run-in period • Adult patients and caregivers of patients under the age of 18 years who were willing and able to read, understand, and sign an informed consent form. Patients aged 12–17 years, whose caregiver provided informed consent, were willing and able to read, understand and sign an assent form • Males and females who were fertile and sexually active must have adhered to contraception requirements for the duration of the study as follows: Females of childbearing potential must have agreed to be abstinent or it was recommended to use highly effective forms of contraception from screening through 30 days after the final study visit. This included progestin-only oral contraceptive associated with inhibition of ovulation (oral, injectable or implantable), Intrauterine Device (IUD) (all types) or intrauterine hormone releasing systems (IUS) – Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months did not require contraception during the study – Males, including males who were surgically sterile (post-vasectomy), with female partners of childbearing potential, must have agreed to be abstinent or else used a medically acceptable form of contraception from screening through 60 days after the final study visit **Exclusion criteria:** • Concomitant diagnosis of another form of chronic, recurrent angioedema, such as AAE, HAE nC1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria	– Either age of onset of first angioedema symptoms ≤30 years, a family history consistent with HAE, or C1q within normal range. • Patients must have a historical baseline attack rate of at least one attack per 12 weeks • Patients and/or their caregivers (as appropriate) must be able to provide informed consent or assent (as appropriate) • Patients must adhere to contraception requirements for the duration of the study **Exclusion criteria:** • Patients who discontinued from the HELP-03 study after enrolment were not be eligible to enrol in the open-label extension study. • If rolling over from the HELP-03 study, the presence of safety concerns that would preclude participation in the extension study. • Concomitant diagnosis of another form of chronic recurrent angioedema such as acquired angioedema, HAE with normal C1-INH, idiopathic angioedema, or recurrent angioedema associated with urticaria. • Exposure to an investigational drug (excluding lanadelumab or other HAE therapies) or investigational device within 4 weeks prior to screening. • Exposure to ACE inhibitors within 4 weeks prior to screening or exposure to any newly initiated or modified dose of systemic oestrogen-containing medications within 3 months prior to screening.

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	• Participation in a prior lanadelumab study • Dosing with an investigational drug or exposure to an investigational device within 4 weeks prior screening • Exposure to ACE inhibitors or any oestrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening • Exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 2 weeks prior to entering the run-in period • Use of LTP therapy for HAE (C1-INH, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to entering the run-in period • Use of short-term prophylaxis for HAE within 7 days prior to entering the run-in period. Short-term prophylaxis was defined as C1-INH, attenuated androgens, or antifibrinolytics used to avoid angioedema complications from medically indicated procedures • Any of the following liver function test abnormalities: ALT >3x upper limit of normal, or AST >3x upper limit of normal, or total bilirubin >2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome) • Pregnancy or breastfeeding • If the patient had any condition that, in the opinion of the investigator or Sponsor, may have compromised their safety or compliance, precluded successful conduct of the study, or interfered with interpretation of the results (e.g. history of substance abuse or dependence, significant pre-existing illness or other major comorbidities that the Investigator may have considered confounding the interpretation of study results)	• Unwilling to discontinue use of long-term prophylaxis (C1-INH, androgens or anti-fibrinolytics) within 3 weeks after starting lanadelumab treatment. • Presence of liver function abnormalities. • Pregnant or breastfeeding. • Presence of any condition that, in the opinion of the investigator or sponsor, may compromise the patient's safety or compliance, preclude successful conduct of the study or interfere with interpretation of the results.

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Settings and locations where the data were collected	125 patients were randomised at 41 clinical sites in 6 countries, as follows: • 32 clinical sites in the US: n=86 • 5 clinical sites in Europe: n=29: – 3 clinical sites in Germany: n=18 – 1 clinical site in Italy: n=6 – 1 clinical site in the UK: n=5 • 3 clinical sites in Canada: n=7 • 1 clinical site in Jordan: n=3	Patients were included from 43 study sites across 6 countries, USA (32 sites), Canada (4 sites), Germany (4 sites), Italy (1 site), Jordan (1 site), UK (1 site).
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	Patients received a SC dose of blinded investigational or reference product every 2 weeks during the 26-week treatment period for a total of 13 doses. Patients were randomised to receive any one of the following dosing regimens: • Lanadelumab 300mg q2w (n=27) • Lanadelumab 300mg q4w (n=29) • Lanadelumab 150mg q4w (n=28) • Placebo q2w (n=41) Placebo doses were administered SC to patients randomised to the placebo arm and in between doses of lanadelumab for patients randomised to the 300mg or 150mg lanadelumab q4w treatment arms. • For each 300mg dose of lanadelumab, each patient received a total of 2ml, divided into two separate 1.0ml SC injections of lanadelumab (Note: lanadelumab drug product is provided at a nominal concentration of 150mg/ml solution) • For each 150mg dose of lanadelumab, each patient received two separate 1.0ml SC injections to maintain the blinding, where one injection was lanadelumab and the other was placebo.	• **Rollover patients (n=109):** Patients received a SC dose of lanadelumab 300mg on day 0 of the open-label extension study. The second dose of lanadelumab will not be administered until after the first investigator-confirmed HAE attack. Thereafter, rollover patients received lanadelumab 300mg q2w until the end of the study. • **Non-rollover patients (n=103):** Patients received a SC dose of lanadelumab 300mg at day 0 of the open-label extension study followed by with dosing for the study continuing q2w until the end of the study, regardless of the first attack, for a total of 26 doses.

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	• For each placebo dose, each patient received a total of 2ml, divided into two separate 1.0ml SC injections of placebo In order to maintain the double-blind design, regardless of treatment assignment, all patients were to receive two SC injections of blinded investigational or reference product administered in the same upper arm (rotated between the left upper arm and the right upper arm for treatment visits), with at least 2cm separation between each injection site. A 27 gauge ½ inch syringe was recommended for subcutaneous injection according to the comfort of the patient.	
Permitted and disallowed concomitant medication	The following concomitant therapies were permitted during the study: • Therapies for co-existing conditions, including those for acute attacks of HAE, were permitted if not mentioned in the list of disallowed drugs below. Acute HAE attacks during the study were to be managed in accord with the investigator's usual care of their patients, including use of individualised acute therapy that the investigator deems as medically appropriate. Use of C1-INH was permitted as an acute attack therapy but not as LTP. Administration of the investigational product and study procedures were to continue without alteration to the protocol specified study schedule, even if the patient received any treatment for an HAE attack • The use of short-term prophylactic treatment for HAE was permitted if medically indicated • Therapies to treat any AEs the patient experienced during the study were permitted Use of the following treatments was disallowed during the study: • Long-term prophylaxis for HAE (e.g. use of C1-INH for long-term prophylaxis, attenuated androgens, or anti-fibrinolytics) • ACE inhibitors	The following concomitant therapies were permitted during the study: • Therapies for coexisting conditions, including the treatment of angioedema attacks and short-term prophylaxis, are permitted as described below • In the absence of formal guidelines for withdrawal of LTP, our approach is based on clinical expert recommendations. Current LTP therapies will be tapered off – Use of C1-INH may continue until Day 15 – Androgens or anti-fibrinolytics may also be used up to Day 15 but, if necessary, may be extended until a maximum of 3 weeks after the first lanadelumab dose – The use of C1-INH as a short-term (pre-procedure) prophylactic treatment for HAE will be permitted if medically indicated Use of the following treatments was disallowed during the study: • LTP is not be permitted once it has been discontinued, as described above

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	• Oestrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) • Androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) • Any other investigational drug or device	• Androgens may not be used for HAE or for any medical condition • Use of ACE inhibitors, oestrogen-containing medications with systemic absorption, and any other investigational drug or device is not permitted
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy endpoint comparing each active treatment group (lanadelumab) to the placebo group was the number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182), assessed in accordance with HAE Attack Assessment and Reporting Procedures (HAARP). For further details of HAARP please refer to the HELP-03 clinical trial protocol (specifically Amendment 3.0, Appendix 4).[67]	The primary outcome of this study is the long-term safety of repeated lanadelumab 300mg q2w administrations, through analyses based on treatment-emergent adverse events.
Other outcomes used in the economic model/specified in the scope	The rank ordered secondary efficacy endpoints comparing each active treatment group (lanadelumab) to the placebo group were as follows: • Number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period (Day 0 through Day 182) • Number of moderate or severe investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182) • Number of investigator-confirmed HAE attacks occurring on Day 14 after administration of study drug to Day 182 (Day 14 to Day 182) Other endpoints comparing each active treatment group (lanadelumab) to the placebo group were as follows: • QoL data as measured by the AE-QoL questionnaire and the EQ-5D-5L in the safety population • PD/PK effects of chronically administered lanadelumab • Safety: the incidence of AEs, clinical laboratory abnormalities, vital signs, physical examination and plasma anti-drug antibody testing • Immunogenicity of chronically administered lanadelumab	The secondary outcome was to evaluate the long-term efficacy of lanadelumab for the prevention of HAE attacks in accordance with the HAARP throughout the treatment period. For rollover patients, attack rates were calculated for the regular dosing stage of the treatment period, while for non-rollover patients, attack rates were calculated for the entire treatment period. Measurements included: • Time to first attack for rollover patients • Number of investigator-confirmed attacks during the treatment period • Number of investigator-confirmed attacks requiring acute treatment during the treatment period • Number of moderate and severe attacks during the treatment period. Attack severity will be assessed as mild (transient or mild discomfort), moderate (mild to moderate limitation in activity; some assistance required) or severe (marked limitation in activity; assistance required)

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	Exploratory analyses comparing each active treatment group (lanadelumab) to the placebo included data summaries for the following: • Time to first investigator-confirmed HAE attack after Day 0 and Day 70 • Achievement of investigator-confirmed HAE attack-free status at 1 month, 3 months, until the Day 182 visit during the treatment period (Day 0 to Day 182) and during steady state treatment period (Day 70 to Day 182) • Number of high-morbidity investigator-confirmed HAE attacks during the treatment period (Day 0 to Day 182) • Number of investigator-confirmed laryngeal HAE attacks during the treatment period (Day 0 to Day 182) and during steady state treatment period (Day 70 to Day 182) • Achievement of a prespecified reduction from the run-in period in the investigator-confirmed HAE attack rate (i.e. responder analysis) • Time to first investigator-confirmed HAE attack after Day 14 and Day 28 • Number of investigator-confirmed HAE attacks resulting in an emergency department visit or admission to the hospital during the treatment period (Day 0 to Day 182) • Number of investigator-confirmed laryngeal HAE attacks during the treatment period (Day 28 to Day 182) • Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, and rescue medication use during the run-in period and treatment period (Day 0 to Day 182) • Percentage of attack-free days during the treatment period (Day 0 to Day 182) • Investigator-confirmed HAE attack rate per month for each study month	• Number of high-morbidity attacks during the treatment period, which are defined as any attack with at least one of the following characteristics: severe, results in hospitalisation, haemodynamically significant or upper airway (laryngeal) Additionally, tertiary outcomes include: • Immunogenicity (anti-drug antibodies [ADAs]) • QoL as measured by the AE-QoL questionnaire, EQ-5D-5L, WPAI:GH, HADS and SF-12 • PK/PD profile of lanadelumab • Safety and efficacy associated with switching from another long-term prophylactic therapy • Characteristics of breakthrough attacks compared with historical baseline • Experience with self-administration of lanadelumab

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Pre-planned subgroups	Subgroup analyses were planned for the primary efficacy endpoint and AEs for the following baseline demographic and disease characteristics: • Age group (<18, 18 to <40, 40 to <65, ≥65 years) • Sex (male, female) • Race group (white, other) • Weight group (<50, 50 to <75, 75 to <100, ≥100kg) • BMI group (<18.5, 18.5 to <25, 25 to <30, ≥30kg/m^2) • Run-in period HAE attack rate (1 to <2, 2 to <3, ≥3 attacks/month) • HAE type (Type I, Type II, unspecified) • Geographical region (US, Canada, Jordan, Europe) • Type of LTP therapy prior to study randomisation (C1-INH, oral therapy, C1-INH and oral therapy, not on LTP) • History of laryngeal HAE attack (with historical laryngeal attack, without historical laryngeal attack)	The attack rate will also be analysed by subgroups, including age group, sex, race, weight, body mass index, baseline angioedema attack rate, HAE type, geographic region, and administration type.
Key: AAE, acquired angioedema; ACE, angiotensin-converting enzyme; ADA, anti-drug antibodies; AEs, adverse events; AE-QoL, Angioedema Quality of Life; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; C1-INH, C1 esterase inhibitor; CSR, clinical study report; EQ-5D-5L, 5-level EQ-5D; GLM, generalised linear model; HAARP, HAE Attack Assessment and Reporting Procedures; HADS, Hospital Anxiety and Depression Scale; HAE, hereditary angioedema; HAE nC1-INH, HAE with normal C1-INH; IUD, intrauterine device; IUS, intrauterine hormone releasing systems; LTP, long-term prophylaxis; PD, pharmacodynamic; PK, pharmacokinetic; q2w, every 2 weeks; q4w, every 4 weeks; QoL, quality of life; SC, subcutaneous; WPAI:GH, Work Productivity and Activity Impairment questionnaire: General Health. **Source:** HELP-03 CSR[59]; Banerji et al., 2018[60] Riedl et al., 2017[62]; Riedl et al. 2018[63]		

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Baseline demographics

HELP-03 study

Patients who participated in HELP-03 were generally representative of the overall population of patients with HAE with respect to demographic factors and baseline disease characteristics. Baseline demographic and disease characteristics of the HELP-03 study intent-to-treat (ITT) population are summarised in Table 8.

Overall, baseline demographics and clinical characteristics were well balanced across treatment groups. The median age of patients in the ITT population was 42.4 years and the majority of patients were aged between 12 and 18 years (adolescents; 36%) or 18 and 40 years (52%). The median age of patients in the ITT population at onset of angioedema was 12 years, similar between treatment groups. Most patients in the ITT population had Type I HAE (90.4%), with only 9.6% with Type II HAE; this was similar across treatment groups.

The median number of HAE attacks in the 1 month, 3 months, and 12 months prior to screening were similar between lanadelumab and placebo-treated patients. In line with the eligibility criteria, all patients in the ITT population had 1 or more attacks in the run-in period, and the median run-in HAE attack rate was similar between all treatment arms. The most common primary attack location was abdominal/peripheral, occurring in 50% (42 of 84) of patients in the three lanadelumab arms and in 36.6% (15 of 41) of patients in the placebo arm. History of laryngeal angioedema attacks was also similar between lanadelumab and placebo-treated patients.

With regard to treatment history, 70 (56.0%) patients in the ITT population were on a prior LTP therapy: 60 (48.0%) were on C1-INH only, four (3.2%) were on an oral therapy (androgens or anti-fibrinolytics), and six (4.8%) patients were on C1-INH and oral therapy. The use of prior LTP therapy was well balanced across treatment groups.

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Table 8: Baseline demographic and disease characteristics HELP-03: ITT population

		Lanadelumab				
Characteristic	**Placebo (n=41)**	**300mg q2w (n=27)**	**300mg q4w (n=29)**	**150mg q4w (n=28)**	**Total (all lanadelumab arms) (n=84)**	**Total (placebo and lanadelumab) (n=125)**
Age (years)[a]						
Mean (SD)	40.1 (16.75)	40.3 (13.35)	39.5 (12.85)	43.4 (14.91)	41.0 (13.66)	40.7 (14.69)
Median (range)	42.4 (12, 70)	38.4 (15, 62)	40.7 (12, 59)	45.3 (16, 73)	42.7 (12, 73)	42.4 (12, 73)
Age categories (years)[a], n (%)						
<18	4 (9.8)	2 (7.4)	3 (10.3)	1 (3.6)	6 (7.1)	10 (8.0)
≥18 to <40	14 (34.1)	12 (44.4)	10 (34.5)	9 (32.1)	31 (36.9)	45 (36.0)
≥40 to <65	21 (51.2)	13 (48.1)	16 (55.2)	15 (53.6)	44 (52.4)	65 (52.0)
≥65	2 (4.9)	0	0	3 (10.7)	3 (3.6)	5 (4.0)
Sex, n (%)						
Male	7 (17.1)	12 (44.4)	10 (34.5)	8 (28.6)	30 (35.7)	37 (29.6)
Female	34 (82.9)	15 (55.6)	19 (65.5)	20 (71.4)	54 (64.3)	88 (70.4)
Race, n (%)						
White	39 (95.1)	26 (96.3)	23 (79.3)	25 (89.3)	74 (88.1)	113 (90.4)
Black or African American	2 (4.9)	1 (3.7)	6 (20.7)	1 (3.6)	8 (9.5)	10 (8.0)
Asian	0	0	0	2 (7.1)	2 (2.4)	2 (1.6)
BMI, kg/m^2						
Mean (SD)	27.5 (7.7)	26.9 (4.7)	28.1 (5.2)	31.0 (7.8)	28.7 (6.2)	28.3 (6.7)
Age at onset of angioedema, mean (years)						
Mean (SD)	11.2 (8.21)	15.0 (8.67)	14.6 (11.16)	12.0 (8.76)	13.8 (9.61)	13.0 (9.22)
Median (range)	8.0 (2, 41)	14.0 (2, 43)	12.0 (1, 49)	10.5 (1, 40)	12.5 (1, 49)	12.0 (1, 49)

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		Lanadelumab				
Characteristic	**Placebo (n=41)**	**300mg q2w (n=27)**	**300mg q4w (n=29)**	**150mg q4w (n=28)**	**Total (all lanadelumab arms) (n=84)**	**Total (placebo and lanadelumab) (n=125)**
HAE type, n (%)						
Type I	38 (92.7)	23 (85.2)	27 (93.1)	25 (89.3)	75 (89.3)	113 (90.4)
Type II	3 (7.3)	4 (14.8)	2 (6.9)	3 (10.7)	9 (10.7)	12 (9.6)
History of laryngeal attacks, n (%)						
Yes	27 (65.9)	20 (74.1)	17 (58.6)	17 (60.7)	54 (64.3)	81 (64.8)
No	14 (34.1)	7 (25.9)	12 (41.4)	11 (39.3)	30 (35.7)	44 (35.2)
Primary attack locations (combined)[b], n (%)						
Laryngeal	10 (24.4)	5 (18.5)	6 (20.7)	3 (10.7)	14 (16.7)	24 (19.2)
Abdominal	35 (85.4)	21 (77.8)	27 (93.1)	20 (71.4)	68 (81.0)	103 (82.4)
Peripheral	30 (73.2)	23 (85.2)	22 (75.9)	25 (89.3)	70 (83.3)	100 (80.0)
Primary attack locations, n (%)						
Laryngeal	0	0	0	0	0	0
Laryngeal/abdominal	0	1 (3.7)	0	0	1 (1.2)	1 (0.8)
Laryngeal/peripheral	1 (2.4)	1 (3.7)	0	0	1 (1.2)	2 (1.6)
Laryngeal/abdominal/peripheral	9 (22.0)	3 (11.1)	6 (20.7)	3 (10.7)	12 (14.3)	21 (16.8)
Abdominal	11(26.8)	3 (11.1)	7 (24.1)	3 (10.7)	13 (15.5)	24 (19.2)
Abdominal/peripheral	15 (36.6)	14 (51.9)	14 (48.3)	14 (50.0)	42 (50.0)	57 (45.6)
Peripheral	5 (12.2)	5 (18.5)	2 (6.9)	8 (28.6)	15 (17.9)	20 (16.0)
Number of attacks in the last month						
Mean (SD)	4.15 (3.978)	2.96 (2.794)	3.76 (3.512)	4.61 (5.953)	3.79 (4.310)	3.90 (4.192)
Median (range)	3.00 (0.0, 15.0)	2.00 (0.0, 12.0)	2.00 (0.0, 14.0)	3.00 (0.0, 30.0)	3.00 (0.0, 30.0)	3.00 (0.0, 30.0)

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		Lanadelumab				
Characteristic	**Placebo (n=41)**	**300mg q2w (n=27)**	**300mg q4w (n=29)**	**150mg q4w (n=28)**	**Total (all lanadelumab arms) (n=84)**	**Total (placebo and lanadelumab) (n=125)**
Number of attacks in the last 3 months						
Mean (SD)	11.46 (10.824)	7.67 (7.504)	9.93 (10.074)	12.61 (17.223)	10.10 (12.346)	10.54 (11.842)
Median (range)	8.00 (0.0, 44.0)	6.00 (0.0, 28.0)	5.00 (1.0, 42.0)	9.00 (0.0, 90.0)	6.50 (0.0, 90.0)	7.00 (0.0, 90.0)
Number of attacks in the last 12 months						
Mean (SD)	45.46 (43.441)	22.15 (18.172)	37.07 (35.516)	47.07 (68.607)	35.61 (46.520)	38.84 (45.595)
Median (range)	30.00 (0.0, 185.0)	20.00 (0.0, 72.0)	24.00 (1.0, 140.0)	34.00 (2.0, 365.0)	24.00 (0.0, 365.0)	24.00 (0.0, 365.0)
Run-in HAE attack rate (attacks/month)[c]						
Mean (SD)	4.02 (3.265)	3.52 (2.327)	3.71 (2.507)	3.22 (1.830)	3.48 (2.225)	3.66 (2.611)
Median (range)	3.00 (1.0, 14.7)	3.11 (1.0, 9.0)	3.00 (1.0, 10.5)	3.18 (1.0, 6.7)	3.00 (1.0, 10.5)	3.00 (1.0, 14.7)
Run-in HAE attack rate category (attacks/month)[c], n (%)						
1 to <2	12 (29.3)	7 (25.9)	9 (31.0)	10 (35.7)	26 (31.0)	38 (30.4)
2 to <3	8 (19.5)	6 (22.2)	5 (17.2)	3 (10.7)	14 (16.7)	22 (17.6)
≥3	21 (51.2)	14 (51.9)	15 (51.7)	15 (53.6)	44 (52.4)	65 (52.0)

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		Lanadelumab				
Characteristic	**Placebo (n=41)**	**300mg q2w (n=27)**	**300mg q4w (n=29)**	**150mg q4w (n=28)**	**Total (all lanadelumab arms) (n=84)**	**Total (placebo and lanadelumab) (n=125)**
Prior long-term prophylactic treatment category, n (%)						
C1-INH only	22 (53.7)	9 (32.1)	18 (62.1)	11 (40.7)	38 (45.2)	60 (48.0)
Oral therapy[d]	1 (2.4)	0	1 (3.4)	2 (7.1)	3 (3.6)	4 (3.2)
C1-INH and oral therapy[d]	1 (2.4)	3 (11.1)	1 (3.4)	1 (3.6)	5 (6.0)	6 (4.8)
No LTP use	17 (41.5)	16 (57.1)	9 (31.0)	13 (48.1)	38 (45.2)	55 (44.0)
Prior long-term prophylactic treatment, n (%)						
Androgens	1 (2.4)	0	0	2 (7.1)	2 (2.4)	3 (2.4)
Androgens, antifibrinolytics, C1-INH	0	1 (3.7)	0	0	1 (1.2)	1 (0.8)
Androgens, C1-INH	1 (2.4)	2 (7.4)	1 (3.4)	1 (3.6)	4 (4.8)	5 (4.0)
Anti-fibrinolytics	0	0	1 (3.4)	0	1 (1.2)	1 (0.8)
C1-INH only	22 (53.7)	9 (32.1)	18 (62.1)	11 (40.7)	38 (45.2)	60 (48.0)
No LTP use	17 (41.5)	16 (57.1)	9 (31.0)	13 (48.1)	38 (45.2)	55 (44.0)

Key: BMI, body mass index; C1-INH, C1 esterase inhibitor; CSR, clinical study report; HAE, hereditary angioedema; ITT, intent-to-treat; LTP, long-term prophylaxis; q2w, every 2 weeks; q4w, every 4 weeks; SD, standard deviation.
Notes: [a], Age is calculated as the difference between date of birth and date of informed consent, truncated to years; [b], Patients may be counted in more than one category; [c], Run-in HAE attack rate is calculated as the number of HAE attacks occurring during the run-in period divided by the number of days the patient contributed to the run-in period multiplied by 28 days. A month is defined as 28 days; [d], Oral therapy includes androgens and antifibrinolytics.
Source: HELP-03 CSR;[59] Banerji et al., 2018.[60]

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Open-label extension study HELP-04

Baseline demographic and disease characteristics of the rollover and non-rollover patients in the open-label extension HELP-04 study are summarised in Table 9.

A total of 212 patients received treatment in the extension study, including 109 patients who entered as rollover patients from the HELP-03 study and 103 non-rollover patients. At the time of analysis of the interim data (data from May 26, 2016 to September 1, 2017), most patients (92.9%) were ongoing in the study. Overall, baseline demographics and clinical characteristics were generally similar among the rollover and non-rollover groups. The mean (SD) age of patients was 40.7 (15.7) years, and the majority of patients were female (67.5%).

Patients in the rollover and non-rollover groups at baseline had a mean of 3.8 and 2.9 attacks in the last month, respectively. Approximately half of patients in the rollover and non-rollover groups (48.6% and 51.5%, respectively) had received prior LTP therapy with C1-INH treatment only.

Table 9: Baseline demographic and disease characteristics for open-label extension study HELP-04

Characteristic	Rollover Patients (n=109)	Non-rollover Patients (n=103)	Total (n=212)
Age, mean (SD) [years]	41.9 (14.7)	39.5 (16.7)	40.7 (15.7)
Age categories (years), n (%)			
<18	8 (7.3)	13 (12.6)	21 (9.9)
≥18 to <40	38 (34.9)	39 (37.9)	77 (36.3)
≥40 to <65	57 (52.3)	46 (44.7)	103 (48.6)
≥65	6 (5.5)	5 (4.9)	11 (5.2)
Sex, n (%)			
Male	34 (32.2)	35 (44.0)	69 (32.5)
Female	75 (68.8)	68 (66.0)	143 (67.5)
Race, n (%)			
White	99 (90.8)	99 (96.1)	198 (93.4)
Black or African American	8 (7.3)	2 (1.9)	10 (4.7)
Asian	1 (0.9)	0	1 (0.5)
Other	1 (0.9)	2 (1.9)	3 (1.4)
BMI, mean (SD) [kg/m^2]	28.3 (6.8)	28.4 (7.5)	28.4 (7.2)

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Characteristic	Rollover Patients (n=109)	Non-rollover Patients (n=103)	Total (n=212)
Age at onset of angioedema, mean (SD) [years]	13.5 (9.5)	11.6 (7.3)	12.6 (8.6)
HAE type, n (%)			
Type I	100 (91.7)	89 (86.4)	189 (89.2)
Type II	9 (8.3)	12 (11.7)	21 (9.9)
Unspecified	0	2 (1.9)	2 (0.9)
History of laryngeal attacks, n (%)	67 (61.5)	63 (61.2)	130 (61.3)
Number of attacks in the last month, mean (SD)	3.8 (4.2)	2.9 (2.9)	3.4 (3.6)
Number of attacks in the last 12 months, mean (SD)	37.7 (46.0)	30.4 (34.2)	34.2 (40.7)
Run-in HAE attack rate (attacks/month)[a]			
Mean (SD)	3.52 (2.46)	2.55 (2.75)	3.05 (2.66)
Median (range)	3.00 (1.0, 14.0)	1.84 (0.0, 15.4)	2.00 (0.0, 15.4)
Baseline HAE attack rate category (attacks/month)[a], n (%)			
<1	0	25 (24.3)	25 (11.8)
1 to <2	35 (32.1)	39 (37.9)	74 (34.9)
2 to <3	19 (17.4)	11 (10.7)	30 (14.2)
≥3	55 (50.5)	28 (27.2)	83 (39.2)
Prior long-term prophylactic treatment category, n (%)			
C1-INH only	53 (48.6)	53 (51.5)	106 (50.0)
Oral therapy[b]	4 (3.7)	8 (7.8)	12 (5.7)
C1-INH and oral therapy[b]	5 (4.6)	2 (1.9)	7 (3.3)
No LTP use	47 (43.1)	40 (38.8)	87 (41.0)

Key: BMI, body mass index; C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; LTP, long-term prophylaxis; q2w, every 2 weeks; q4w, every 4 weeks; SD, standard deviation.
Notes: [a], Run-in HAE attack rate is calculated as the number of HAE attacks occurring during the run-in period divided by the number of days the patient contributed to the run-in period multiplied by 28 days. A month is defined as 28 days; [b], oral therapy includes androgens and antifibrinolytics.
Source: Lanadelumab AMPC Dossier[68]; Riedl et al. 2018[63]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

HELP-03

There were two analysis populations in the HELP-03 study. The first was the ITT population, which included all randomised patients who received any exposure to the

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investigational product. The second was the safety population, which included all patients who received any exposure to the investigational product.

All efficacy analyses were carried out based on the ITT principle, i.e. patients were analysed according to their randomised treatment assignment, regardless of the treatment actually received, except for safety, pharmacokinetic (PK), pharmacodynamic (PD) and QoL analyses that were performed using the safety population. The hypothesis and associated statistical analysis methods adopted for the primary efficacy endpoint and the rank-ordered secondary endpoints in the HELP-03 study are presented in Table 10.

Long-term extension HELP-04

In the long-term extension study HELP-04, the safety population includes all patients who received any study drug after entering the open-label extension study. The rollover safety population is the subset of patients who participated in the double-blind study and received any study drug after entering the open-label extension study. The non-rollover safety population is the subset of patients who directly entered the open-label extension study and subsequently received any study drug.

The sample size for this single-arm, open-label study is not based on a formal statistical sample size calculation. This study does not have a control arm; therefore, no formal statistical hypothesis testing will be performed, and all p-values will be considered descriptive. All available data will be included in the analysis. No imputation of missing data will be performed. Summary tabulations conducted with the non-rollover safety population will be presented by patient's type of LTP prior to study entry.

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Table 10: Summary of statistical analyses of HELP-03

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT02586805 (HELP-03)	The primary efficacy endpoint comparing each active treatment group (lanadelumab) to the placebo group was the number of investigator-confirmed HAE attacks during the treatment period (Day 0 to Day 182). The HELP-03 study was considered to be positive if the lanadelumab groups were significantly superior to the placebo group for the primary endpoint.	Efficacy analyses included all patients randomised at Week 0 and were based on the ITT principle. The primary efficacy endpoint was compared for each active treatment group (lanadelumab) to the placebo group using a GLM for count data, assuming a Poisson distribution with a log link function and Pearson chi-squared scaling of SEs to account for potential overdispersion. The model included fixed effects for treatment group (categorical) and the normalised baseline attack rate (continuous). The logarithm of time in days each patient was observed during the treatment period was used as an offset variable in the model. From this model, the LS mean rate and SE for each treatment group as well as the mean rate ratios relative to the placebo group and corresponding 95% CIs for each active treatment group was estimated. These estimates were reported as mean event rates per unit of time (week and monthly) by transforming the estimates using the exponential function and scaling by the unit of time. The primary endpoint was tested by the following hypothesis: H_0: $\lambda_{DX-2930} / \lambda_{placebo} = 1$ versus H_1: $\lambda_{DX-2930} / \lambda_{placebo} \neq 1$ $\lambda_{DX-2930}$ refers to the mean investigator-confirmed HAE attack rate in the lanadelumab group and $\lambda_{Placebo}$ refers to the mean investigator-confirmed HAE attack rate in the placebo group. The null hypothesis was that the mean investigator-confirmed HAE attack rate ratio is 1 (no difference between treatment groups) versus the alternative hypothesis that the HAE attack rate ratio was not 1. Estimated attack rate ratios less than 1 would indicate that patients treated with lanadelumab, on average, had a lower incidence of	Power analysis and sample size estimation was based on 1,000 computer simulations using a GLM for count data, assuming a Poisson distribution with Pearson chi-squared scaling of SEs to account for potential overdispersion. The active treatment dose in each active treatment arm to placebo ratio was set at 1:1.5. A 10% missing data/dropout rate for both active treatment and placebo was also built into the empirical sample size simulations. For a treatment effect of 60% reduction in angioedema attacks compared with placebo, assuming a placebo attack rate of 0.3 per week over a 26-week period for an average total of 7.8 attacks	All available data were included in the primary and secondary efficacy analyses. The length of time a patient was observed during the treatment period was included as a variable in the GLM to adjust for differences in follow-up time. Tipping point analysis was utilised to measure the potential effect of missing data on the reliability of efficacy results.

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		investigator-confirmed HAE attacks during the treatment period. The primary hypothesis was tested using the model-based LS means estimate of the treatment difference using a Wald-based chi-squared test. The percentage difference in mean investigator confirmed HAE attack rate of each active treatment group from the attack rate of placebo was calculated as 100% * (mean rate ratio – 1). Similarly, the estimated upper and lower confidence limits for the mean rate ratio were transformed by subtracting 1 and multiplying by 100% to calculate 95% Cis for the percentage change. The mean rate ratios and corresponding 95% Cis were estimated from the generalised linear model as described above. To maintain the overall Type I error at 0.05, a conservative Bonferroni-based procedure was used for the comparisons of each of the active treatment groups with the placebo group, with equal weights for each test set at 1.67% significance level (α/3). The secondary endpoints were analysed using the same method as described for the primary efficacy endpoint. To adjust for the potential of inflated overall Type I error rate, the rank-ordered secondary endpoints were tested in a fixed sequence for each active treatment group to placebo group comparison using a general gatekeeping approach consistent with the logical restrictions of the rank ordering of the endpoints. Secondary endpoints were not declared statistically significant unless the primary endpoint for that active treatment group to placebo group comparison was found to be statistically significant.	during the treatment period, a sample size of 24 actively treated patients for the primary active treatment arm and 36 patients treated with placebo would provide at least 95% power (at α=0.025, one-sided). A 60% reduction was well below the smallest expected reduction in attacks since in Study DX-2930-02 the observed reduction in attacks neared 100%. These sample sizes also provided an adequately sized safety population for evaluation. Up to 120 patients (approximately 80 patients in the three active treatment arms and 40 patients in the placebo arm) were to be enrolled to account for potential early drop-outs during the study.	
Key: CI, confidence interval; CSR, clinical study report; GLM, generalised linear model; HAE, hereditary angioedema; ITT, intent-to-treat; LS, least squares; SAP, statistical analysis plan; SE, standard error. **Source:** HELP-03 SAP[69]; HELP-03 CSR.[59]				

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Five pre-specified sensitivity analyses were performed on the primary efficacy endpoint to evaluate the robustness of the results. In addition, two *ad hoc* sensitivity analyses were performed on the primary endpoint. Details of these sensitivity analyses are presented in Table 11.

Table 11: Sensitivity analyses performed on the primary efficacy endpoint

Sensitivity analyses	Methods
Pre-specified	
The primary analysis was repeated using the Safety Population.	The primary analysis model presented in Table 10 was used for this analysis. Patients were analysed according to the treatment actually received. This analysis will only be presented if the Safety Population is different from the ITT Population or if patients did not receive treatment as randomised.
The primary analysis was repeated counting HAE attacks occurring on Day 7 after administration of study drug to Day 182, instead of Day 0 to Day 182.	The primary analysis model presented in Table 10 was used for this analysis.
The primary analysis was repeated using all patient-reported HAE attacks instead of limiting the analysis to those attacks that were investigator confirmed.	The primary analysis model presented in Table 10 was used for this analysis.
The primary analysis was repeated using a GEE analysis method, counting HAE attacks occurring on Day 14 after administration of study drug to Day 182, in order to descriptively compare the results from this study with those from DX-2930-02 study.	HAE attack rates for each active treatment group will be compared with the placebo group using an MMRM analysis of covariance (ANCOVA) for count data (assuming a Poisson distribution with log link function) using GEE. The model will include a fixed effect for treatment (categorical), pre-treatment period attack rate (continuous), and a random effect for patient. Repeated measurement analysis will be employed, with a 7-day time period (i.e. 168 hours) serving as the discrete unit of measurement. Patient weeks for which completed observation is less than the full 168 hours will be treated as a full week if at least 3 or more days of data were recorded during the week. Weeks with fewer than 3 days will not be included. In the event that there are 0 events in one of the treatment groups, a small value of 0.000001 will be added in order to calculate event rates.

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Sensitivity analyses	Methods
The tipping point analysis was conducted to measure the potential effect of missing data on the reliability of efficacy results. Other planned sensitivity analyses supported the robustness of the outcome of the primary endpoint analysis.	Using the primary efficacy model, Bayesian Gibbs sampling was run to generate 1,000 posterior estimates of the Poisson regression parameters. For each patient with missing days from the treatment period, 1,000 estimates of the Poisson distribution parameter lambda (λ) were calculated using the imputations from the Bayesian Gibbs sampling (λ =exp(B0+B1*run-in attack rate + B2*treatment). For each patient with missing data, 1,000 estimates of the number of attacks for Poisson (t*λ) were generated, where t is the number of days missing from the treatment period. For the tipping point analysis, a multiplication factor delta (δ) was applied to parameter t*λ for patients in lanadelumab treatment groups with missing days from the treatment period. For each value of δ, random sampling of Poisson (δ* t*λ) was made for the 1,000 estimates of λ. In contrast, for patients in the placebo group with missing days from the treatment period, random sampling was made from Poisson (t* λ). The primary analysis Poisson GLM was then used to derive rate ratios between each of the active treatment groups and the placebo group after imputation. The estimates of the rate ratios were combined using Rubin's rules. The tipping point was achieved for a lanadelumab treatment group if the combined p-value was ≥0.0167. The total number of study drug administrations were summarised by treatment group and lanadelumab overall. Furthermore, for each treatment group and lanadelumab overall, the percentage of injections with injection site reaction was derived by dividing numbers of events by the total number of study drug administrations. Number of C1-INH uses (i.e. number of C1-INH doses per week) by patient and treatment group.
***Ad hoc* sensitivity analyses**	
Using the primary analysis model, analyse the attack rate during steady state, or Day 70 visit to Day 182 visit.	The primary analysis model presented in Table 10 was used for this analysis.
Use of negative binomial GLM instead of Poisson GLM to analyse the number of attacks between Day 0 and Day 182 visit	This model is a modelling approach that is appropriate to analyse over-dispersed count data.

Key: ANCOVA, analysis of covariance; C1-INH, C1 esterase inhibitor; GEE, generalised estimating equations; GLM, generalised linear model; HAE, hereditary angioedema; ITT, intent-to-treat; MMRM, mixed-model repeated measures.
Source: HELP-03 SAP[69]; HELP-03 CSR.[59]

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See Appendix D for the number of participants eligible to enter the study and the CONSORT flow chart for patient disposition for HELP-03.

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

The HELP-03 study was conducted in accordance with Good Clinical Practice (GCP) guidelines, with a single protocol to promote consistency across sites and measures taken to minimise bias.

The accuracy and reliability of the clinical study data were assured by the selection of qualified investigators and an appropriate study centre, review of protocol procedures with the investigator and associated personnel before the study, and by periodic monitoring visits by the Sponsor. In addition, an Independent Data Monitoring board was established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of patients participating in the study.

Randomisation in the HELP-03 study was successfully carried out such that baseline characteristics of patients randomised were well balanced across treatment groups. There were few drop-outs in the study, and the numbers and reasons were well balanced across treatment arms. Patients, carers and investigators remained blinded throughout the study, and all outcome assessments were conducted in accordance with trial-validated methodology and based on the ITT principle.

Quality assessment of the HELP-03 study in accordance with the NICE-recommended checklist for RCT assessment of bias is presented in Appendix D. The risk of bias in the HELP-03 study is considered to be low.

Quality assessment of the interim analysis of the ongoing HELP-04 extension study has been conducted using the Downs and Black checklist, which is recommended for use with non-RCTs.[70] Results are presented in Appendix D.

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B.2.6. Clinical effectiveness results of the relevant trials

The current licence for lanadelumab relates to the 300mg solution for SC injection.[1, 3] Therefore, although data are presented for the 150mg dose investigated in the trials throughout this submission for completeness, no discussion of the results for the 150mg dose is included, as this dose will not be available.

HELP-03

Primary endpoint

The primary efficacy endpoint was the number of investigator-confirmed HAE attacks during the treatment period (Day 0 [after treatment administration] to Day 182). Both lanadelumab 300mg treatment arms met the primary endpoint, providing statistically significant ($p<0.001$) and clinically meaningful reductions (i.e., a reduction of ≥ 50% in HAE attacks[71]) in the number of attacks during the 26-week treatment period, compared with placebo (Figure 4 and Table 12).[59, 60, 72]

The median HAE attack rate during the run-in period was similar across all treatment arms (Table 12). During the treatment period, the least squares (LS) mean HAE attack rate (95% confidence interval [CI]) was (Figure 4):[59, 60, 72]

- 0.257 (0.145, 0.458) in the 300mg q2w arm
- 0.526 (0.358, 0.771) in the 300mg q4w arm
- 1.967 (1.640, 2.358) in the placebo arm

Lanadelumab 300mg q2w and 300mg q4w significantly reduced the percentage of investigator-confirmed HAE attacks per month by 86.9% and 73.3% (adjusted $p<0.001$ for both doses), respectively, relative to placebo (Table 12).[59, 72]

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Table 12: Primary efficacy endpoint – ITT population

		Lanadelumab		
	Placebo (n=41)	**300mg q2w (n=28)**	**300mg q4w (n=28)**	**150mg q4w (n=28)**
Primary endpoint: number of investigator confirmed HAE attacks from Day 0 to 182				
Run-in period HAE attack rate (attacks/4 weeks)				
Mean (SD)	4.022 (3.265)	3.519 (2.327)	3.711 (2.507)	3.216 (1.830)
Median (range)	3.00 (1.0, 14.7)	3.11 (1.0, 9.0)	3.00 (1.0, 10.5)	3.18 (1.0, 6.7)
Treatment period HAE attack rate (attacks/4 weeks)				
Mean (SD)	2.455 (2.079)	0.309 (0.505)	0.604 (0.801)	0.483 (0.627)
Median (range)	1.69 (0.0, 8.3)	0.15 (0.0, 1.8)	0.45 (0.0, 2.9)	0.15 (0.0, 2.0)
Model based treatment period HAE attack rate (attacks/4 weeks)[a]				
LS mean (95% CI)	1.967 (1.640, 2.358)	0.257 (0.145, 0.458)	0.526 (0.358, 0.771)	0.480 (0.313, 0.735)
% Change mean attack rate versus placebo[b]	N/A	-86.921	-73.271	-75.609
(95% CI)		(-92.828, -76.150)	(-82.379, -59.456)	(-84.650, -61.243)
Adjusted p-values[c]		<0.001	<0.001	<0.001

Key: CI, confidence interval; ITT, intent-to-treat; HAE, hereditary angioedema; N/A, not applicable; SD, standard deviation; LS, least squares; q2w, every 2 weeks; q4w, every 4 weeks.
Notes: [a], Results are from a Poisson regression model with fixed effects for treatment group (categorical) and normalised baseline attack rate (continuous), and the logarithm of time in days each patient was observed during the treatment period as an offset variable in the model. Pearson chi-squared scaling of standards errors was employed to account for potential over dispersion; [b], % change in mean rate corresponds to 100% * (rate ratio - 1); [c], Adjusted p-values are adjusted for multiple testing.
Source: HELP-03 CSR[59]; Banerji et al. 2017[72]; Banerji et al. 2018.[60]

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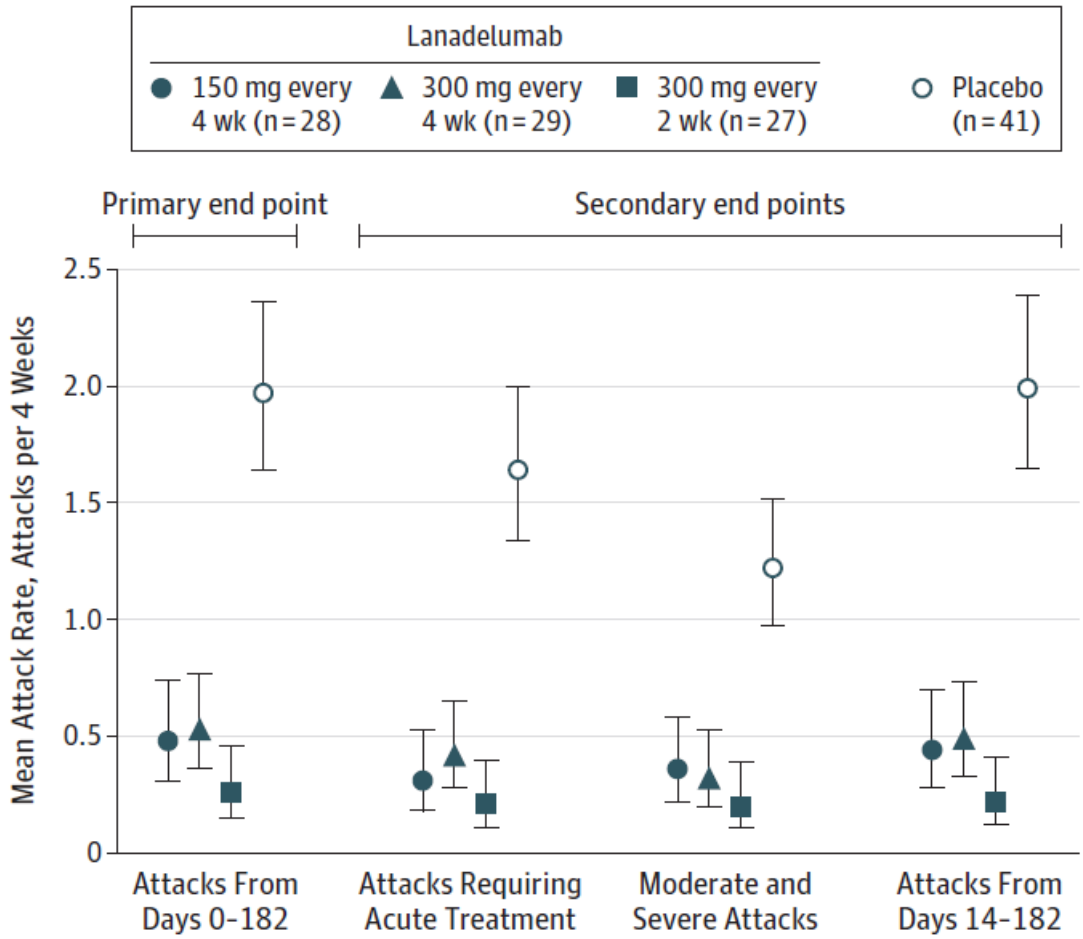
Figure 4: Primary and secondary endpoints by treatment group – ITT population



Key: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; wk, week.
Note: Attack rates are model-based mean attacks per month, with a month defined as 4 weeks. The mean attack rate for each group is presented with error bars representing 95% CI.
Source: Banerji et al. 2018.[60]

Five pre-specified and two *ad hoc* sensitivity analyses were performed on the primary efficacy endpoint to evaluate the robustness of the results (described in Table 11). Results of the pre-specified and *ad hoc* sensitivity analyses are presented in Appendix M; all analyses supported the outcome of the primary endpoint analysis. These included repeating the primary analysis using all patient-reported HAE attacks instead of limiting the analysis to those attacks that were investigator confirmed, as well as repeating the primary analysis using investigator-confirmed HAE attacks from Day 70 to Day 182 and using a negative binomial generalised linear model (GLM) instead of a Poisson GLM.[59, 72] Analyses on HAE attacks observed after Day 70 are

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particularly important as this represents the timepoint at which plasma concentrations of lanadelumab reach steady state. In fact, with a half-life of about 14 days, the anticipated pharmacokinetic steady state period in the HELP Study was Days 70–182 (~16 weeks).[1 64]

Secondary endpoints

Number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period

The first rank-ordered secondary efficacy endpoint was the number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period. Both lanadelumab 300mg treatment arms resulted in statistically significant ($p<0.001$) and clinically meaningful[71] percentage reductions in the number of investigator-confirmed HAE attacks requiring acute treatment, compared with placebo (Figure 4 and Table 13). [redacted][59, 72]

[redacted]

During the treatment period, the estimated LS mean HAE attack rate for attacks requiring acute treatment was (Figure 4):[59, 60, 72]

- 0.208 (0.109, 0.396) in the 300mg q2w arm
- 0.423 (0.276, 0.648) in the 300mg q4w arm
- 1.637 (1.337, 2.005) in the placebo arm

Lanadelumab 300mg q2w and 300mg q4w significantly reduced the percentage of investigator-confirmed HAE attacks requiring acute treatment per month by 87.3% and 74.2% (adjusted $p<0.001$ for both doses), respectively, relative to placebo (Table 13).[59, 72]

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Table 13: Rank-ordered secondary efficacy endpoints – ITT population

	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=28)	300mg q4w (n=28)	150mg q4w (n=28)
1st rank secondary endpoint: number of investigator-confirmed HAE attacks requiring acute treatment from Day 0–182				
Run-in period HAE attack rate requiring acute treatment (attacks/4 weeks)				
Mean (SD)	3.596 (3.485)	3.110 (2.589)	3.460 (2.740)	2.391 (1.916)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment period HAE attack rate requiring acute treatment (attacks/4 weeks)				
Mean (SD)	2.212 (2.156)	0.263 (0.505)	0.508 (0.793)	0.326 (0.523)
Median (range)	1.46 (0.0, 8.3)	0.00 0.0, 1.8)	0.15 (0.0 2.9)	0.08 (0.0, 2.0)
Model based treatment period HAE attack rate requiring acute treatment (attacks/4 weeks)[a]				
LS Mean (95% CI)	1.637 (1.337, 2.005)	0.208 (0.109, 0.396)	0.423 (0.276, 0.648)	0.314 (0.184, 0.535)
% Change mean attack rate versus placebo[b] (95% CI) Adjusted p-values[c]		-87.299 (-93.494, -75.204) <0.001	-74.169 (-83.733, -58.983) <0.001	-80.842 (-89.169, -66.114) <0.001
2nd rank secondary endpoint: number of moderate or severe investigator-confirmed HAE attacks from Day 0–182				
Run-in period HAE moderate or severe attack rate (attacks/4 weeks)				
Mean (SD)	2.341 (2.147)	2.169 (2.228)	2.576 (2.396)	2.378 (1.867)
Median (range)	1.93 (0.0, 9.3)	1.75 (0.0, 8.6)	1.93 (0.0, 7.6)	1.93 (0.0, 6.7)
Treatment period HAE moderate or severe attack rate (attacks/4 weeks)				
Mean (SD)	1.418 (1.252)	0.246 (0.482)	0.374 (0.551)	0.370 (0.526)
Median (range)	1.22 (0.0, 6.5)	0.0 (0.0, 1.7)	0.0 (0.0, 2.3)	0.15 (0.0, 2.0)

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	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=28)	300mg q4w (n=28)	150mg q4w (n=28)
Model based treatment period moderate or severe HAE attack rate (attacks/4 weeks)[a]				
LS Mean (95% CI)	1.216 (0.971, 1.522)	0.202 (0.106, 0.386)	0.325 (0.199, 0.529)	0.359 (0.221, 0.581)
% Change mean attack rate versus placebo[b]		-83.394	-73.285	-70.497
(95% CI)		(-91.618, -67.099)	(-84.316, -54.496)	(-82.696, -49.699)
Adjusted p-values[c]		<0.001	<0.001	<0.001
3rd rank secondary endpoint: number of investigator confirmed HAE attacks from Day 14–182				
Day 14–182 HAE attack rate (attacks/4 weeks)				
Mean (SD)	2.342 (2.011)	0.307 (0.604)	0.558 (0.770)	0.452 (0.617)
Median (range)	1.66 (0.0, 8.2)	0.0 (0.0, 2.7)	0.33 (0.0, 3.0)	0.08 (0.0, 2.0)
Model based HAE attack rate from day 14–182 (attacks/4 weeks)[a]				
LS Mean (95% CI)	1.988 (1.652, 2.391)	0.218 (0.115, 0.414)	0.489 (0.326, 0.734)	0.445 (0.283, 0.698)
% Change mean attack rate versus placebo[b]		-89.008	-75.377	-77.622
(95% CI)		(-94.325, -78.707)	(-84.115, -61.833)	(-86.253, -63.572)
Adjusted p-values[c]		<0.001	<0.001	<0.001

Key: CI, confidence interval; CSR, clinical study report; ITT, intent-to-treat; HAE, hereditary angioedema; SD, standard deviation; LS, least squares; q2w, every 2 weeks; q4w, every 4 weeks.
Notes: [a], Results are from a Poisson regression model with fixed effects for treatment group (categorical) and normalised baseline attack rate (continuous), and the logarithm of time in days each patient was observed during the treatment period as an offset variable in the model. Pearson chi-squared scaling of standards errors was employed to account for potential over dispersion; [b], % change in mean rate corresponds to 100% * (rate ratio - 1); [c], Adjusted p-values are adjusted for multiple testing.
Source: HELP-03 CSR[59]; Banerji et al. 2017[72]; Banerji et al. 2018.[60]

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Number of moderate or severe investigator-confirmed HAE attacks during the treatment period

The second rank-ordered secondary efficacy endpoint was the number of moderate or severe investigator-confirmed HAE attacks during the treatment period. The overall severity of the patient's attack was determined by the investigator using the following definitions:[59, 72]

- Mild: transient or mild discomfort; no medical intervention/therapy required
- Moderate: mild to moderate limitation in activity – some assistance needed; no or minimal medical intervention/therapy required
- Severe: marked limitation in activity, assistance required; medical intervention/therapy required, hospitalisations possible

Both lanadelumab 300mg treatment arms resulted in statistically significant ($p<0.001$) and clinically meaningful[71] percentage reductions in the number of moderate or severe investigator-confirmed HAE attacks during the treatment period compared with placebo (Figure 4 and Table 13).[59, 72]

The median rate for attacks that were moderate or severe during the run-in period was similar across all treatment arms (Table 13). During the treatment period, the LS mean HAE attack rate for attacks that were moderate or severe was (Figure 4):[59, 60, 72]

- 0.202 (0.106, 0.386) in the 300mg q2w arm
- 0.325 (0.199, 0.529) in the 300mg q4w arm
- 1.216 (0.97, 1.52) in the placebo arm

Lanadelumab 300mg q2w and 300mg q4w significantly reduced the percentage of moderate or severe investigator-confirmed HAE attacks during the treatment period by 83.4% and 73.3% (adjusted $p<0.001$ for both doses), respectively, relative to placebo (Table 13).[59, 72]

Number of investigator-confirmed HAE attacks occurring on Day 14, after administration of the study drug through to Day 182

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The third rank-ordered secondary efficacy endpoint was the number of investigator-confirmed HAE attacks occurring on Day 14, after administration of the study drug through to Day 182. Both lanadelumab 300mg treatment arms resulted in statistically significant ($p<0.001$) and clinically meaningful[71] percentage reductions in the number of investigator-confirmed HAE attacks occurring on Day 14, after administration of study drug through to Day 182 (Figure 4 and Table 13).[59, 72]

The estimated LS mean HAE attack rate occurring on Day 14, after administration of the study drug through to Day 182 was (Figure 4):[59, 60, 72]

- 0.218 (0.115, 0.414) in the 300mg q2w arm
- 0.489 (0.326, 0.734) in the 300mg q4w arm
- 1.988 (1.652, 2.391) in the placebo arm

Lanadelumab 300mg q2w and 300mg q4w significantly reduced the percentage of investigator-confirmed HAE attacks occurring on Day 14 after administration of the study drug through to Day 182 by 89.0% and 75.4% (adjusted $p<0.001$ for both doses), respectively, relative to placebo (Table 13).[59, 72]

In summary, as shown in Table 13, similar to the primary efficacy endpoint outcome, treatment with lanadelumab 300mg q2w and 300mg q4w resulted in clinically meaningful[71] and statistically significant ($p<0.001$) reductions in the mean HAE attack rate for all rank-ordered secondary efficacy endpoints, compared with placebo.

Exploratory endpoints

As described in Table 7, several exploratory outcomes were reported in the HELP-03 study to provide additional insight into the efficacy of lanadelumab. Statistically significant and clinically important exploratory endpoints or exploratory endpoints related to the economic model are presented below. Further exploratory analyses are presented in Appendix N. All exploratory efficacy endpoints were considered supportive and any statistical tests comparing treatments were made without adjustment for multiplicity.

Time to first investigator-confirmed HAE attack after Day 0 and Day 70

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Ad hoc analyses were conducted to analyse the time to first attack after Day 0 (after 1 dose) and after Day 70 (when lanadelumab concentration appeared to reach steady state).[59]

Time (days) to the first investigator confirmed HAE attack after Day 0 was summarised using Kaplan–Meier (KM) methods (Figure 5), and was calculated from the date of the Day 0 visit to the date of the first attack after the Day 0 visit. As shown in Figure 5, the median (95% CI) number of days to first attack after Day 0 was [redacted] days in the 300mg q2w arm and [redacted] days in the 300mg q4w arm, compared to [redacted] days in the placebo arm.[59]

Figure 5: Time to first investigator-confirmed attack Day 0 to Day 182 – ITT Population

Key: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; NE, non-estimable; Wk, week
Source: HELP-03 CSR.[59]

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Lanadelumab has a half-life of ~14 days and steady state concentrations are expected to be achieved by Day 70, this is supported by data presented in Figure 9. Therefore, an *ad hoc* analysis was also conducted to analyse the time to first attack after Day 70. Time (days) to the first investigator-confirmed HAE attack after Day 70 was summarised using KM methods (Figure 6), and was calculated from the date of the Day 70 visit to the date of the first attack after the Day 70 visit.[59]

As shown in Figure 6, more than [redacted] (median) of patients in the lanadelumab 300mg q2w treatment arm did not have an attack after Day 70 through the end of the treatment period (Day 182). Therefore, the median number of days to first investigator-confirmed attack was not estimable. The median (95% CI) number of days to first attack after Day 70 was [redacted] days in the 300mg q4w arm compared to [redacted] days in the placebo arm.[59]

Similar results were observed for time to first attack after day 14 and day 28, results are presented in Appendix N.[59]

Figure 6: Time to first investigator-confirmed attack Day 70 to Day 182 visit – ITT Population

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Key: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; NE, non-estimable; Wk, week.
Source: HELP-03 CSR.[59]

Achievement of investigator-confirmed HAE attack-free status at 1 month, 3 months, until the Day 182 visit during the treatment period (Day 0 to Day 182) and during steady state treatment period (Day 70 to Day 182)

An attack-free day was defined as a calendar day with no investigator-confirmed HAE attack. As shown in Table 14, at every specified interval after the first dose (Day 0) during the treatment period (1 month, 3 months, until the Day 182 visit or during steady state treatment period [Day 70 to Day 182]), the percentage of patients that were attack-free in both lanadelumab 300mg treatment arms was significantly higher compared with the placebo arm, with the 300mg q2w arm containing the highest percentage of patients who were attack-free at each interval.[59]

As shown in Table 14, in comparison with 2.4% of patients in the placebo arm, 44.4% of patients in the lanadelumab 300mg q2w arm and 31.0% of patients in the lanadelumab 300mg q4w arm were attack-free until the Day 182 visit (Table 14).[59, 60] Similarly, as shown in Table 14, during Day 70 (when lanadelumab concentrations appeared to reach steady state) to Day 182, a higher percentage of patients in both 300mg lanadelumab treatment arms were attack-free compared to placebo: 76.9% in the 300mg q2w arm and 44.8% in the 300mg q4w arm, compared to 2.7% in the placebo arm.[59] These attack-free data for the lanadelumab 300mg q2w arm have been used to inform the economic model (see section B.3.3).

Results for the percentage of attack-free days are presented in Appendix N. Briefly, the mean percentage of attack-free days was higher for both lanadelumab 300mg treatment arms in comparison with placebo and was highest in the 300mg q2w arm. Results ranged from [redacted] for lanadelumab compared with [redacted] for placebo.[59]

A similar trend was observed for attack-free days at intervals specified after Day 14, results are presented in Appendix N.[59]

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Table 14: Achievement of investigator-confirmed HAE attack-free status at 1 month, 3 months, or until the Day 182 visit during the treatment period – ITT population

Parameter	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	150mg q4w (n=28)
Attack-free 1 month (Day 0 to Day 28), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Risk difference (95% CI of Risk Difference)	[redacted]	[redacted]	[redacted]	[redacted]
Attack-free 3 months (Day 0 to Day 84), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Risk difference (95% CI of Risk Difference)	[redacted]	[redacted]	[redacted]	[redacted]
Attack-free until the Day 182 visit, n (%)	1 (2.4)	12 (44.4)*	9 (31.0)	11 (39.3)
Risk difference (95% CI of Risk Difference)		-42.01 (-61.81, -18.09)	-28.60 (-50.00, -4.97)	-36.85 (-57.54, -13.11)
Attack-free day 70 to Day 182 visit, n (%)	1 (2.7)	20 (76.9)*	13 (44.8)	15 (53.6)

Key: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; q2w, every 2 weeks; q4w, every 4 weeks.
Notes: Patients who discontinued during a time period were considered as non-responder for that time period. In case no events were observed in one or both groups in a comparison, 0.5 was added to all four cells of the result tables to enable calculation of relative risk. *, these data have been used in the economic model.
Source: HELP-03 CSR[59]; Banerji et al. 2018.[60]

Number of high-morbidity investigator-confirmed HAE attacks during the treatment period (Day 0 to Day 182)

A high-morbidity HAE attack was defined as any attack that had at least one of the following characteristics: severe, resulted in hospitalisation (except hospitalisation for observation <24 hours), haemodynamically significant (systolic blood pressure <90, required IV hydration, or was associated with syncope or near-syncope) or laryngeal.

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If the length of hospitalisation could not be determined due to missing dates and times, then that hospitalisation was conservatively counted as being greater than 24 hours.[59, 60]

The number of high-morbidity HAE attacks occurring during the treatment period was significantly lower across both lanadelumab 300mg treatment arms compared with placebo (Figure 7). The LS mean (95% CI) high-morbidity investigator-confirmed HAE attack rate was:[59, 60]

- 0.034 (0.008, 0.133) in the 300mg q2w arm
- 0.030 (0.008, 0.119) in the 300mg q4w arm
- 0.219 (0.137, 0.351) in the placebo arm

The percentage reduction in the incidence of high-morbidity investigator-confirmed HAE attacks during the treatment period compared with placebo was statistically significant for both lanadelumab 300mg treatment arms: 84.7% (p=0.011) and 86.3% (p=0.007) in the 300mg q2w and 300mg q4w arms, respectively (Figure 7).[59, 60]

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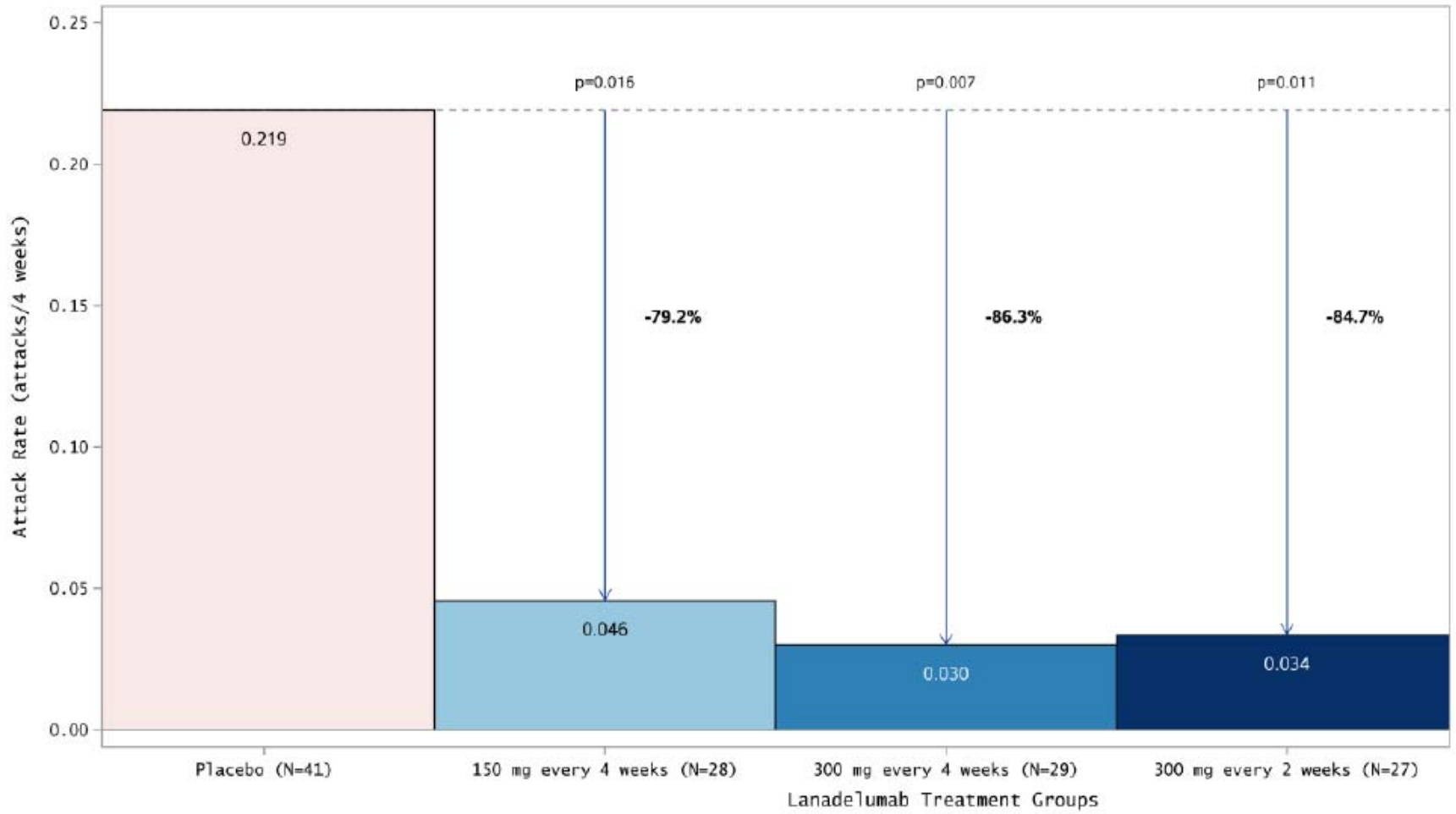
Figure 7: Investigator-confirmed high-morbidity HAE attacks during the treatment period (Day 0 to Day 182) by treatment group – ITT population



Key: HAE, hereditary angioedema; ITT, intent-to-treat.
Source: HELP-03 CSR.[59]

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Number of investigator-confirmed laryngeal HAE attacks during the treatment period (Day 0 to Day 182) and during steady state treatment period (Day 70 to Day 182)

Laryngeal, or upper airway attacks, are life threatening and considered the most severe of all HAE attacks. The number of investigator-confirmed laryngeal HAE attacks (both at primary and secondary location) during the treatment period were analysed using the same method as that for the primary efficacy endpoint, with an addition of history of laryngeal HAE attacks (categorical) as a fixed effect in the model.[59]

The history of laryngeal angioedema attacks was similar between lanadelumab and placebo-treated patients (Table 8). During the run-in period, [redacted] patients in the placebo arm had any laryngeal HAE attacks. In contrast, [redacted] patients in the lanadelumab 300mg q2w arm and [redacted] in the lanadelumab 300mg q4w arm had laryngeal HAE attacks during the run-in-period. However, during the treatment period, [redacted] patients had [redacted] events of laryngeal HAE attacks in the placebo arm, compared with [redacted] patients with [redacted] each and one patient with [redacted] in the 300mg q2w arm, and [redacted] patients with [redacted] each in the 300mg q4w arm.[59]

During the treatment period (Day 0 to Day 182), the LS mean investigator-confirmed laryngeal HAE attack rate was lower in both 300mg lanadelumab treatment arms compared with placebo (Figure 8), although the number of patients who had investigator-confirmed laryngeal HAE attacks was too low in each treatment arm for a statistically significant comparison with placebo. As shown in Figure 8, the percentage reduction in the investigator-confirmed laryngeal HAE attack rate ranged from [redacted] in the lanadelumab treatment arms compared with placebo.[59]

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Figure 8: Investigator-confirmed laryngeal HAE attacks during the treatment period (Day 0 to Day 182) by treatment group – ITT population

Key: HAE, hereditary angioedema; ITT, intent-to-treat.
Note: Unadjusted p-values.
Source: HELP-03 CSR.[59]

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Similar observations were made during Day 70 to Day 182 (when lanadelumab concentration appeared to reach steady state), as the LS mean investigator-confirmed laryngeal HAE attack rate was lower in both 300mg lanadelumab treatment arms compared to placebo. During Day 70 to Day 182, the reduction in the investigator-confirmed laryngeal HAE attack rate compared to placebo ranged from [redacted] (Table 15). However, the number of patients with investigator-confirmed laryngeal HAE attacks was too low in each treatment arm for a statistically significant comparison with placebo.[59]

Table 15: Investigator-confirmed laryngeal HAE attacks during steady state treatment period (Day 70 to Day 182) (ITT Population)

		Lanadelumab		
	Placebo (n=41)	**300mg q2w (n=28)**	**300mg q4w (n=28)**	**150mg q4w (n=28)**
Laryngeal HAE attacks during steady state treatment period (Day 70 to Day 182)				
Treatment period HAE attack rate (attacks/4 weeks)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Model-based treatment period HAE attack rate (attacks/4 weeks)[a]				
LS mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
% Change mean attack rate vs placebo[b] (95% CI) Adjusted p-values[c]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; ITT, intent-to-treat; HAE, hereditary angioedema; SD, standard deviation; LS, least squares; q2w, every 2 weeks; q4w, every 4 weeks.
Notes: [a], Results are from a Poisson regression model with fixed effects for treatment group (categorical) and normalised baseline attack rate (continuous), and the logarithm of time in days each patient was observed during the treatment period as an offset variable in the model. Pearson chi-squared scaling of standards errors was employed to account for potential over dispersion; [b], % change in mean rate corresponds to 100% * (rate ratio - 1); [c], unadjusted p-values are derived from Poisson modelling.
Source: HELP-03 CSR.[59]

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Responder analysis achievement of a reduction from run-in period in the investigator-confirmed HAE attack rate

The percentage of responders, an endpoint that is considered clinically meaningful and relevant to patients, compared normalised attack rates for each 26-week lanadelumab treatment to the 4-8-week run-in period. There were five classes of responders based on percentage reduction in the investigator-confirmed HAE attack rate from the run-in period attack rate: ≥50% reduction, ≥60% reduction, ≥70% reduction, ≥80% reduction, and ≥90% reduction. The percentage reduction was calculated as the run-in period HAE attack rate minus the treatment period HAE attack rate divided by the run-in period HAE attack rate.[59, 60]

As shown in Table 16, over the 26-week treatment period, the percentage of responders with a ≥50% reduction in HAE attack rates from the run-in period was 100% in both the 300mg q2w arms and 300mg q4w arms, compared with 31.7% in the placebo arm. Of note, the percentage of patients with a ≥90% reduction in investigator-confirmed HAE attacks from the run-in period attack rates was 66.7% in the 300mg q2w arm and 55.2% in the 300mg q4w arm, compared to placebo at 4.9%.[59, 60]

Table 16: Responder analysis comparing investigator-confirmed HAE attacks during the treatment period (Day 0 to Day 182) by responder threshold and treatment group – ITT population

Criteria, n (%)	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	150mg q4w (n=28)
≥50% reduction	13 (31.7)	27 (100.0)	29 (100.0)	25 (89.3)
≥60% reduction	9 (22.0)	27 (100.0)	26 (89.7)	24 (85.7)
≥70% reduction	4 (9.8)	24 (88.9)	22 (75.9)	22 (78.6)
≥80% reduction	3 (7.3)	22 (81.5)	17 (58.6)	22 (78.6)
≥90% reduction	2 (4.9)	18 (66.7)	16 (55.2)	18 (64.3)
100% reduction	1 (2.4)	12 (44.4)	9 (31.0)	11 (39.3)

Key: HAE, hereditary angioedema; ITT, intent-to-treat; q2w, every 2 weeks; q4w, every 4 weeks.
Notes: For each patient, the percentage reduction was calculated as the run-in period attack rate minus the treatment period attack rate divided by the run-in period attack rate, multiplied by 100. The percentage reduction groups are not mutually exclusive; patients may appear in more than one group as applicable based on their percentage reduction.
Source: HELP-03 CSR[59]; Banerji et al. 2018.[60]

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Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, and rescue medication use

Full details of this exploratory analysis are presented in Appendix N. However, given the impact attack duration can have on patients (see Section B.1.3), this is an important additional endpoint to highlight. In summary, during the treatment period, the mean attack duration was reduced, albeit not significantly, in both lanadelumab 300mg treatment arms compared with placebo (q2w: [redacted] vs, [redacted]; q4w: [redacted] vs. [redacted]).[60] In addition, a [redacted] percentage of patients in the lanadelumab treatment arms had investigator-confirmed HAE attacks that lasted >12-24h, >24-48h and >48h, compared to those in the placebo arm.[60]

Health-related quality of life endpoints

In the HELP-03 study, the AE-QoL and EQ-5D-5L index were used to evaluate the effect of lanadelumab on QoL.

The AE-QoL tool is a 17-item self-administered disease-specific questionnaire that has been developed and validated to assess QoL impairment in recurrent angioedema (including HAE) patients over time, including changes due to treatment.[34] Each item in the AE-QoL tool has a five-point response scale ranging from 1 (Never) to 5 (Very Often). The AE-QoL total score and four domain scores (functioning, fatigue/mood, fear/shame, and nutrition) are rescaled using linear transformations into scores ranging from 0 to 100, where lower scores indicate lower impairment (or better functioning). A change in score of 6 points is recommended as the minimal clinically important difference (MCID) for the AE-QoL total score for both improvement and worsening of angioedema-related QoL.[34]

Patients treated with either of the lanadelumab 300mg doses achieved statistically significant and clinically meaningful improvement in QoL as measured by the AE-QoL during the 26-week treatment period (Day 0 to Day 182). Statistically significant reductions (improvement) between the two lanadelumab 300mg treatment arms and placebo were observed for the mean change in AE-QoL total score and functioning

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domain score compared with placebo from Day 0 to Day 182 ($p<0.05$; Table 17). When all three lanadelumab treatment arms were combined, statistically significant ($p<0.05$) and clinically meaningful reductions (i.e. improvement) in AE-QoL total score and all domain scores was observed compared with placebo; the largest improvement was observed in the [redacted] ($p<0.01$; Table 17).[59, 73]

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Table 17: ANCOVA results for change in AE-QoL scores from Day 0 to Day 182 by treatment arm, adjusted for baseline scores – ITT population

Treatment arm	AE-QoL least square mean change (SD)				
	Total	**Functioning**	**Fatigue/mood**	**Fear/ shame**	**Nutrition**
Placebo (n=38)	-4.72 (18.75)	-5.42 (22.72)	-1.79 (23.25)	-9 (24.02)	0.51 (22.5)
Lanadelumab 300mg q2w	-21.29 (18.35)#	-35.97 (22.29)#	-15.78 (22.79)	-17.59 (23.29)	-18.03 (22.01)#
Change vs. placebo, mean (95% CI); p-value	−16.57 (−28.53 to −4.62); 0.003	NR			
Lanadelumab 300mg q4w	-17.38 (18.67)#	-24.29 (22.66)#	-13.86 (23.22)	-16.3 (23.71)	-13.34 (22.32)
Change vs. placebo, mean (95% CI); p-value	−12.66 (−24.51 to −0.80); p=0.03	NR			
Lanadelumab 150mg q4w (n=26)	-19.82 (19.07)#	-27.76 (23.12)#	-9.33 (23.62)	-22.53 (24.38)	-19.82 (22.76)#
Change vs. placebo, mean (95% CI); p-value	−15.11 (−27.12 to −3.09); p=0.008	NR			
F and p-value	6.97****	12.23***	2.95*	3.8**	3.86**
Lanadelumab total versus placebo: least square mean change (SD)					
Placebo	-4.71 (18.64)	-5.41 (22.92)	-1.79 (23.17)	-9.05 (23.92)	0.49 (22.43)
Lanadelumab total	-19.47 (18.59)	-29.28 (22.88)	-13 (23.12)	-18.75 (23.74)	-17.01 (22.33)
F and p-value	20.67***	32.7***	7.82**	9.27***	10.68***

Key: AE-QoL, Angioedema Quality of Life Questionnaire; ANCOVA, analysis of covariance; CI, confidence interval; ITT, intent-to-treat; q2w, every 2 weeks; q4w, every 2 weeks; SD, standard deviation.
Notes: For ANCOVAs: p-value ****<0.001 ***<0.01, **0.01- <0.04, *0.04<0.05, - ≥0.05; For *post-hoc* comparisons: p-value *<0.05; #: Significant differences between treatment and placebo arms on *post-hoc* pairwise comparison tests (Tukey-Kramer; p<0.05).
Source: HELP-03 CSR.[59]; Banerji et al., 2018[60]

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Lanadelumab 300mg q2w led to a significantly greater proportion of patients achieving a clinically meaningful improvement (at least 6-point reduction) in QoL (81%; p=0.001), compared with placebo (37%) (Table 18).[60] A greater proportion of patients receiving lanadelumab 300mg q4w also had a clinical meaningful improvement in QoL compared with placebo, although this was not statistically significant (63% vs. 37%; p=0.07).[60] Similar trends were observed for functioning, fatigue/mood, fear/shame, and nutrition domain scores.[59, 73]

Table 18: Proportion of patients achieving a clinically meaningful improvement in AE-QoL total and domain scores from Day 0 to Day 182

Treatment Arms	% Responders†† (95% CI)				
	Total	Functioning	Fatigue/Mood	Fear/Shame	Nutrition
Placebo (N=38)	36.8 (22, 54)	53 (36, 69)	42 (26, 59)	45 (29, 62)	42 (26, 59)
Lanadelumab 300mg q2w (N=26)	80.8 (61, 93)	81 (61, 93)	54 (33, 73)	73 (52, 88)	65 (44, 83)
P-value vs. placebo	0.001	NR			
Lanadelumab 300mg q4w (N=27)	63.0 (42, 81)	78 (58, 91)	67 (46, 83)	67 (46, 83)	52 (32, 71)
P-value vs. placebo	0.07	NR			
Lanadelumab 150mg q4w (N=26)	65.4 (44, 83)	73 (52, 88)	46 (27, 67)	81 (61, 93)	58 (37, 77)
P-value vs. placebo	0.047	NR			
Lanadelumab total (N=79)	70 (58, 79)	77 (66, 86)	56 (44, 67)	73 (62, 83)	58 (47, 69)

Key: CI, confidence interval; q2w, every 2 weeks; q4w, every 2 weeks.
Notes: ††, Responders were defined as patients who observed at least 6-point reduction in the AE-QoL total score from Day 0 to Day 182.
Source: QoL data summary[73]; Banerji et al., 2018[60]

In addition, based on a logistic regression model, patients treated with lanadelumab had higher odds (7.2 [p<0.01] for lanadelumab 300mg q2w; 2.9 [p=0.04] for

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lanadelumab 300mg q4w) of achieving clinically meaningful improvement (6-point improvement) in AE-QoL total scores compared with placebo (Table 19).[59, 73 60]

Table 19: Logistic regression model for patients achieving a clinically meaningful improvement in AE-QoL total score

Treatment arms	OR	95% CI	p-value
Lanadelumab 300mg q2w	7.2	2.2–23.4	0.001
Lanadelumab 300mg q4w	2.9	1.1–8.1	0.04
Lanadelumab 150mg q4w	3.2	1.1–9.2	0.03
Lanadelumab total	3.9	1.7–8.9	<0.01

Key: AE-QoL, Angioedema Quality of Life Questionnaire; CI, confidence interval; OR, odds ratio; q2w, every 2 weeks; q4w, every 4 weeks.
Notes: p-values represent comparisons with the placebo arm.
Source: Lanadelumab QoL data summary[73]; Banerji et al., 2018[60]

The HELP-03 trial also measured QoL using the generic measure, the EQ-5D-5L. No differences were observed across the lanadelumab treatment arms and placebo arm (as well as between the lanadelumab total arm and placebo).[59, 73] However, it should be noted that the EQ-5D-5L questionnaire is a generic questionnaire on patient utility and therefore can be insensitive to changes in a particular disease area, and unable to capture the effects of treatment on health status. Full details of the EQ-5D-5L results are presented in Appendix N.

PK/PD

Figure 9 shows the relationship between the exposure to lanadelumab and HAE attack rates, demonstrating that the higher the lanadelumab concentration, the lower the HAE attack rates. These data support the results of the primary efficacy analysis.[59]

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Figure 9: Correlation between mean lanadelumab concentration and HAE attack rate over time, by treatment group

Key: HAE, hereditary angioedema; SD, standard deviation; SHP643, lanadelumab; Q2W, every 2 weeks; Q4W, every 4 weeks.
Source: HELP-03 CSR.[59]

Long term extension study HELP-04: Interim results

HAE attack rates (rollover patients)

Rollover patients who had received lanadelumab in the HELP-03 study maintained low HAE attack rates over 6 months (182 days) of the long-term extension study HELP-04, demonstrating the persistent efficacy of lanadelumab (Figure 10 and Table 20). Baseline attack rates for patients who received lanadelumab during the HELP-03 ranged from 3.18 to 3.54, which reduced to 0.26–0.54 by the end of the 26-week HELP-03 study. These same patients had a mean attack rate of 0.19–0.47 attacks per month at interim data readout for the long-term extension study HELP-04, which amounts to a total 83.9–90.5% reduction from baseline in attacks per month (Figure 10 and Table 20). Furthermore, patients who had received placebo in the HELP-03 study also showed a substantial reduction in mean attack rate of 90.7% at the interim

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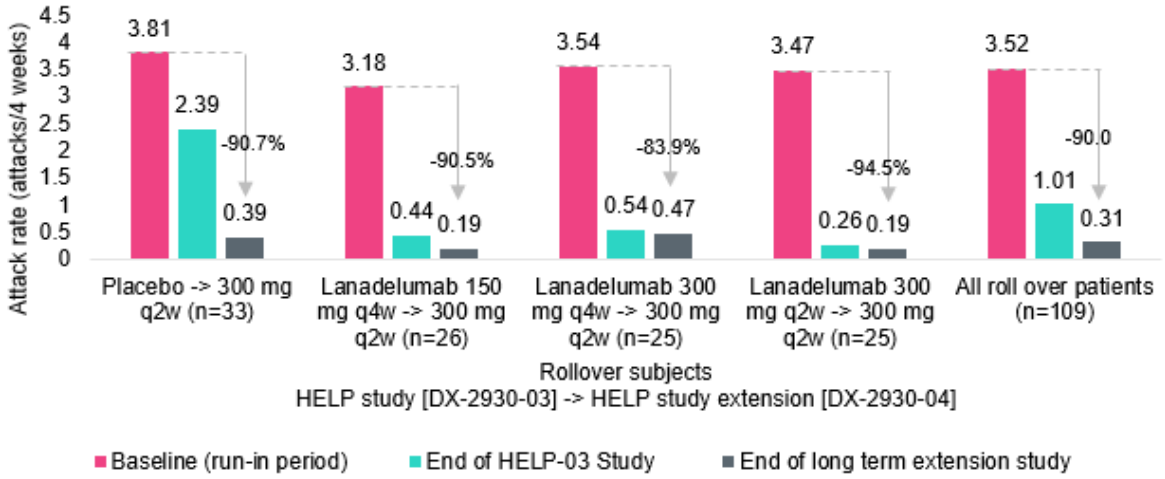
data readout from the long-term extension study HELP-04 compared to their baseline attack rate as measured during the run-in period of the HELP-03 Study (Figure 10 and Table 20).[68]

Figure 10: Mean HAE attack rates at baseline and at interim analysis after 182 days of lanadelumab treatment in patients in the long-term extension study HELP-04 who had rolled over from the HELP-03 study



Key: HAE, hereditary angioedema, q2w, every 2 weeks, q4w, every 4 weeks
Source: Lanadelumab AMPC dossier[68]; Riedl et al. 2018[63]

Table 20: Mean HAE attack rates reduction in rollover patients

	Rollover patients Study 03 treatment to Study 04 treatment				
	Placebo → 300mg q2w (n=33)	**300mg q2w → 300mg q2w (n=25)**	**300mg q4w → 300mg q2w (n=25)**	**150mg q4w → 300mg q2w (n=26)**	**All rollover patients (n=109)**
Mean HAE attack rate in attacks per month (SD)					
Baseline	3.81 (2.997)	3.47 (2.392)	3.54 (2.580)	3.18 (1.739)	3.52 (2.48)
HELP-03	2.39 (1.935)	0.26 (0.451)	0.54 (0.785)	0.44 (0.569)	1.01 (1.49)
HELP-04	0.39 (0.897)	0.19 (0.303)	0.47 (0.648)	0.19 (0.292)	0.31 (0.62)

Key: q2w, every 2 weeks; q4w, every 2 weeks; SD, standard deviation.
Source: Lanadelumab AMPC dossier[68]; Riedl et al. 2018[63]

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HAE attack rates (non-rollover patients)

Non-rollover patients who received lanadelumab 300mg q2w in the long-term extension study HELP-04 showed substantial reductions in the number of HAE attacks per month over 6 months (182 days), irrespective of the long-term prophylaxis they had received previously (Figure 11 and Table 21). Patients entering the long-term extension study without having previously been in the HELP-03 Study had experienced a mean of [redacted] attacks per month; this decreased to [redacted] attacks per month after 182 days of lanadelumab 300mg q2w (Figure 11 and Table 21). These reductions corresponded to a [redacted] reduction in attack rate, and the majority of results were consistent with the reduction in attack rate observed with lanadelumab 300mg q2w in the HELP-03 Study (86.9%).[68]

Figure 11: Mean HAE attack rates at baseline and at interim analysis after 182 days of lanadelumab treatment in the long-term extension study HELP-04 who had not rolled over from the HELP-03 study

Source: Lanadelumab AMPC dossier[68]; Riedl et al. 2018[63]

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Table 21: HAE attack reduction in non-rollover patients by prior therapy

	Non-rollover patients Treatment prior to Study 04 treatment				
	On demand only → 300mg q2w (n=40)	**C1-INH only → 300mg q2w (n=53)**	**Oral therapy → 300mg q2w (n=8)**	**C1-INH & oral therapy → 300mg q2w (n=2)**	**All non-rollover patients (n=103)**
Mean HAE attack rate in attacks per month (SD)					
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	2.55 (2.75)
Study 03	[redacted]	[redacted]	[redacted]	[redacted]	NA
Study 04	[redacted]	[redacted]	[redacted]	[redacted]	0.28 (0.64)

Key: C1-INH, C1 inhibitor; HAE, hereditary angioedema; q2w, every 2 weeks; NA, not applicable; SD, standard deviation.
Source: Lanadelumab AMPC dossier[68]; Riedl et al. 2018[63]

Rates of moderate/severe attacks

Treatment with lanadelumab reduced the occurrence of moderate/severe HAE attacks, consistent with the overall pattern of reductions in HAE attack rate (Figure 12).[63] In the total population, median and mean attack rates during the treatment period were 0.0 and 0.23, respectively, reflecting substantial reductions from baseline in the monthly rate of moderate/severe attacks (median reduction of 100%; mean reduction of 81.9%).

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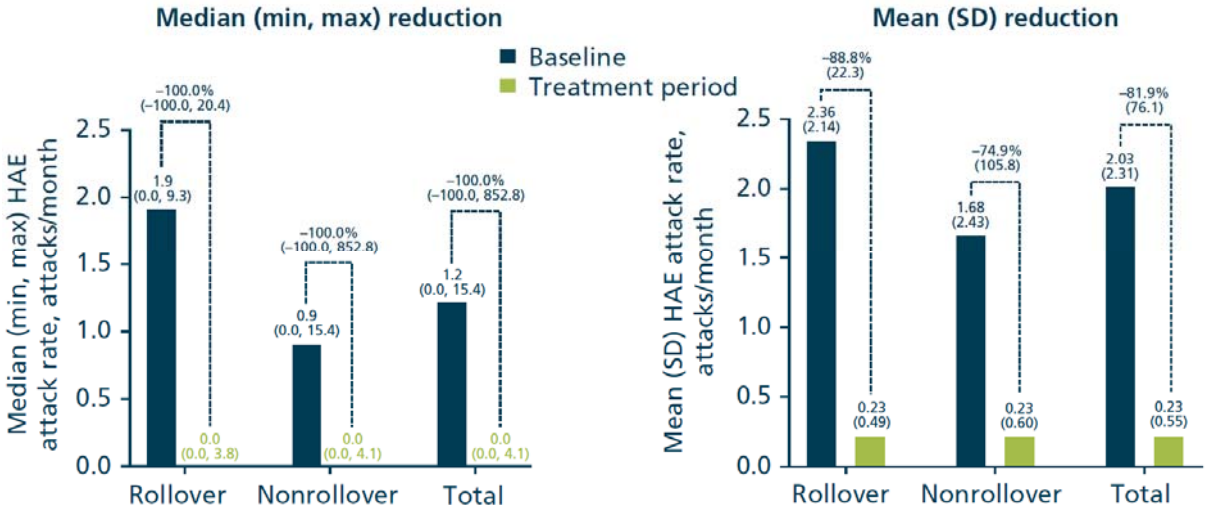
Figure 12. Rate of moderate/severe HAE attacks and reduction from baseline* during the treatment period†



Key: HAE, hereditary angioedema, SD, standard deviation.
Notes: *Baseline for the rollover population was defined as the number of investigator-confirmed HAE attacks occurring during the run-in period of the phase 3 HELP Study divided by the total number of days in the run-in period multiplied by 28 days. Baseline for the non-rollover population was defined as the historical rate of HAE attacks in the previous 12 weeks before screening divided by the number of days the patient contributed to the historical reporting period multiplied by 28 days. †Regular dosing period for rollover patients.
Source: Riedl et al. 2018[63]

Rates of high morbidity attacks

Treatment with lanadelumab led to substantial reductions in the rate of high morbidity attacks too, and rates were similar between rollover and non-rollover patients during the treatment period.[63] The mean rate of high morbidity attacks decreased in rollover patients, from 0.48 at baseline to 0.03 during the treatment period, reflecting a mean reduction of 97.1%. Although the baseline rate of high-morbidity attacks in non-rollover patients could not be determined, the mean rate of high morbidity attacks was 0.05 during the treatment period, which was similar to the rate in rollover patients.[63]

Attack-free days

Patients treated with lanadelumab in HELP-04 were attack-free on most days during the treatment period, with patients reporting a median of 100% attack-free days (mean: 97.4%), for a median duration of 105.0 days (mean: 125.7 days) (Table 22).[63] The number and percentage of attack-free days per month were similar for rollover

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and non-rollover patients, although the median duration of the attack-free period was shorter for the rollover population (88.3 vs 164.5 days).[63]

Table 22. Percentage, number, and duration of attack-free days during treatment period

	Rollover (n=109)	Non-rollover (n=103)	Total (n=212)
Number of HAE attack-free days* per month[†,‡]			
N	106	103	209
Mean (SD)	27.2 (1.8)	27.3 (1.6)	27.3 (1.7)
Median (range)	28 (14-28)	28 (16-28)	28 (14-28)
Percentage of HAE attack-free days[§]			
N	106	103	209
Mean (SD)	97.3 (6.3)	97.6 (5.9)	97.4 (6.1)
Median (range)	100 (50-100)	100 (57-100)	100 (50-100)
Average duration of attack-free period (days)[‖]			
N	106	103	209
Mean (SD)	110.5 (78.6)	141.3 (82.0)	125.7 (81.5)
Median (range)	88.3 (3.0-325.0)	164.5 (3.9-323.0)	105.0 (3.0-325.0)

Key: HAE, hereditary angioedema; SD, standard deviation.
Notes: *Attack-free day was defined as no HAE attack on a particular day. †A month was defined as 28 days. ‡Regular dosing period for rollover patients. n=106 because 3 patients had not received their second dose of lanadelumab (and therefore did not enter the regular dosing period). §Calculated by counting the number of days in the treatment period without an HAE attack and dividing by the number of days the patient spends in the treatment period. ‖For each patient, the average duration of the attack-free period will be derived by taking the average of the attack-free periods for the patients.
Source: Riedl *et al.* 2018[63]

B.2.7. Subgroup analysis

In the HELP-03 study, pre-specified subgroup analyses were performed for the primary efficacy endpoint. The subgroup analyses were conducted using the same method described for the primary efficacy endpoint (See Section B.2.4) and were based on the following baseline demographic and disease characteristics:[59]

- Age (<18, 18 to <40, 40 to <65, ≥65 years)
- Sex (male, female)
- Race (white, other)
- Weight group (<50, 50 to <75, 75 to <100, ≥100kg)
- Body mass index (BMI) group (<18.5, 18.5 to <25, 25 to <30, ≥30kg/m^2)

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- Baseline period HAE attack rate (1 to <2, 2 to <3, ≥3 attacks/month)
- HAE type (Type I, Type II)
- Geographic region (US, Canada, Jordan, Europe)
- Type of LTP prior to study randomisation (C1-INH and oral therapy, C1-INH only, no LTP use and oral therapy)
- History of laryngeal HAE attack (yes, no)

In the pre-specified subgroup analyses of the HELP-03 study, [redacted] was observed in subgroups with adequate numbers of patients, as summarised in Appendix E.[59]

B.2.8. Meta-analysis

The HELP-03 clinical trial is the only study of lanadelumab versus placebo. Therefore, a meta-analysis of available evidence was not applicable to this appraisal.

B.2.9. Indirect and mixed treatment comparisons

Methods

After consideration of all relevant data sources obtained in the SLR (Section B.2.1), the final evidence network included two studies (HELP-03, CHANGE, Figure 13). As described in Section B.2.3, HELP-03 was a Phase III, parallel-arm, placebo-controlled trial investigating the following lanadelumab dosing schedules: 300mg q2w, 300mg q4w, and 150mg q4w. Although the lanadelumab 150mg dose has been included in the figures within this section for completeness, no discussion of the results for the 150mg dose is included herein, given that this dose is not included in the current licence for lanadelumab.[1, 3] CHANGE was a Phase III crossover trial comparing placebo and C1-INH (C1-INH IV 1000IU twice weekly [bw]). Further details of each study in the final network diagram presented in Figure 13 are presented in Appendix D.1.

Figure 13: Final network diagram for ITC

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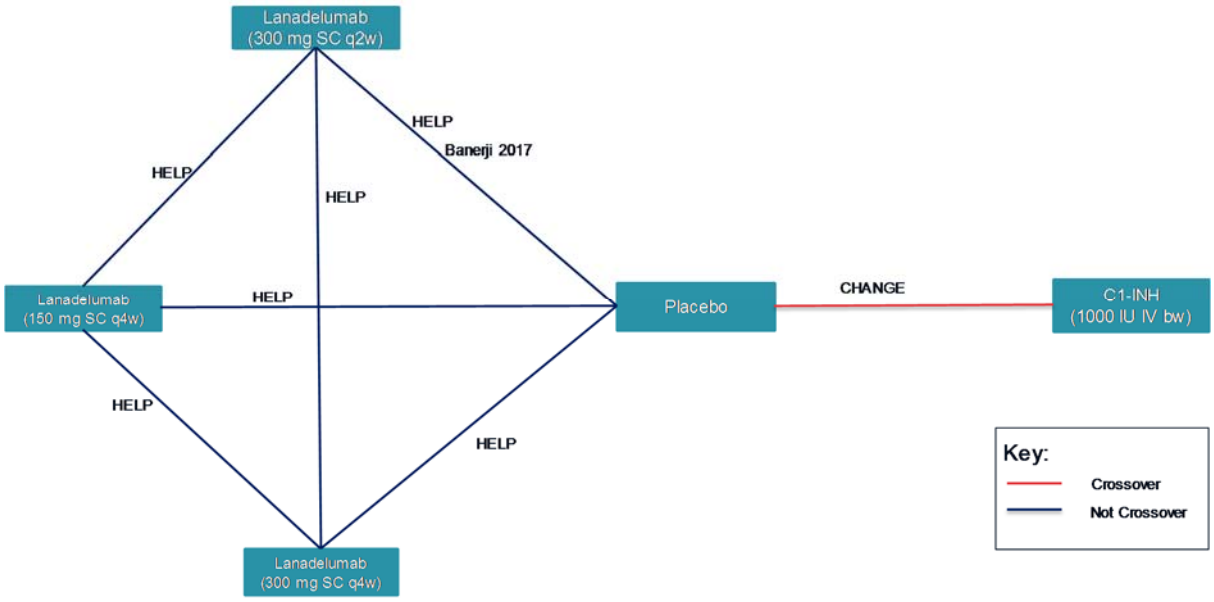

Key: bw, twice weekly; C1-INH, C1 esterase inhibitor; IV, intravenous; q2w, every 2 weeks; q4w, every 4 weeks; SC, subcutaneous.

As described in Appendix D.1, the outcomes of interest in the ITC were:

- Attack rate: the number of attacks per 28-day cycle. The relative treatment effects were estimated as rate ratios, i.e. the rate of attacks per 28-day cycle while on Treatment A divided by the rate of attacks per 28-day cycle on Treatment B. For example, a rate ratio of 0.25 corresponds to a 75% reduction in the rate of attacks on Treatment A compared to Treatment B.
- Time to first attack after Day 0: the time a patient has their first attack after Day 0. The relative treatment effects were estimated as hazard ratios comparing time to first attack after Day 0 while on Treatment A relative to Treatment B.
- Time to first attack after Day 70: the time a patient has their first attack after Day 70. The relative treatment effects were estimated as hazard ratios comparing time to first attack after Day 70 while on Treatment A relative to Treatment B.

Bayesian network meta-analyses (NMAs) were developed for the attack rate and hazard ratio outcomes. Bayesian analyses rely upon the use of Markov Chain Monte Carlo (MCMC) methods, combining prior distributions with the data to construct a posterior distribution upon which to base summary results. Relative efficacy was estimated using treatment effect models detailed in NICE Decision Support Unit

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(DSU) Technical Support Document (TSD) 2[74], which allows direct and indirect evidence to be synthesised in one analysis while accounting for correlation arising from multi-arm trials. A Bayesian approach was used to capture the uncertainty in model parameters while preserving correlation between treatment effects. Full details of the methodology for the NMAs and all evidence networks and outcomes are provided in Appendix D.1.

Results

Attack rate

A Bayesian NMA was performed using attack rate data from the HELP-03 and CHANGE trials. A fixed-effects model and three random-effects models with alternative priors on the between-trials standard deviation parameter were considered. The three priors considered were Uniform (0,5), Uniform (0,3) and Half-Normal (0,2). The data used in the NMA of the attack rate ratio for each study and treatment is presented in Appendix D.1. The value of the log attack rate ratio is the log of the attack rate ratio of treatment versus placebo. Standard error values are the standard errors of the log rate ratio for each treatment relative to placebo except for the placebo row of the HELP-03 study. In this case the standard error is the standard error of the log rate, not rate ratio, for the placebo arm of the HELP-03 study. This is required to control for the correlation in the relative treatment effects, which occur since all three doses of lanadelumab are compared to the same placebo arm (see Appendix D.1).[74]

The results of the random effect model using the Uniform (0,5), Uniform (0,3) and Half-Normal (0,2) prior distributions are presented in Appendix D.1. For each comparison, the credible intervals (CrIs) vary between the choice of priors. In each of the three random-effects models the CrIs are wide, showing that the results have a high level of uncertainty. This is due to the small sample of studies in the data set and the use of a vague prior distribution. The high uncertainty can also be observed in the posterior distribution of the between-trials standard deviation, for each alternative prior distribution (Appendix D.1). The uncertainty in the value of the between-trials standard deviation is likely to be the main cause of the high uncertainty in the estimation of the attack rate ratio. Appendix D.1 presents the trial

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design and demographic details for each trial. As there does not appear to be any systematic difference between the populations used in each trial, and it is difficult to estimate the uncertainty using a random-effects model due to the small sample size, it was concluded that the fixed-effects model is the most appropriate model to use. The fixed-effects model has been used also for all other endpoints described below.

Figure 14 presents a forest plot of the median attack rate ratio and 95% CrIs for all treatments of interest versus placebo for the fixed-effects model. The median rate ratios are less than 1 for all treatments compared to placebo. This shows that treatment reduces the risk of attack compared to placebo; therefore, patients receiving prophylactic treatment experience fewer attacks each month than patients taking placebo.

The rate ratio for patients treated with lanadelumab 300mg q2w compared to those receiving placebo [redacted], which corresponds to [redacted] reduction in the attack rate. For patients treated with lanadelumab 300mg q4w compared to placebo, the rate ratio was [redacted], which corresponds to a [redacted] reduction in the attack rate. In each case, the CrIs for treatment versus placebo [redacted]

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Figure 14: Fixed-effects model: attack rate ratio of treatment versus placebo

Key: C1-INH, C1 esterase inhibitor; CrI, credible interval; IV, intravenous; q2w, every 2 weeks; q4w, every 4 weeks; SC, subcutaneous.

Forest plots of lanadelumab 300mg q2w versus all other treatments and lanadelumab 300mg q4w versus all other treatments are presented in Appendix D.1. A median rate ratio of less than 1 in these forest plots indicates a reduction in the attack rate for patients treated with lanadelumab 300mg q2w and 300mg q4w, compared to the corresponding alternative treatments. Therefore, patients taking the relevant lanadelumab dose would experience fewer attacks than patients taking the corresponding alternative treatment.

For example, the rate ratio for lanadelumab 300mg q2w versus C1-INH is [redacted]. This means that patients treated with lanadelumab 300mg q2w have a [redacted] reduction in attack rate compared to patients receiving C1-INH. Since [redacted].

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It is important to note that the CrIs of lanadelumab (300mg q2w) versus the other treatments tend to be wider than those for lanadelumab (300mg q2w) versus placebo. This is due to the number of steps required to form the comparison in the network diagram in Figure 13. All treatments can be connected to placebo in only one step. Therefore, the variance for each relative treatment effect is mainly informed by the primary study comparing a given treatment with placebo. If there are two steps in the network, then the total variance incorporates the variance from both studies involved in a given comparison. For example, to compare C1-INH and lanadelumab 300mg q2w, the total variance is the variance of the C1-INH versus placebo comparison added to the variance of the placebo versus lanadelumab 300mg q2w comparison. This increased variance will increase the width of the credible intervals.

Time to first attack after Day 0

A Bayesian NMA was performed using hazard data from the HELP-03 and binary data from the CHANGE trial. A fixed-effects model and three random-effects models were considered. The three priors considered were Uniform (0,5), Uniform (0,3) and Half-Normal (0,2). Appendix D.1 presents the hazard ratios and binary data used for the NMA, as described by Woods (2010)[75], and the log hazard ratios and standard errors for each treatment in the HELP-03 trial.

The value of the log hazard ratio is the log of the hazard ratio of treatment versus placebo. The standard error for placebo is the standard error for the log of the hazard for placebo in the HELP-03 trial, which is used as a comparison. The standard error of the log hazard in the placebo arm is used to adjust for the correlation between treatment effects in multi-arm trials that arises from each treatment being compared to the same control group. All other standard error values are the standard errors of the log of the hazard ratio of treatment versus placebo. The input into the NMA is the number of patients who have experienced at least one attack for each treatment and trial. In the CHANGE trial, all patients in the placebo treatment group experienced at least one attack. As described in Appendix D.1, the method for binary data cannot be used if any studies report that either all patients had an attack, or no patients had an attack in at least one treatment arm. Therefore, for the placebo treatment group of the CHANGE trial, a continuity correction as

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described by Cochrane[76] was used. The standard continuity correction is to either add 0.5 or subtract 0.5. As the binary observation is the number of people, a continuity correction of 1 was subtracted from the total number of patients.

Figure 15 presents a forest plot of the median hazard ratio and 95% CrIs for all treatments of interest versus placebo for the fixed-effects model. The median hazard ratio values are less than 1 for all treatments compared to placebo. This shows that treatment reduces the risk of experiencing a first attack compared to patients taking placebo, and patients receiving prophylactic treatment therefore have a longer time before first attack than patients taking placebo.

The results of the random effect model using the Uniform (0,5), Uniform (0,3) and Half-Normal (0,2) prior distributions are presented in Appendix D.1.

Figure 15: Time to first attack after Day 0: Fixed-effects model: Hazard ratio of treatment versus placebo

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Key: C1-INH, C1 esterase inhibitor; CrI, credible interval; IV, intravenous; q2w, every 2 weeks; q4w, every 4 weeks; SC, subcutaneous.

For patients treated with lanadelumab 300mg q4w compared to placebo, the hazard ratio was [redacted], which corresponds to a [redacted] reduction in risk of experiencing a first attack. The hazard ratio for patients treated with lanadelumab 300mg q2w compared to those receiving placebo was [redacted], which corresponds to a [redacted] reduction in the risk of experiencing a first attack. For patients treated with C1-INH the hazard ratio compared to placebo was [redacted]

In all cases apart from the comparison of C1-INH and placebo, the CrIs for treatment versus placebo [redacted].

Appendix D.1 presents forest plots of lanadelumab 300mg q4w versus all other treatments and lanadelumab 300mg q2w versus all other treatments. A median hazard ratio less than 1 in these three forest plots means that lanadelumab 300mg q4w and 300mg q2w reduces the risk of experiencing a first attack compared to the corresponding alternative treatments. Therefore, patients taking the relevant lanadelumab dose have a longer time to first attack than patients taking the corresponding alternative treatment.

For example, for lanadelumab 300mg q2w versus all other treatments, the hazard ratio versus C1-INH 1000IU IV is [redacted] which implies patients have a [redacted] of experiencing a first attack when treated with lanadelumab 300mg q2w than when treated with C1-INH 1000IU IV. However, the 95% CrIs [redacted], and the result therefore [redacted]

The CrIs of lanadelumab (300mg q2w) versus the other treatments tend to be wider than those for lanadelumab (300mg q2w) versus placebo. This is due to the number of steps required to form the comparison in the network diagram in Figure 13, as treatments can all be connected to placebo in only one step, further details can be found in the previous section.

Time to first attack after Day 70

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A Bayesian NMA was performed using hazard data from HELP-03 and binary data from the CHANGE trial. The method used is the same as for the NMA for the time to first attack after Days 0 and 14, as described by Woods (2010).[75] A fixed-effects model and three random-effects models were considered. The three priors considered were Uniform (0,5), Uniform (0,3) and Half-Normal (0,2). The hazard ratios used for the NMA derived from the HELP-03 data for time to first attack after Day 70 are presented in Appendix D.1. The value of the log hazard ratio is the log of the hazard ratio of treatment versus placebo. The standard error for placebo is the standard error for the log of the hazard for placebo in the HELP-03 trial, which is used as a comparison. The standard error of the log hazard in the placebo arm is used to adjust for the correlation between treatment effects in multi-arm trials that arises from each treatment being compared to the same control group. All other standard error values are the standard errors of the log of the hazard ratio of treatment versus placebo.

Figure 16 presents a forest plot of the median hazard ratio and 95% CrIs for all treatments of interest versus placebo for the fixed-effects model. The median hazard ratio values are less than 1 for all treatments compared to placebo. This shows that treatment reduces the risk of experiencing a first attack compared with patients taking placebo and that patients receiving prophylactic treatment therefore have a longer time before their first attack than patients taking placebo.

The results of the random-effects model using the Uniform (0,5), Uniform (0,3) and Half-Normal (0,2) prior distributions are presented in Appendix D.1.

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Figure 16: Time to first attack after Day 70: Fixed-effects model: Hazard of treatment versus placebo

Key: C1-INH, C1 esterase inhibitor; CrI, credible interval; IV, intravenous; q2w, every 2 weeks; q4w, every 4 weeks; SC, subcutaneous.

For patients treated with lanadelumab 300mg q4w compared to placebo, the hazard ratio [redacted], which corresponds to a [redacted] reduction in risk of experiencing a first attack. The hazard ratio for patients treated with lanadelumab 300mg q2w compared to those receiving placebo was [redacted], which corresponds to a [redacted] reduction in the risk of experiencing a first attack. The reduction in risk of experiencing a first attack for patients receiving C1-INH compared to placebo [redacted]

In all cases apart from the comparison of C1-INH and placebo, the CrIs for treatment versus placebo [redacted], therefore; the results [redacted]

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[redacted].

Appendix D.1 presents forest plots of lanadelumab 300mg q4w versus all other treatments and lanadelumab 300mg q2w versus all other treatments. A median hazard ratio less than 1 in these forest plots means that lanadelumab 300mg q4w and 300mg q2w reduces the risk of experiencing a first attack compared to the corresponding alternative treatment. Therefore, patients taking the relevant lanadelumab have a longer time to first attack than patients taking the corresponding alternative treatment.

For example, the hazard ratio versus C1-INH 1000IU IV is [redacted] which means that patients treated with lanadelumab 300mg q2w have [redacted] reduction in risk of having a first attack compared to patients receiving C1-INH. Since the 95% CrIs [redacted]

The CrIs of lanadelumab (300mg q2w) versus the other treatments tend to be wider than those for lanadelumab (300mg q2w) versus placebo. This is due to the number of steps required to form the comparison in the network diagram in Figure 13, as treatments can be connected to placebo in only one step, further details can be found in the previous sections.

Uncertainties in the indirect and mixed treatment comparisons

Sensitivity analysis of the choice of prior for the between-trials standard deviation used in the random-effects model showed results were highly uncertain in the estimated relative treatment effects for the attack rate analyses, and in the time to first attack after Day 0, and Day 70 analyses. This was due to the small number of trials in the data set, the small patient numbers within the trial, given HAE is a very rare disease, and the use of a vague prior distribution for the between-trial standard deviation parameter.

The high uncertainty in the between-trial standard deviation can be observed in Appendix D.1, which presents the posterior distribution of the between-trials standard deviation, by prior distribution.

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The wide CrIs show there is high uncertainty in the value of the standard deviation for each prior distribution. The uncertainty in the value of standard deviation will cause high uncertainty in the values generated from the posterior distribution for both the attack rate ratio and the hazard ratio analyses. Therefore, the CrIs will be wide and show high uncertainty in the median. As there does not appear to be any systematic difference between the populations used in each trial (see Appendix D.1), and it is difficult to estimate the uncertainty using a random-effects model due to the small sample size, it was concluded that the fixed-effects model is the most appropriate model to use.

Conclusion

Attack rate

In the fixed-effects model for the attack rate, the comparison of all treatments versus placebo showed that all doses of lanadelumab had an attack rate ratio [redacted] This means [redacted] than patients taking placebo, and this can be considered [redacted]. All doses of lanadelumab showed a [redacted] in relative risk of attack compared to C1-INH.

Hazard ratio for time to first attack analyses

In the fixed-effects model for time to first attack, the comparison of all treatments versus placebo showed that all doses of lanadelumab had a hazard ratio less than 1. This means that patients taking lanadelumab have a lower risk of having a first attack. This finding was consistent across the Day 0 and Day 70 analyses.

Comparing lanadelumab (300mg q4w, and 300mg q2w) with C1-INH (1000IU) across the endpoints of interest (Day 0 and 70), the results demonstrate [redacted] with the majority of credible intervals [redacted] Numerically, the results tend to [redacted], but this is not consistent, with some results [redacted]. Overall, the [redacted] could be due to the small data set or because of the increased variance from combining two treatment comparisons in the NMA.

Limitations

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The two studies used in this ITC report different endpoints; therefore, it might not be appropriate to compare to the Day 0 and 70 endpoints. Extrapolation is over several years and is based on a short observation period, particularly for the time to first attack after Day 70 data. These analyses assume the treatment benefit is maintained in the long term.

B.2.10. Adverse reactions

HELP-03 safety data

As described in Section B.2.4, all safety analyses were performed using the safety population, which included 84 patients in the lanadelumab group and 41 patients in the placebo group.

Treatment exposure

Within the study, 106 (84.8%) of the patients in HELP-03 were exposed to 26 weeks of study treatment, administered as 13 doses (26 injections) of blinded treatment[59]:

- Lanadelumab 300mg q2w: [redacted] patients [redacted]
- Lanadelumab 300mg q4w: [redacted] patients [redacted]
- Lanadelumab 150mg q4w: [redacted] patients [redacted]
- Placebo: [redacted] patients (75.6%)

The remaining [redacted] patients either discontinued the study early but received all of their planned doses, or they continued in the study but missed at least one of their planned doses. A summary of these patients, doses received and their duration in the study is presented in Table 23, by treatment arm.

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Table 23: Patients ([redacted]) who did not receive all doses of study treatment in HELP-03

Treatment arm	Number of doses received	Number of planned doses	Doses received (%)	Duration on study (weeks)
[redacted]				
[redacted]				
[redacted]				
[redacted]				

Key: q2w, every 2 weeks; q4w, every 2 weeks.
Source: HELP-03 CSR.[59]

Adverse events

In the HELP-03 study, all AEs were categorised using MedDRA® Version 20.0 and were analysed based on the principle of treatment emergence. Treatment-emergent AEs (TEAEs) were defined as events with an onset date on or after the start of study treatment, or those that worsened after the start of study treatment. The TEAEs were monitored and reported through the last study visit, including monitoring of AEs through 4 weeks if the onset was after a placebo injection given to maintain the blinding in either the lanadelumab 150mg or 300mg q4w dosing regimen. Patients who experienced the same AE more than once were counted only once in the incidence of that event; the data are presented accordingly.

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In the HELP-03 study, HAE attacks were also recorded as AEs. Therefore, to avoid complicating the interpretation of safety, two mutually exclusive subgroups of AEs, based on whether the AE was identified as a patient-reported HAE attack or not, were defined as follows:

- **Non-HAE-attack-reported AEs**: included the subset of AEs identified in electronic data capture (EDC) as not a reported HAE attack (all AEs excluding HAE-attack-reported events)
- **HAE-attack-reported AEs:** included the subset of AEs identified in EDC as a reported HAE attack (included investigator-confirmed HAE attacks). The HAE-attack-reported AEs were different from the efficacy endpoint analyses in the following ways:
  - The AE analysis includes all HAE AEs, not just those confirmed by the investigator
  - The AE analysis presents all HAE AEs as reported, compared to the efficacy analysis where we use an algorithm to define unique attacks that need to be at least 24 hours apart
  - AE analysis presents relatedness to study drug, severity based on AE grading, and seriousness

As the HAE-attack-reported AEs included investigator-confirmed HAE attacks, which were already captured in Section B.2.6, the safety data presented throughout this section and used to support this submission are for non-HAE-reported AEs.

A summary of AEs that occurred during the pre-treatment period (AEs starting at or after informed consent to those starting before the first exposure to study drug) is presented in Appendix O. Briefly, there were 41 AEs in 23 (24.4%) patients during the pre-treatment period. Two patients in the 150mg q4w arm had a serious adverse event (SAE), and two patients were hospitalised due to an AE in the same treatment arm. There were no deaths during the pre-treatment period.

A summary of TEAEs during the treatment period (Day 0 to Day 182) is presented in Table 24. Lanadelumab SC was generally well tolerated at all three doses. Seventy-six patients (90.5%) in the three lanadelumab treatment arms had at least one TEAE

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(26 [96.3%] in the 300mg q2w arm, 25 [86.2%] in the 300mg q4w arm, and 25 [89.3%] in the 150mg q4w arm), compared with 31 patients (75.6%) in the placebo arm. Of these, 50 patients (59.5%) treated with lanadelumab had TEAEs, compared with 14 patients (34.1%) treated with placebo. Four patients (4.8%) in the lanadelumab treatment arms had four SAEs, compared with none in the placebo group; however, these were considered unrelated to treatment. The proportion of patients with severe TEAEs was comparable across treatment groups. There were no deaths due to a TEAE in the study. One patient in the lanadelumab 300mg q2w arm and three patients in the lanadelumab 300mg q4w treatment arm were hospitalised due to an AE, but all four of these events were reported as SAEs and were considered unrelated to study treatment. One patient in the placebo arm and one patient in the lanadelumab 300mg q4w arm discontinued due to a TEAE.

Table 24: Summary of TEAEs during the treatment period by treatment group- safety population

		Lanadelumab			
Event, n (%) m	**Placebo (n=41)**	**300mg q2w (n=27)**	**300mg q4w (n=29)**	**150mg q4w (n=28)**	**Total (N=84)**
Any TEAE	31 (75.6) 231	26 (96.3) 235	25 (86.2) 182	25 (89.3) 268	76 (90.5) 685
Any treatment-related TEAE	14 (34.1) 85	19 (70.4) 131	14 (48.3) 121	17 (60.7) 167	50 (59.5) 419
Any serious TEAE	0 (0.0) 0	1 (3.7) 1	3 (10.3) 3	0 (0.0) 0	4 (4.8) 4
Risk difference (95% CI)		3.70 (-20.34, 27.39)	10.34 (-13.36, 33.42)	0 (NE)	4.76 (-14.20, 23.47)
Any related serious TEAE	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Any severe TEAE	4 (9.8) 7	2 (7.4) 2	4 (13.8) 6	2 (7.1) 2	8 (9.5) 10
Any related severe TEAE	1 (2.4) 4	0 (0.0) 0	1 (3.4) 2	0 (0.0) 0	1 (1.2) 2
Any investigator-reported AESI	0 (0.0) 0	3 (11.1) 4	1 (3.4) 2	1 (3.6) 2	5 (6.0) 8
Risk difference (95% CI)		11.11 (-13.17, 34.31)	3.45 (-20.22, 26.91)	3.57 (-20.32, 26.96)	5.95 (-13.03, 24.62)

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Event, n (%) m	Placebo (n=41)	Lanadelumab			
		300mg q2w (n=27)	300mg q4w (n=29)	150mg q4w (n=28)	Total (N=84)
Deaths due to TEAE	0 (0.0) -	0 (0.0) -	0 (0.0) -	0 (0.0) -	0 (0.0) -
Hospitalisation due to TEAE	0 (0.0) 0	1 (3.7) 1	3 (10.3) 3	0 (0.0) 0	4 (4.8) 4
Discontinuation due to TEAE	1 (2.4) -	0 (0.0) -	1 (3.4) -	0 (0.0) -	1(1.2) -

Key: AESI, adverse event of special interest; EDC, electronic data capture; HAE, hereditary angioedema; n, number of patients experiencing the event, NE, non-estimated; m, number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.
Notes: Percentages are based on all patients in the safety population. Patients were counted once per category per treatment. TEAEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. Related TEAEs are TEAEs classified as related to study drug by the investigator; severe TEAEs are TEAEs classified as severe (Grade 3) or life threatening (Grade 4) by the investigator; Non-HAE attack reported AEs include the subset of AEs identified in EDC as not a reported HAE attack. 95% CI for relative risk is calculated by exact method.
Source: HELP-03 CSR[59];

Common adverse events

A summary of common AEs by system organ class and preferred term (≥5% in any treatment group) that occurred during the pre-treatment period is presented in Appendix O. Briefly, there were [redacted] AEs in [redacted] of patients randomised to the lanadelumab treatment arms, [redacted] AEs in [redacted] of patients in those randomised to the placebo arm. [redacted] were some of the common AEs during that period.

The most commonly occurring TEAEs (≥5% in any treatment arm) during the treatment period are presented in Table 25. During the treatment period, the most frequently reported TEAEs were [redacted] of lanadelumab-treated patients compared with [redacted] in placebo-treated patients), [redacted] of lanadelumab-treated patients compared with [redacted] of placebo-treated patients), [redacted] of lanadelumab-treated patients compared with [redacted] of placebo-treated patients), [redacted] of lanadelumab-treated patients compared with [redacted] of placebo-treated patients) and

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[redacted] of lanadelumab-treated patients compared with [redacted] in the placebo-treated arm).

Increases in frequency of TEAEs were predominantly driven by injection site pain (two separate 1ml injections separated by 2cm in the upper arm to maintain blind). No dose response pattern, dose dependence or dose limiting toxicity was observed for any TEAE.

Table 25: Most common TEAEs (≥5% in any treatment arm) during the treatment period by treatment group and preferred term

Event, n (%) m	Placebo (n=41)	Lanadelumab			
		300mg q2w (n=27)	300mg q4w (n=29)	150mg q4w (n=28)	Total (n=84)
[redacted]					

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Event, n (%) m	Placebo (n=41)	Lanadelumab			
		300mg q2w (n=27)	300mg q4w (n=29)	150mg q4w (n=28)	Total (n=84)

Key: Adverse events, AEs; n, Number of patients experiencing the event, NE, non-estimated; m, Number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.
Notes: Percentages are based on all patients in the Safety Population; patients were counted once per system organ class and once per preferred term. TEAEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. Non-HAE-attack-reported AEs include the subset of AEs identified in electronic data capture as not a reported HAE attack.
Source: HELP-03 CSR[59]; Banerji et al. 2018.[60]

Grade 3 or higher adverse events

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A summary of the Grade 3 or higher (severe) AEs that occurred during the pre-treatment period is presented in Appendix O. Briefly, [redacted] patients randomised to lanadelumab 150mg q4w arm had [redacted]

A summary of Grade 3 or higher (severe) TEAEs that occurred in >2% of patients in any treatment arm during the treatment period is presented in Table 26. Overall, the percentage of severe TEAEs was similar across all treatment arms. No dose response pattern or dose dependence was observed. As shown in Table 26, during the treatment period, eight (9.5%) patients had 10 severe TEAEs in the three lanadelumab treatment arms and four (9.8%) patients had seven severe TEAEs in the placebo arm.

Table 26: Grade 3 or higher (severe) TEAEs (>2% in any treatment arm) during the treatment period by treatment group and preferred term – Safety population

Event, n (%) m	Placebo (n=41)	Lanadelumab			
		300mg q2w (n=27)	300mg q4w (n=29)	150mg q4w (n=28)	Total (n=84)
Any severe TEAE	4 (9.8) 7	2 (7.4) 2	4 (13.8) 6	2 (7.1) 2	8 (9.5) 10
Alanine aminotransferase increased	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	0 (0.0) 0	1 (1.2) 1
Aspartate aminotransferase increased	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	0 (0.0) 0	1 (1.2) 1
Bipolar II disorder	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	0 (0.0) 0	1 (1.2) 1
Catheter site infection	0 (0.0) 0	1 (3.7) 1	0 (0.0) 0	0 (0.0) 0	1 (1.2) 1
Cervical radiculopathy	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	0 (0.0) 0	1 (1.2) 1
Fibula fracture	0 (0.0) 0	1 (3.7) 1	0 (0.0) 0	0 (0.0) 0	1 (1.2) 1
Musculoskeletal pain	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	0 (0.0) 0	1 (1.2) 1
Pyelonephritis	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	0 (0.0) 0	1 (1.2) 1
Retinal detachment	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (3.6) 1	1 (1.2) 1
Upper limb fracture	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (3.6) 1	1 (1.2) 1
Cellulitis	1 (2.4) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0

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Event, n (%) m	Placebo (n=41)	Lanadelumab			
		300mg q2w (n=27)	300mg q4w (n=29)	150mg q4w (n=28)	Total (n=84)
Injection site pain	1 (2.4) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Nephrolithiasis	1 (2.4) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Tonsillitis	1 (2.4) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0

Key: AEs, adverse events; EDC, electronic data capture; n, Number of patients experiencing the event, NE, non-estimated; m, Number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.
Notes: Percentages are based on all patients in the Safety Population. Adverse events were classified into preferred term using Version 20.0 of MedDRA. Patients were counted once per preferred term. TEAEs are defined as AEs with onset at the time of or following the start of treatment with study; medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. Severe AEs are AEs classified as severe (Grade 3) or life threatening (Grade 4) by the investigator. Non-HAE-attack-reported AEs include the subset of AEs identified in EDC as not a reported HAE attack.
Source: HELP-03 CSR.[59]

Treatment-related TEAEs

A summary of the treatment related TEAEs that occurred during the treatment period is presented in Table 27. Overall, [redacted] patients in lanadelumab treatment arms and [redacted] patients in the placebo arm had related TEAEs. As shown in Table 27, the most common TEAEs (≥5% of patients) considered related to the treatment in all three lanadelumab treatment arms were [redacted]

Table 27: Treatment related TEAEs (≥5% of safety population) during the treatment period by treatment group and preferred term – Safety population

Event, n (%) m	Placebo (n=41)	Lanadelumab			
		300mg q2w (n=27)	300mg q4w (n=29)	150mg q4w (n=28)	Total (n=84)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

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Event, n (%) m	Placebo (n=41)	Lanadelumab			
		300mg q2w (n=27)	300mg q4w (n=29)	150mg q4w (n=28)	Total (n=84)
					

Key: AEs, adverse events; n, Number of patients experiencing the event, NE, non-estimated; m, Number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.

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Event, n (%) m	Placebo (n=41)	Lanadelumab			
		300mg q2w (n=27)	300mg q4w (n=29)	150mg q4w (n=28)	Total (n=84)
Notes: Percentages are based on all patients in the Safety Population; patients were counted once per system organ class and once per preferred term. TEAEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. Related TEAEs are TEAEs classified as related to study drug by the investigator. Non-HAE-attack-reported AEs include the subset of AEs identified in electronic data capture as not a reported HAE attack. **Source:** HELP-03 CSR.[59]; Banerji et al. 2018.[60]					

Grade 3 or higher treatment-related TEAEs

A summary of Grade 3 or higher (severe) treatment-related TEAEs that occurred during the treatment period is presented in Table 28. Overall, one (1.2%) patient in the lanadelumab 300mg q4w arm had two events of severe related TEAEs (alanine transaminase [ALT] and aspartate transaminase [AST] increased), and one (2.4%) patient in the placebo arm had four events of injection site reaction.

Table 28: Grade 3 or higher (severe) treatment-related TEAEs during the treatment period by treatment group and preferred term – Safety population

Event, n (%) m	Placebo (n=41)	Lanadelumab			
		300mg q2w (n=27)	300mg q4w (n=29)	150mg q4w (n=28)	Total (n=84)
Any related severe TEAE	1 (2.4) 4	0 (0.0) 0	1 (3.4) 2	0 (0.0) 0	1 (01.2) 2
Injection site pain	1 (2.4) 4	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
ALT increased	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	0 (0.0) 0	1 (1.2) 1
AST increased	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	0 (0.0) 0	1 (1.2) 1
Key: AEs, adverse events; ALT, alanine transaminase; AST, aspartate transaminase; EDC, electronic data capture; n, Number of patients experiencing the event, NE, non-estimated; m, Number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event. **Notes:** Percentages are based on all patients in the Safety Population; patients were counted once per preferred term. Adverse events were classified into preferred term using Version 20.0 of MedDRA; TEAEs are defined as AEs with onset at the time of or following the start of treatment with study. Medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment; Severe AEs are AEs classified as severe (Grade 3) or life threatening (Grade 4) by the investigator. Non-HAE-attack-reported AEs include the subset of AEs identified in EDC as not a reported HAE attack. **Source:** HELP-03 CSR.[59]					

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Serious treatment-emergent adverse events in treatment period

A summary of serious TEAEs that occurred during the treatment period is presented in Table 29. Overall, four (4.8%) lanadelumab-treated patients and no placebo-treated patients had an SAE during the treatment period. None of the serious TEAEs that occurred during the treatment period were considered related to the study treatment.

Table 29: Serious treatment emergent adverse events during the treatment period by treatment group, and preferred term – Safety population

Event, n (%) m	Placebo (n=41)	Lanadelumab			
		300mg q2w (n=27)	300mg q4w (n=29)	150mg q4w (n=28)	Total (n=84)
Any serious TEAE	0 (0.0) 0	1 (3.7) 1	3 (10.3) 3	0 (0.0) 0	4 (4.8) 4
Catheter site infection	0 (0.0) 0	1 (3.7) 1	0 (0.0) 0	0 (0.0) 0	1 (1.2) 1
Pyelonephritis	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	0 (0.0) 0	1 (1.2) 1
Meniscus injury	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	0 (0.0) 0	1 (1.2) 1
Bipolar II disorder	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1		1 (1.2) 1

Key: AEs, adverse events; EDC, electronic data capture; n, Number of patients experiencing the event, NE, non-estimated; m, Number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.
Notes: Percentages are based on all patients in the Safety Population; patients were counted once per system organ class and once per preferred term. AEs were classified into system organ class and preferred term using Version 20.0 of MedDRA; TEAEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. Non-HAE-attack-reported AEs include the subset of AEs identified in EDC as not a reported HAE attack.
Source: HELP-03 CSR.[59]; Banerji et al. 2018.[60]

Injection site reactions

Injection site reactions were the most frequently reported TEAEs. During the treatment period, 84 lanadelumab-treated patients received 2,118 injections and 42 placebo-treated patients received 962 injections of investigational product. Full

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details of injection site reactions occurring during the treatment period including frequencies, types and duration are presented in Appendix O.

Overall, 44 (52.4%) lanadelumab-treated patients and 14 (34.1%) placebo-treated patients experienced a total of 398 and 85 injection site reactions, respectively. In both treatment groups, the majority of the injection site reactions were considered to be related to the investigational product: 391 (98.2%) for lanadelumab and 77 (90.6%) for placebo. Within each lanadelumab treatment arm, the proportion of all injections associated with an injection site reaction was 17.5%, 15.6%, and 23.3% in the lanadelumab 300mg q2w, 300mg q4w and 150mg q4w arms, respectively, compared with 8.8% in the placebo arm.

Overall, most of the injection site reactions in the lanadelumab group were mild in severity; reports of moderate injection site reactions were infrequent and generally occurred in a single patient. Similarly, the majority of the injection site reactions in the placebo arm were mild in severity. However, one placebo-treated patient experienced four severe related injection site reactions. Furthermore, injection site reactions were short in duration with a median duration of 0 hours for lanadelumab 300mg q2w, 0.1 hours for lanadelumab 300mg q4w, and 0.1 hours for placebo.[59]

Adverse events of special interest

Adverse events of special interest (AESIs) in the HELP-03 study were defined prior to the start of the study and included hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events). No patients in the placebo treatment arm experienced and AESI and the rates of AESIs were low in the lanadelumab treatment arms, as only five patients (6.0%) experienced a total of eight AESIs. The AESIs included microcytic anaemia, injection site erythema, injection site induration, injection site reaction, immune system disorders, and hypersensitivity. Each of these AESIs occurred in one patient (1.2%). Further details of the investigator-reported AESIs that occurred during the treatment period are presented in Appendix O.

Immunogenicity

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As with all therapeutic proteins, there is a potential for immunogenicity. In the HELP-03 study, 10 (11.9%) lanadelumab-treated and two (4.9%) placebo-treated patients had at least one treatment-emergent antidrug antibody (ADA)-positive sample during the treatment period; all antibody titres were low (range: 20–1,280). A summary of immunogenicity responses is presented in Table 30.

The ADA response observed was transient in two of the 10 lanadelumab-treated patients and one of the two placebo-treated patients. Baseline low-titre antibodies were observed in three of the lanadelumab-treated patients and one of the placebo-treated patients with ADAs. Two patients receiving 150mg q4w had low-titre antibodies classified as neutralising, but these were found to not be clinically significant. The development of ADA including neutralising antibodies against lanadelumab did not appear to adversely affect pharmacokinetics, pharmacodynamics, safety or clinical response.

Table 30: Summary of immunogenicity responses of patients in the HELP-03 trial – Safety population

Parameter	Placebo (n=41)	Lanadelumab			
		300mg q2w (n=28)	300mg q4w (n=29)	150mg q4w (n=27)	Total (n=84)
ADA prevalence[a]	3 (7.3)	5 (17.9)	3 (10.3)	4 (14.8)	12 (14.3)
ADA incidence[b]	2 (4.9)	5 (17.9)	3 (10.3)	2 (7.4)	10 (11.9)
Pre-existing ADA[c]	1 (2.4)	0 (0.0)	1 (3.4)	2 (7.4)	3 (3.6)
Treatment-induced[d]	2 (4.9)	5 (17.9)	2 (6.9)	2 (7.4)	9 (10.7)
Treatment-boosted[e]	0 (0.0)	0 (0.0)	1 (3.4)[f]	0 (0.0)	1 (1.2)
Non-neutralising ADA	3 (7.3)	3 (10.7)	3 (10.3)	4 (14.8)	10 (11.9)
Neutralising ADA	0 (0.0)	2 (7.1)	0 (0.0)	0 (0.0)	2 (2.4)

Key: ADA, antidrug antibody; q2w, every 2 weeks; q4w, every 2 weeks.
Notes: All numbers are patient numbers (% in parentheses). Percentages are based on all patients in the Safety Population.
[a] Prevalence is defined as the proportion of study population having drug-reactive antibodies (including pre-existing antibodies) at any time point.

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Parameter	Placebo (n=41)	Lanadelumab			
		300mg q2w (n=28)	300mg q4w (n=29)	150mg q4w (n=27)	Total (n=84)
[b] Incidence is defined as the proportion of study population found to have seroconverted or boosted their pre-existing ADA during the study period. [c] Pre-existing ADA refers to a signal detected prior to treatment. [d] Treatment-induced responses are characterised by a negative pre-treatment sample with at least one positive sample at a subsequent timepoint. [e] Treatment-boosted responses are characterized by a positive pre-treatment sample that are boosted to a higher level following drug administration. [f] One additional patient with pre-existing ADA had a positive sample post-dose, however since the titre was the same as the pretreatment sample it was not considered to be "treatment-boosted". **Source:** HELP-03 CSR[59]; Banerji et al. 2018.[60]					

Long-term extension study HELP-04

Treatment exposure

At the time of the interim analysis, rollover and non-rollover patients had received a median of 15 (range 1 to 26) doses of lanadelumab during the extension study.

In total, 3,157 doses have been administered in the extension study – most of which were self-administered (56.4%), either at home (655 doses) or in-clinic (1,127 doses). Most patients (159/212; 75%) self-administered lanadelumab at least once during the extension study. Overall, 130 patients (62.2%) self-administered ≥50% of doses and 63 patients (30.1%) self-administered ≥90% of doses.[68]

Of patients who self-administered lanadelumab either at home or in the clinic, the majority of injections (74.3% and 73.0%, respectively) were performed over 10–60 seconds.[68]

Adverse events

The safety results from the long-term extension study HELP-04 (n=212) 6-month interim report were consistent with those in the HELP-03 Study. TEAEs were reported by 85.8% of all patients. A higher proportion of patients in the non-rollover group had TEAEs considered related to lanadelumab by the investigator (51.5%) compared with rollover patients (33.0%; Table 31).

The majority (98.2%) of TEAEs were mild to moderate in severity. Eight (3.8%) patients had 11 serious TEAEs, none of which were related to lanadelumab

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treatment. Severe TEAEs (28 events) were reported by 9.9% of all patients in the safety population.

A total of 5 patients (2.4%; four non-rollover and one rollover) withdrew from the study due to TEAEs. Two non-rollover patients withdrew due to hypersensitivity AESIs (oedema, wheals and joint pain; and rash at site of injection and slight swelling under the eyes). Neither event was serious, but one event was classified as treatment-related and severe because it coincided with a HAE attack and ongoing disease. One non-rollover patient withdrew due to a treatment-related injection site reaction (papules), also classified as a hypersensitivity AESI. One non-rollover patient withdrew due to elevated ALT and AST; this event was considered unrelated to study drug. One rollover patient withdrew due to upper gastrointestinal bleeding and pneumonia following ingestion of a caustic substance.

A total of eight (3.8%) patients had an investigator-reported AESI (four rollover [8 events] and four non-rollover [5 events]; Table 31). Most of these AESIs (six events in eight patients) were considered treatment related. A total of seven investigator-reported hypersensitivity AESIs occurred in six patients (four in rollover and three in non-rollover patients), all of which were classified as treatment related (Table 31). A total of four AESIs of disordered coagulation (vaginal bleeding) occurred in two rollover patients, but these were considered not related to study drug.

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Table 31: Summary of TEAEs in long term extension study HELP-04

Event, n (%) events	Rollover Patients	Non-rollover Patients	Total
	n=109	n=103	N=212
Any TEAE	95 (87.2) 760	87 (84.5) 771	182 (85.8) 1531
Any treatment-related TEAE	36 (33.0) 287	53 (51.5) 427	89 (42.0) 714
Any serious TEAE	5 (4.6) 6	3 (2.9) 5	8 (3.8) 11
Any treatment-related Serious TEAE	0	0	0
Any severe TEAE	10 (9.2) 12	11 (10.7) 16	21 (9.9) 28
Any treatment-related severe TEAE	0	3 (2.9) 5	3 (1.4) 5
Any Investigator-reported AESI	4 (3.7) 8	4 (3.9) 5	8 (3.8) 13
Deaths due to TEAE	0	0	0
Hospitalisation due to TEAE	5 (4.6) 6	3 (2.9) 5	8 (3.8) 11
Any discontinuation due to TEAE	1 (0.9)	4 (3.9)	5 (2.4)

Key: AESI, Adverse event of special interest; HAE, hereditary angioedema; TEAE, treatment-emergent adverse event.
Notes: Data are from an interim analysis. Excludes HAE attack-reported events
Source: Lanadelumab AMPC dossier[68]; Riedl et al. 2018[63]

Table 32 presents the common TEAEs and treatment-related TEAEs in the long-term extension study HELP-04. The most common TEAEs were injection site pain (35.8% of patients), viral upper respiratory tract infection (20.8% of patients), and headache (15.6% of patients; Table 32). The most common treatment-related TEAEs were injection site pain (31.6% of patients) and injection site erythema (11.8%; Table 32).

Table 32: Common TEAEs (≥5% of patients) and related TEAEs in long term extension study HELP-04

Event, n (%)	Rollover Patients	Non-rollover Patients	Total
	n=109	n=103	N=212
Common TEAEs			
Injection site pain	34 (31.2)	42 (40.8)	76 (35.8)
Viral upper respiratory tract infection	26 (23.9)	18 (17.5)	44 (20.8)
Headache	17 (15.6)	16 (15.5)	33 (15.6)
Injection site erythema	12 (11.0)	14 (13.6)	26 (12.3)
Upper respiratory tract infection	13 (11.9)	13 (12.6)	26 (12.3)
Injection site bruising	4 (3.7)	12 (11.7)	16 (7.5)

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Event, n (%)	Rollover Patients	Non-rollover Patients	Total
	n=109	n=103	N=212
Arthralgia	4 (3.7)	8 (7.8)	12 (5.7)
Back pain	10 (9.2)	2 (1.9)	12 (5.7)
Urinary tract infection	5 (4.6)	6 (5.8)	11 (5.2)
Nausea	6 (5.5)	5 (4.9)	11 (5.2)
Injection site swelling	3 (2.8)	7 (6.8)	10 (4.7)
Abdominal pain	3 (2.8)	6 (5.8)	9 (4.2)
Pain in extremity	6 (5.5)	2 (1.9)	8 (3.8)
Common treatment-related TEAE			
Injection site pain	31 (28.4)	36 (35.0)	67 (31.6)
Injection site erythema	11 (10.1)	14 (13.6)	25 (11.8)
Injection site bruising	2 (1.8)	10 (9.7)	12 (5.7)

Key: HAE, hereditary angioedema; TEAE, treatment emergent adverse event.
Notes: Data are from an interim analysis. Excludes HAE attack-reported events
Source: Lanadelumab AMPC dossier[68]; Riedl et al. 2018[63]

Immunogenicity

Overall, ADAs occurred in [redacted] of lanadelumab-treated patients ([redacted] rollover and [redacted] non-rollover). Of the [redacted] patients with detectable ADAs, [redacted] rollover patients had pre-existing low-titre ADAs that were present prior to lanadelumab treatment in the double-blind HELP-03 Study. [redacted] were negative for ADAs during the extension study treatment period.[63, 68]

A total of [redacted] patients developed neutralising ADAs; therefore, the prevalence of ADAs was [redacted].[63, 68] Neutralising ADAs [redacted] patients who had prior exposure to lanadelumab during the Phase Ib study (DX-2930-02) and later entered the long-term extension study as a non-rollover patient after a lengthy pause. As observed in the HELP-03 Study, all ADA titres were low (range, [redacted]), and the formation of ADAs did not impact efficacy or exposure.[68]

No withdrawals were associated with ADAs. No episodes of hypersensitivity were associated with ADAs.[68]

Safety profile summary

Overall, lanadelumab was well tolerated, and there was no discernible dose response pattern or limiting toxicity for any related TEAEs over the 26-week treatment period of the HELP-03 study and during the long-term extension study.

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The majority (98.5%) of AEs in the HELP-03 study were mild to moderate in severity and largely managed with supportive care; there were no anaphylactic reactions. Predefined AESIs occurred infrequently and were reported in only five patients (6%) who received lanadelumab. Similarly, in the long-term extension study, the majority of AEs were mild to moderate in severity (98.2%) and pre-defined AESIs were only reported in eight patients (3.8%). Discontinuations due to TEAEs were also infrequent in the HELP-03 and the long-term extension study, and there were no deaths reported in either study. In the HELP-03 study, the development of ADA (including neutralising antibodies) against lanadelumab in 11.9% of patients did not appear to adversely affect pharmacokinetics, pharmacodynamics, safety or clinical response. Similar results were observed in the long-term extension study: ADAs occurred in 9.0% of lanadelumab-treated patients.

LTP therapies currently available for HAE include plasma-derived C1-INH and androgens, both associated with safety concerns.[41, 77] Plasma-derived C1-INHs carry a special warning for thrombotic events[41], and androgens are associated with significant side effects;[77] as a result androgens are now only recommended as second-line therapy in the majority of countries (not in the UK).[5, 6] By contrast, lanadelumab demonstrated a well-tolerated safety profile in the HELP-03 study and the long-term extension study and was not associated with the safety concerns of androgens and plasma-derived C1-INH.

No other studies reported additional AEs.

B.2.11. Ongoing studies

The long-term extension study HELP-04, which includes rollover patients from HELP-03 and non-rollover patients, is currently ongoing. No other studies investigating lanadelumab in patients with HAE Type I and II are due to provide additional evidence within the next 12 months.

B.2.12. Innovation

Lanadelumab represents a significant innovation in the management of patients with HAE, as it is the first monoclonal antibody to be licensed and reviewed by NICE in the treatment of patients with HAE. The CHMP of the EMA granted a positive opinion

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on 18 October 2018 with marketing authorisation expected in December 2018.[1-3] Lanadelumab was designated as an orphan medicinal product on 9 October 2015 and reviewed under EMA's accelerated assessment programme.[4] Lanadelumab was also granted priority review by both the US Food and Drug Administration (FDA) and Health Canada for the long-term prevention of attacks in HAE patients aged 12 years and older. Full FDA approval for prophylaxis of HAE attacks for patients 12 years and over occurred on 23 August 2018[78], and Health Canada approval for routine prevention of attacks of HAE in adolescents and adults aged 12 years and older was authorised on 19 September 2018.[79]

Lanadelumab's unique mechanism of action provides sustained inhibition of active plasma kallikrein, directly addressing the biological mechanism responsible for attacks in patients with HAE, and its 14-day half-life helps provides long-lasting protection from angioedema attacks. As described in Section B.2.6, lanadelumab offers a significant benefit for HAE patients in reducing the mean number of attacks (up to 87% from Day 0 to Day 182) and significantly increasing the time to first attack compared with placebo ($p<0.001$ for all three lanadelumab treatment arms). Furthermore, lanadelumab treatment caused a reduction in laryngeal attacks (up to [redacted] from Day 0 to Day 182), which are life threatening and considered the most severe of all HAE attacks. The ability of lanadelumab to significantly reduce the number of HAE attacks and increase the proportion of patients who become attack-free is anticipated to improve patient QoL, relieve patient fear/stress, and reduce caregiver burden.

In clinical practice, lanadelumab is given SC once every 2 or 4 weeks; it is anticipated that patients will self-administer lanadelumab. Due to its method of administration and less frequent dosing regimen, patients may find lanadelumab a more convenient treatment option than currently available C1-INH LTP treatments. This should help facilitate patient treatment and compliance, as well as offer improved convenience for patients and carers, and may indirectly improve overall outcomes.

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B.2.13. Interpretation of clinical effectiveness and safety evidence

Principal findings from the available clinical evidence to support lanadelumab

In the HELP-03 study, lanadelumab provided long-acting protection from attacks across all patients with HAE from Day 0. During the 26-week treatment period, both 300mg doses of lanadelumab provided statistically significant (adjusted p<0.001) and clinically meaningful reductions in the number of HAE attacks by up to 87% compared with placebo, with 300mg q2w having the greatest effect.

Furthermore, compared with placebo, both 300mg doses of lanadelumab significantly increased the time to first attack (unadjusted p<0.001) and significantly reduced the number of high-morbidity HAE attacks occurring during the treatment period (p<0.05). The benefits observed with lanadelumab treatment also contributed toward a significant improvement in patient QoL, and to date, lanadelumab is the only LTP treatment that has demonstrated improvement in QoL using a disease-specific instrument directly within a clinical trial.

In the HELP-03 study, lanadelumab treatment demonstrated significant improvements in QoL in patients with HAE, as measured by the disease-specific AE-QoL tool during the 26-week treatment period (Day 0 to Day 182). Patients treated with both 300mg doses of lanadelumab achieved statistically significant (p<0.05) and clinically meaningful reductions (i.e. improvement) in AE-QoL total score and functioning domain score compared with placebo. When all three lanadelumab treatment arms were combined, statistically significant (p<0.05) and clinically meaningful reductions (i.e. improvement) in AE-QoL total score and all domain scores was observed compared with placebo; the largest improvement was observed in the functioning domain of the AE-QoL (p<0.01).

Results from the long-term extension study HELP-04 demonstrated meaningful and durable responses with lanadelumab treatment for over a 1-year period for rollover patients treated with lanadelumab in both Phase III studies ([redacted] reduction from baseline in attacks per month). Furthermore, lanadelumab treatment caused meaningful and durable responses in rollover patients previously treated with placebo ([redacted] reduction from baseline in attacks per month). In non-rollover

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patients, lanadelumab treatment demonstrated consistent and meaningful responses regardless of prior therapy ([redacted] reduction in attack rate), demonstrating that all patient with HAE can benefit from lanadelumab treatment, irrespective of their previous treatment. The baseline attack rates observed in non-rollover patients ([redacted] attacks per month) highlights the unmet need, as HAE patients receiving today's available LTP therapy continue to experience attacks.

Although reducing the number of HAE attacks is the key aim of LTP HAE treatment, being attack-free will have a greater benefit on patients' QoL in a real-world setting, as patients will be less anxious and will be able to work and participate in both physical and social activities. Furthermore, a longer attack-free period will have significant impact on the cost of patient care as patients will not consume any healthcare resources related to the treatment of acute attacks. Lanadelumab treatment enabled up to [redacted] of patients to be attack-free during the 26-week treatment period and up to [redacted] of patients to be attack-free during steady state (Day 70–182). These data potentially suggest superiority of lanadelumab over C1-INH, as only [redacted] of patients taking C1-INH remained attack-free during a 12-week treatment period.[52]

Subgroup analyses of the primary endpoint demonstrated that the effect of lanadelumab on the reduction of HAE attacks was consistent across various subgroups, including age, sex, weight, BMI, LTP use, and history of laryngeal HAE attacks. This demonstrates lanadelumab treatment offers effective HAE control across a broad range of HAE patients and addresses the needs of patients who cannot achieve adequate HAE control with existing prophylactic therapies.

In patients who suffered breakthrough attacks in the HELP-03 study, lanadelumab treatment not only reduced attack severity but also the need for rescue treatment. Lanadelumab treatment significantly reduced the number of moderate or severe HAE attacks by up to 83.4% from Day 0 to Day 182 compared with placebo. As a result, the use of acute (on demand) therapies was significantly reduced in patients treated with lanadelumab compared with placebo (74.2%–87.3%; adjusted $p<0.001$), with the greatest reduction observed for 300mg q2w (87.3%). As a result of the reductions in both attack severity and the use of acute medication, there will be an

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overall reduction in the healthcare resources required for patients taking lanadelumab.

Lanadelumab is well tolerated with a low rate of AEs and no anaphylactic or anaphylactoid reactions. In the HELP-03 study, most AEs (98.6%) associated with lanadelumab treatment were mild/moderate in severity, and very low levels of treatment discontinuation due to TEAEs were observed. Similarly, in the long-term extension study HELP-04, the majority of AEs in were mild/moderate in severity (98.2%), and very low levels of treatment discontinuation due to TEAEs were observed. Furthermore, lanadelumab is not associated with the contraindications, poor tolerability and long-term safety concerns of androgens[77] or the increased risk of thromboembolic events associated with plasma-derived C1-INH.[41]

Internal validity

HELP-03 was a well-designed, multicentre, randomised, double-blind, placebo-controlled, Phase III study providing comparative evidence of lanadelumab versus placebo in patients aged 12 years and older with HAE Types I or II who have frequent recurrent angioedema attacks. The HELP-03 study was conducted in line with GCP guidelines, with steps taken to minimise the risk of bias, and an Independent Data Monitoring board was established to provide independent oversight of safety and efficacy considerations and study conduct. The overall risk of bias in the HELP-03 study is considered to be low (Appendix D).

The HELP-03 study compared only lanadelumab with placebo; therefore, it does not provide head-to-head data with comparator treatments. In the absence of head-to-head trial data, an ITC analysis was conducted to compare lanadelumab with comparator treatments.

External validity

The HELP-03 trial was a multicentre study conducted in 41 locations in six countries. Of the patients with HAE Type I and II included in this study, 23.2% were enrolled in site in Europe (including five patients from one site in the UK).

In the HELP-03 study, HAE Type I was the predominant form of HAE and the majority of patients were female, which is similar to the observed HAE patient

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population in the UK.[15, 80] The median age of onset of angioedema symptoms in the HELP-03 study was 12, similar to the median age of 10 observed for patients in UK clinical practice.[80] Similarly, both the HELP-03 trial and UK patient level data demonstrated that abdominal attacks were the most frequent, followed closely by peripheral attacks; laryngeal attacks were the least frequent.[80] However, the percentage of patients experiencing abdominal and peripheral attacks was significantly higher in the HELP-03 study than observed in UK clinical practice. Although the baseline characteristics in patient population in the HELP-03 may differ from patients in clinical practice, [redacted].[46]

[redacted][46][redacted][80][redacted]. Similar acute treatment was used in the HELP-03 trials; when patients required rescue medication, they were mainly given icatibant, or C1-INH.

While in current practice the majority of patients receiving lanadelumab would have received previous oral LTP treatment, only a small proportion of the HELP-03 population had received this treatment prior to study enrolment. However, subgroup analyses from HELP-03 (Appendix E) and HELP-04 (Figure 11) did not find any statistically significant difference in lanadelumab effectiveness based on prior LTP treatment received; [redacted].[46]

Overall, the HELP-03 study population is representative of the intended patient population in NHS England.

Lanadelumab is not relevant for end-of-life considerations.

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B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

The full details of the economic SLR are presented in Appendix G. Evidence found primarily considered the treatment of acute attacks, with only two studies investigating the cost effectiveness of prophylactic treatments in HAE. These studies are summarised in Table 33.

Table 33: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Health states	Patients/ setting	Intervention/ comparators	Relevance
Graham (2017)[81]	2017	Decision tree	Not reported	Patients with HAE in the US	Intervention: Haegarda Comparator: C1-estarase inhibitors (IV)	Setting of study not relevant
Javaud (2018)[82]	2018	Not Reported	Not Reported	Patients with HAE in France	Intervention: national call centre management facility (SOS-HAE) strategy Comparator: Usual practice	Relevant comparators not included

Key: HAE, hereditary angioedema.

Graham (2017)[81] investigated the cost effectiveness of Haegarda, a prophylactic treatment which is currently unavailable in UK clinical practice and outside the scope of this appraisal, versus other C1-INHs from a US payer perspective. Javaud (2018)[82] conducted a cost–utility analysis comparing a national call centre management facility (SOS-HAE) with current clinical practice from a French payer's perspective.

Additionally, subsequent to completion of the SLR, an evidence report was published by the Institute for Clinical and Economic Review in the US, investigating prophylaxis for HAE with lanadelumab and C1-INH. This report presents evidence from a US perspective and is therefore not directly relevant to the decision problem. However, the findings of this review are utilised for validation purposes in Section B.3.10.

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B.3.2. Economic analysis

Given that no models were identified that investigated the cost effectiveness of prophylactic treatments in the relevant patient population, a *de novo* economic model was developed to evaluate the cost effectiveness of lanadelumab for the long-term prophylaxis of HAE. A description of the model and key features of the analysis are presented in the subsequent sections.

Patient population

In line with the marketing authorisation and the final scope, the cost-effectiveness analysis evaluated lanadelumab in patients aged 12 years and older with HAE, using data for the ITT population from HELP-03.[59] The baseline patient characteristics from HELP-03 are presented in Table 8. The population enrolled in the HELP-03 trial consisted of patients aged 12 or older with a documented history of Type I or II HAE who experienced a minimum of one attack every 4 weeks during the baseline run-in period prior to advancing to the treatment phase of the trial.[59] Clinicians participating at the NICE scoping workshop suggested this attack rate was considered a reasonable threshold for when clinicians would want to provide routine prophylactic treatment for these patients. Additionally, patients with Type I or II HAE represent virtually all HAE patients, as highlighted in Section B.1.3 and in the final scope.[83]

As described in Section B.2.9, a Bayesian ITC was conducted to allow for a comparison of lanadelumab with C1-INH in the cost-effectiveness model; this utilised data from the intent-to-treat (ITT) populations from both the HELP-03 and CHANGE trials.[59, 84] A comparison of the patient characteristics and the inclusion criteria from each of these studies is presented in Appendix D. These results demonstrate the consistency that exists between the two patient populations, with similarities in terms of age, sex and the percentage of patients with Type I or Type II HAE. Both studies had small differences in their inclusion criteria involving the baseline attack rate (one per month in HELP-03 versus two attacks per month in CHANGE). Some differences also existed in the percentage of patients receiving prior LTP therapy (56% in HELP-03 versus 14% in CHANGE).[59, 84] However, subgroup analyses presented from the HELP-03 trial demonstrated that there were no statistically significant differences in efficacy outcomes between patients with differing levels of baseline attack risk, or

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patients with and without prior prophylactic therapy, as shown in Appendix E, providing no evidence that these characteristics are treatment effect modifiers.[59] Therefore, the population presented in the cost-effectiveness model is consistent with the decision problem.

Lanadelumab is expected to be prescribed for patients with HAE whose condition is not adequately controlled with oral prophylactic treatment or for whom oral prophylactic treatment is not suitable. As only 8% of patients in HELP-03 and 14% of patients in CHANGE received oral therapy prior to trial enrolment, it was not feasible to specifically address efficacy in the decision problem population. However, as there were no statistically significant differences in efficacy between patients with and without prior prophylactic therapy in HELP-03, as shown in Appendix E, the population investigated in the model appears to be broadly consistent with the decision problem. Additionally, [redacted][46]

Model structure

In selecting the most appropriate model structure the following factors were considered:

- The status of HAE as an orphan disease and the limitations in terms of data availability
- The primary treatment effect being a reduction in the number of attacks experienced over time and a delay in time to first attack
- The evidence available from the trial data and the literature on the impact of HAE on health-related quality of life (HRQL) and resource use
- The need to capture attack severity and the subsequent impact on HRQL and resource use

A cohort-level model was selected as the most appropriate based on consideration of these factors, and the data available for lanadelumab and the relevant comparators. Given the small patient numbers within the relevant clinical trials, a

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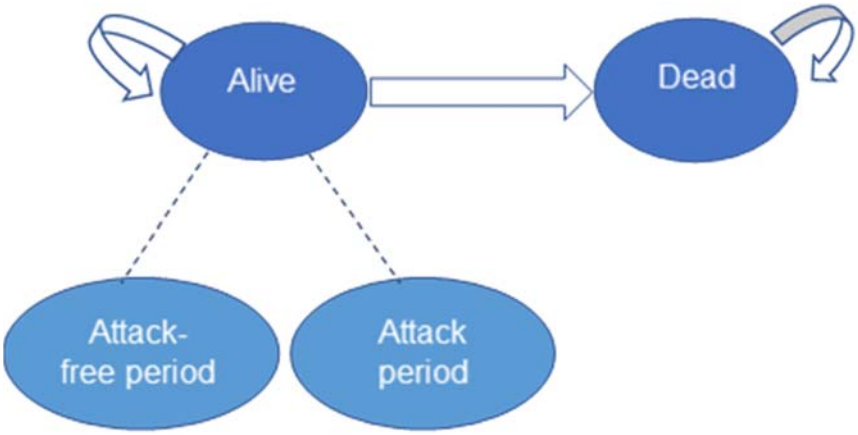
patient level model was considered inappropriate due to the limited amount of data available to inform the parameters.

A two-health-state model was developed (presented in Figure 17), with health states included for patients who were ‘alive with HAE’ or ‘dead’. Within the ‘alive with HAE’ state the average number of attacks experienced by patients was estimated in each model cycle by utilising the coefficients of a Poisson regression analysis that was conducted using the HELP-03 trial data.

The assumed average duration of each attack was utilised to estimate the time patients spent experiencing an attack or being attack-free within each model cycle. The model also included the functionality to apply an assumed distribution of attack severity to estimate the number of attacks that could be categorised as mild, moderate or severe in each cycle. Based on the average number of attacks predicted, and the assumed severity and duration of these attacks, the impact on patients in terms of costs and HRQL were estimated.

Figure 17: Model structure



A Poisson regression analysis was selected as the most appropriate method to estimate the average number of attacks per cycle given its suitability to model count data as it is concerned with the number of events within a given time period, e.g. each model cycle. A Poisson distribution expresses the probability of a given number of events occurring in a fixed interval of time.

Other regression techniques that can model count data such as the negative binomial were considered. However, as the Poisson regression provided a good fit to the observed trial data this was selected as the most parsimonious.

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Poisson regression analyses were conducted for each treatment independently with two covariates included in the regression:

- Baseline attack risk
- Number of attacks in the previous cycle

No other covariates were considered for inclusion as subgroup analysis results presented from the HELP-03 trial did not indicate other factors being key drivers of the treatment effect.[59] Additionally, due to the limited sample size within the trial, a simple model was considered appropriate to minimise any potential risks of overfitting the regression.

The estimated coefficient values were applied in the model in each cycle to estimate the average number of attacks experienced using the formula outlined in Figure 18. As the Poisson regression coefficients were estimated on the log scale, the output was exponentiated in order to calculate the mean number of attacks. This formula was applied to individual patient level data taken from HELP-03, with the method outlined in Section B.3.3.

Figure 18. Poisson regression formula

$$No.of\ attacks = EXP(Intercept + (baseline\ coefficient * baseline\ no.of\ attacks) + (Previous\ attacks\ coefficient * no.of\ attacks\ in\ previous\ cycle))$$

The health effects in the model were calculated in terms of both life years (LYs) and quality-adjusted life years (QALYs). In line with the dosing regimen for lanadelumab and the length of each period in the HELP-03 trial, a cycle length of 28 days was applied. Given the lifelong nature of the disease and the prophylactic nature of the treatment, a lifetime time horizon, assumed to be equal to 60 years, was adopted in the model based on the average age (41 years) of the patients within HELP-03.

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Table 34: Features of the economic analysis

	Current appraisal	
Factor	**Chosen values**	**Justification**
Time horizon	60 years	Given the lifelong nature of the disease and the prophylactic nature of the treatment, a lifetime time horizon (assumed to be equal to 60 years) was adopted in the model based on the average age (41 years) of the patients within HELP-03.[59]
Source of utilities	Attack utility values were based on EQ-5D-5L data from Nordenfelt (2014)[32] Treatment administration utilities were based on data from Jørgensen (2017)[85]	The EQ-5D data from the HELP-03 trial were collected at limited timepoints (Days 0, 98 and 182) with only two patients completing the EQ-5D-5L questionnaires while experiencing an attack.[59] These data were therefore deemed unsuitable for representing the HRQL benefit associated with the prevention of attacks, as these events represent the main HRQL burden for patients. Alternative sources of HRQL data, identified within the SLR, which did collect information on the impact of acute attacks, were therefore utilised in the cost-effectiveness model. Utility values from Nordenfelt (2014)[32] were selected in the base-case analysis. An alternative utility source was identified but this utilised an unvalidated method to derive utility values.[33] The utilities reported by Nordenfelt (2014) for patients not experiencing an attack most closely matched the EQ-5D-5L values estimated from HELP-03, which would reflect utilities for an attack-free population for the reasons explained above. The values from Nordenfelt (2014)[32] were also utilised in the evidence report that was published by the Institute for Clinical and Economic Review in the US.[86] In addition, lanadelumab reduces the burden of treatment administration on patients because it is administered subcutaneously rather than intravenously and is administered less frequently than its comparator. Jørgensen (2017)[85] conducted a TTO study in 1,645 adult respondents from the UK general population. The study asked participants to value health states for subcutaneous and intravenous therapies given at different frequencies. A utility increment estimated from this study was applied in the base-case analysis to patients treated with lanadelumab to capture this benefit.
Source of costs	NHS reference costs, literature and expert opinion	Unit costs were taken from recognised national databases. Resource use estimates were elicited from clinical expert opinion given the paucity of relevant data in the wider literature due to the rare nature of HAE.[46]

Key: EQ-5D-5L, EuroQol 5-dimensional 5-level descriptive system; HAE, hereditary angioedema; HRQL, health-related quality of life; SLR, systematic literature review; TTO, time-trade off.

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Intervention technology and comparators

As outlined in Section B.1.2 the intervention, lanadelumab, is a fully human monoclonal antibody inhibitor of plasma kallikrein. Moreover, lanadelumab's safety profile, as a fully human antibody inhibitor, enables continuous use as a prophylactic treatment. The treatment is administered subcutaneously, with patients able to self-administer at home.

Within HELP-03 three different dosing regimens of lanadelumab were evaluated:

- 150mg every 4 weeks (q4w)
- 300mg q4w
- 300mg every 2 weeks (q2w)

The marketing authorisation and SPC for lanadelumab state that clinicians should initiate patients on a dose of 300mg q2w, but in patients who are stably attack-free on treatment, a dose reduction of 300mg q4w may be considered, especially in patients with low weight.[1] The base-case analysis therefore reflected this dosing regimen. As the dose of 150mg q4w is not included within the marketing authorisation, this option was not considered within the cost-effectiveness model.

Consistent with the final scope, the model compared lanadelumab with IV C1-INH. Based on feedback from six UK clinical experts[46] the two most commonly used C1-INHs used in UK clinical practice are Cinryze IV and Berinert IV. Therefore, a weighted C1-INH comparator, consisting of patients receiving Cinryze IV and Berinert IV in proportions based on clinical use, is presented in the base-case analysis.

The presentation of a mix of these treatments is considered appropriate as although Cinryze IV is the only C1-INH licensed for prophylactic treatment, [redacted] [46, 87] Both Cinryze IV and Berinert IV are administered every 3–4 days, with patients treated with Cinryze IV receiving 1000 IU at each dose[88], while patients on Berinert IV typically receive an average initial dose of approximately [redacted], based on clinical expert opinion and consistent with its licensed dose for the treatment of acute attacks.[46, 48] These doses were therefore

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applied in the base-case analysis. [redacted] The assumption of no up-dosing applied in the base case analysis was conservative in terms of treatment costs as it potentially underestimates the true cost of the comparator in UK clinical practice.

In the base-case analysis [redacted] of patients were assumed to receive Berinert IV and [redacted] were assumed to receive Cinryze IV. These figures were based on Hospital Pharmacy Audit data, which is hospital dispensing data collected retrospectively by IQVIA (formerly known as QuintilesIMS and IMS Health) based on units of drugs dispensed by individual hospitals in the country.[87] The data presents the number of vials of each treatment used in UK clinical practice per month. The figures applied in the model were calculated by estimating the ratio between the number of vials of Berinert IV and Cinryze IV that were used over the last 3 months of reported data. These proportions were varied in scenario analyses, using a range around the base case estimate (i.e. both increase and decrease from base case assumption).

As highlighted in Section B.1.3, lanadelumab is expected to be prescribed for patients with HAE whose condition is not adequately controlled with oral prophylactic treatment or for whom oral prophylactic treatment is not an option. Therefore, oral attenuated androgens or anti-fibrinolytics were not considered a relevant comparator and therefore are not presented as part of the analysis.

Other treatments such as non-plasma derived C1-INH (Ruconest) were also deemed unsuitable for inclusion [redacted].[46]

B.3.3. Clinical parameters and variables

As outlined in Section B.2.9, the comparison of lanadelumab to IV C1-INH was made utilising results of a Bayesian ITC which used data from both the HELP-03 and CHANGE trials, as no head-to-head clinical trial data were available.

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Attack rate: lanadelumab

As outlined in Section B.3.2, a Poisson regression analysis was conducted to allow for the average number of attacks experienced by patients in each model cycle to be estimated based on the treatment they received. The observed mean number of attacks in each period throughout the HELP-03 trial is presented in Table 35.

For patients treated with lanadelumab, the number of HAE attacks experienced decreased significantly over time. In the placebo arm, the distribution of HAE attacks remained approximately stable over time, with the data demonstrating a slight downward trend in the number of attacks in the first few periods. This trend could indicate the presence of a placebo effect or could be a result of the inclusion criteria of the HELP-03 trial. Patients were required to experience at least one attack during the baseline run-in period prior to entry into the study period, which may have resulted in a regression to the mean effect in the first period of the trial. This downward trend was captured in the Poisson regression analysis, ensuring that treatment effect of lanadelumab against placebo was not overestimated.

Table 35: Observed number of attacks in HELP-03

Treatment	Average number of attacks						
	Baseline	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**
Placebo	4.02	2.65	2.38	2.24	2.05	2.22	2.44
Lanadelumab 300mg q4w	3.71	1.17	0.59	0.54	0.39	0.39	0.25
Lanadelumab 300mg q2w	3.52	0.70	0.26	0.19	0.23	0.19	0.12
Key: q4w, every 4 weeks; q2w, every 2 weeks.							

Independent Poisson regression models were used for each lanadelumab dosing regimen and the placebo arm separately. This was in line with NICE DSU guidance (TSD 14) which outlines that independent models should be fitted when patient level data are available.[89]

Each of the coefficients were first examined in univariate regression models, utilising the data across all treatment arms, to assess the statistical significance of their association with the outcome. The results of the univariate regression analysis presented in Table 36 found that both a patient's baseline attack risk and the number

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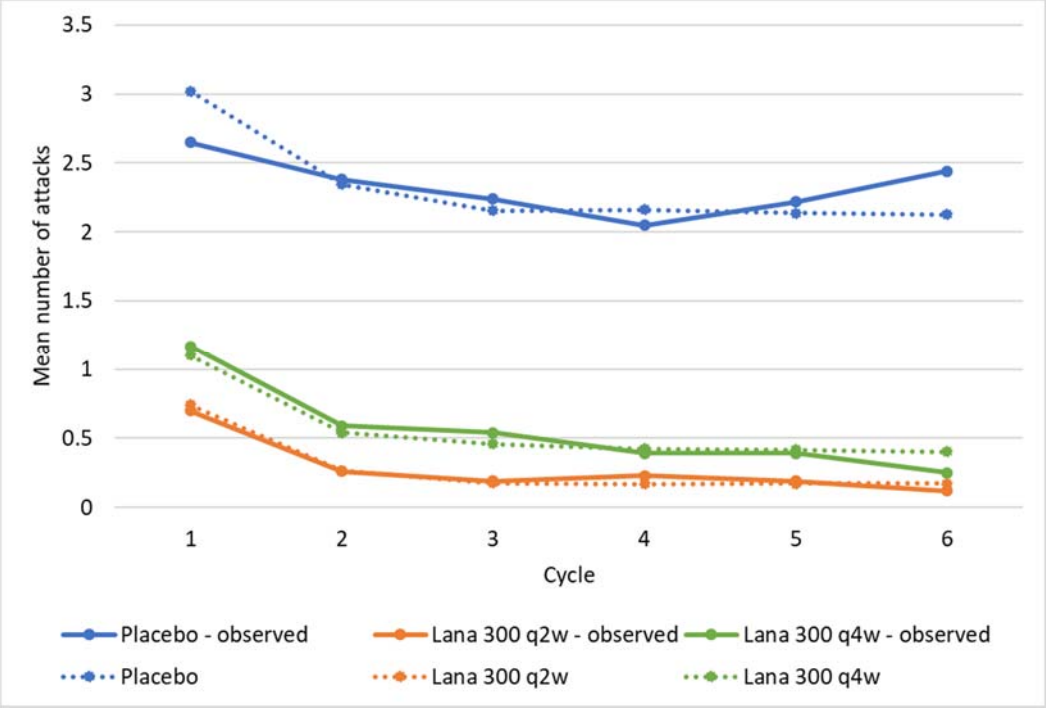
of attacks they experienced in the previous 28-day cycle were strong predictors of a patient's attack risk.

Table 36: Univariate Poisson regression analysis

Variable	Univariate estimates	Univariate SE	Univariate p-value	Univariate lower CI	Univariate upper CI
Baseline attack risk	0.2649	0.0168	<0.01	0.2321	0.2977
Attacks in the previous cycle	0.3358	0.0120	<0.01	0.3122	0.3594
Key: CI, confidence interval; SE, standard error.					

The fit of the mean number of attacks per cycle estimated by the full regression including both covariates was then assessed against the observed data from the HELP-03 trial. Figure 19 demonstrates that the Poisson regression model provided a good fit to the observed trial data.

Figure 19: Full regression model – predicted number of attacks over time



Key: Lana, lanadelumab; PBO, placebo; q4w, every 4 weeks; q2w, every 2 weeks.

Information on the covariate coefficients applied in the economic model, p-values and 95% confidence intervals are presented in Table 37.

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Table 37: Poisson regression estimates

Coefficient	Estimate	P-value	Lower bound	Upper bound
Lanadelumab 300mg q4w				
Intercept	-1.6702	<0.0001	-2.0964	-1.2440
Attacks previous cycle	0.1943	<0.0001	0.1152	0.2733
Attacks at baseline	0.1592	0.0002	0.0749	0.2434
Lanadelumab 300mg q2w				
Intercept	-1.8062	<0.0001	-2.4069	-1.2056
Attacks previous cycle	0.3437	<0.0001	0.2075	0.4799
Attacks at baseline	-0.0137	0.8711	-0.1797	0.1522
Placebo				
Intercept	0.1499	0.0392	0.0074	0.2924
Attacks previous cycle	0.1033	<0.0001	0.0594	0.1473
Attacks at baseline	0.0766	0.0001	0.0386	0.1145

Key: q4w, every 4 weeks; q2w, every 2 weeks.

Notes: The larger the coefficient value the greater impact it has on the prediction, a negative number does not show change in direction of correlation, only reduced impact, a coefficient of 0 would result in a 1:1 ratio of impact.

The Poisson regression models were fitted by utilising the attack rate reported in each 28-day period of the clinical trial. The attack rate was calculated as the number of attacks occurring during the period divided by the number of days the patient contributed to the period multiplied by 28 days. This method accounted for patients withdrawing from the trial and aligned with the method applied in the HELP-03 CSR.

Application of the Poisson regression in the cost-effectiveness model

The Poisson regression coefficients were applied in the model utilising the following approach to estimate the average number of attacks experienced in each model cycle:

- For each individual patient from HELP-03, for each 28-day period of the trial (Cycles 1–6) the number of attacks a patient experienced during the baseline run-in period and in the previous 28-day cycle were recorded
- These observed data were utilised to inform the Poisson regression in order to predict the number of attacks patients experienced in the first seven 28-day

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cycles. This was achieved by applying the Poisson regression equation presented in Figure 18 to each individual recorded observation to estimate the predicted number of attacks for each patient in each model cycle. The Poisson regression coefficients applied were selected based on the treatment the patient received during the HELP-03 trial based on coefficients shown in Table 37.

- An average of these individual predictions was then taken for each treatment in each model cycle during the trial period to estimate the mean number of attacks experienced in the first seven cycles of the model across the cohort of patients. These predictions are presented below in Table 38

Table 38: Predicted number of attacks by treatment

Cycle (28 days)	Treatment		
	Lanadelumab 300mg q4w	**Lanadelumab 300mg q2w**	**Placebo**
1	1.10	0.74	3.02
2	0.54	0.26	2.34
3	0.46	0.17	2.15
4	0.42	0.17	2.16
5	0.42	0.17	2.14
6	0.40	0.17	2.12
7	0.40	0.17	2.15
Key: q4w, every 4 weeks; q2w, every 2 weeks.			

- As values for the number of attacks experienced in the previous 28 days, which are required to populate the Poisson regression, change over time, estimates were required for each individual patient in each cycle beyond the trial period. For example, to estimate the number of attacks a patient experienced in Cycle 8, then the number of attacks they experienced in the previous 28-day cycle (Cycle 7), which extended beyond the trial period, needed to be estimated.
- This was achieved by fitting a Poisson distribution to the mean number of attacks experienced by the cohort of patients in Cycle 7 and randomly sampling from this distribution to predict a value for each patient.
- Once these data were estimated for each patient, then the predicted number of attacks for each patient in Cycle 8 was estimated by applying the Poisson regression equation to each individual observation as before, and then taking an average over these individual predictions.

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- This method was then repeated over the total number of cycles in the model (770) for each patient to allow for the estimation of the average number of attacks experienced in each cycle over a lifetime horizon.
- Given that the values for the number of attacks experienced in the previous cycle for each patient in the long term were drawn from a distribution, the values were varied over 1,000 iterations, and an average was taken across these iterations to estimate the final attack numbers in each cycle.

This method of applying the regression coefficients to patient level data was utilised to allow for a more precise estimate of the attack rate over time, compared to simply applying the regression coefficients to the average baseline attack risk across the patient cohort, leading to the predicted number of attacks being very similar to the observed data in HELP-03.

To allow for uncertainty in the regression analysis to be explored, the model utilised the covariance matrices for each regression to investigate the joint uncertainty of each of the regression parameters in probabilistic sensitivity analysis. Additionally, the lower and upper bounds for each parameter were also utilised to explore the impact on the results of varying each parameter individually.

Figure 20 presents the attack rate over the first year for the two lanadelumab dosing regimens investigated in the cost-effectiveness model (300mg q2w and 300mg q4w) when the Poisson regression formula is applied. The number of attacks was predicted to decline, before plateauing and remaining at a constant rate in the longer term. The exploratory Day 70 analysis conducted in HELP-03 (presented in Section B.2.6 and Appendix L) indicates that over time treatment became more effective when lanadelumab concentration appeared to reach a steady state; this is considered to be reached at Day 70 for lanadelumab. In addition, the 6-month data from the HELP extension study (HELP-04) highlighted how the attack rate remained constant beyond the HELP-03 trial period, supporting the long-term extrapolation of attack rate beyond trial period. These results are presented in Section B.3.10.

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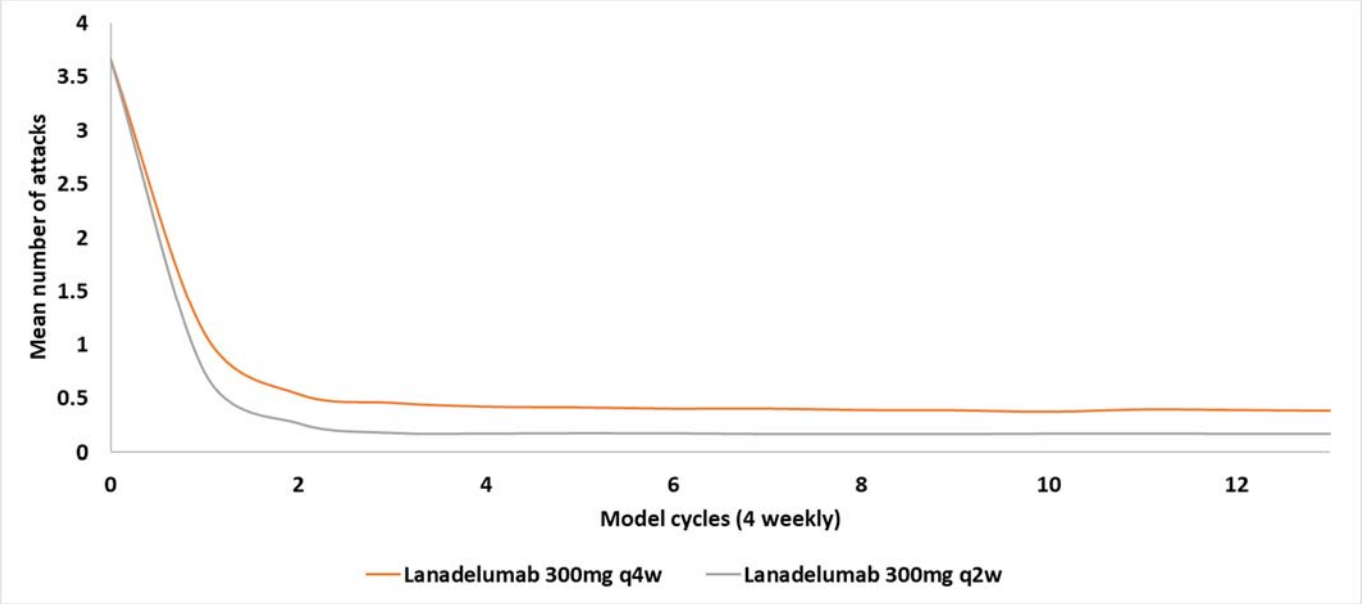
Figure 20: Poisson regression extrapolation



Key: q4w, every 4 weeks; q2w, every 2 weeks.

As noted in Section B.3.2, the model assumed that patients initiate therapy with a dose of 300mg q2w, with a proportion of patients who remain stably attack-free subsequently moving on to a dose of 300mg q4w in line with the SPC and marketing authorisation. Based on feedback from clinicians, patients would typically be assessed approximately [redacted].[46] Therefore, the base-case analysis assumed that after 6 months 44.4% of patients switch to the lower dose, and it was assumed that 76.9% of patients would receive the lower dose 12 months following initiation of their first treatment of lanadelumab.

These proportions were based on the time to first attack data from the HELP-03 trial which are presented in Section B.2.6. These data demonstrate that by the end of the 6-month trial period, 44.4% of patients treated with a dosing regimen of 300mg every 2 weeks were attack-free. The analysis conducted in HELP-03 from Day 70 onwards also indicated that treatment became more effective when lanadelumab concentration reached a steady state, which is anticipated to be after 70 days from initiation of treatment with lanadelumab. The analysis, presented in Section B.2.6 and Appendix M, showed that not only did the attack rate fall across patients treated with a dosing regimen of 300mg every 2 weeks, but also that 76.9% of patients were attack-free between Day 70 and Day 182. The assumption that a proportion of patients would receive the lower dose in clinical practice [redacted]

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[redacted][46] To ensure that the treatment effect was not overestimated in these patients, the Poisson regression coefficients for the 300mg q4w dose were applied to this proportion of patients at the point of switch.

In clinical practice, if patients are switched onto the dosing regimen of 300mg q4w but their condition is then deemed not to be adequately controlled, they may be switched back to the 300mg q2w dosing regimen. However, it may also be the case that patients who remain on the 300mg q2w dosing regimen will experience a period where they are attack-free and are, as a result, switched to the 300mg q4w dosing regimen. Therefore, although the proportion of patients assumed to be on each dosing regimen may vary over time, in the absence of long-term data it was assumed that on average 76.9% of patients will be treated with 300mg q4w over a lifetime horizon. Additionally, data from the HELP-04 extension study presented in Section B.2.6 demonstrate that a patient's attack rate remains stable over time, indicating that any switching of dosing regimens would be limited in the longer term.

Attack rate: C1-INH

To allow for the estimation of the number of attacks experienced in each cycle for patients treated with C1-INH, a Bayesian NMA was conducted (details provided in Section B.2.9). This ITC utilised data from the HELP-03 and CHANGE trials to estimate the rate ratio of attack frequency for each of the studies versus the common comparator, which was placebo.

The rate ratio estimated for C1-INH was used to estimate the mean number of attacks in each cycle for the comparator by multiplying the rate ratio with the placebo arm output from the HELP-03 Poisson regression analysis. The rate ratio estimated for C1-INH was [redacted], which compares to rate ratios of [redacted] for lanadelumab 300mg q2w and [redacted] for lanadelumab 300mg q4w. In scenario analyses, the number of attacks experienced in each cycle for patients treated with lanadelumab was estimated by utilising the results from the NMA in the same manner as for the C1-INH comparator.

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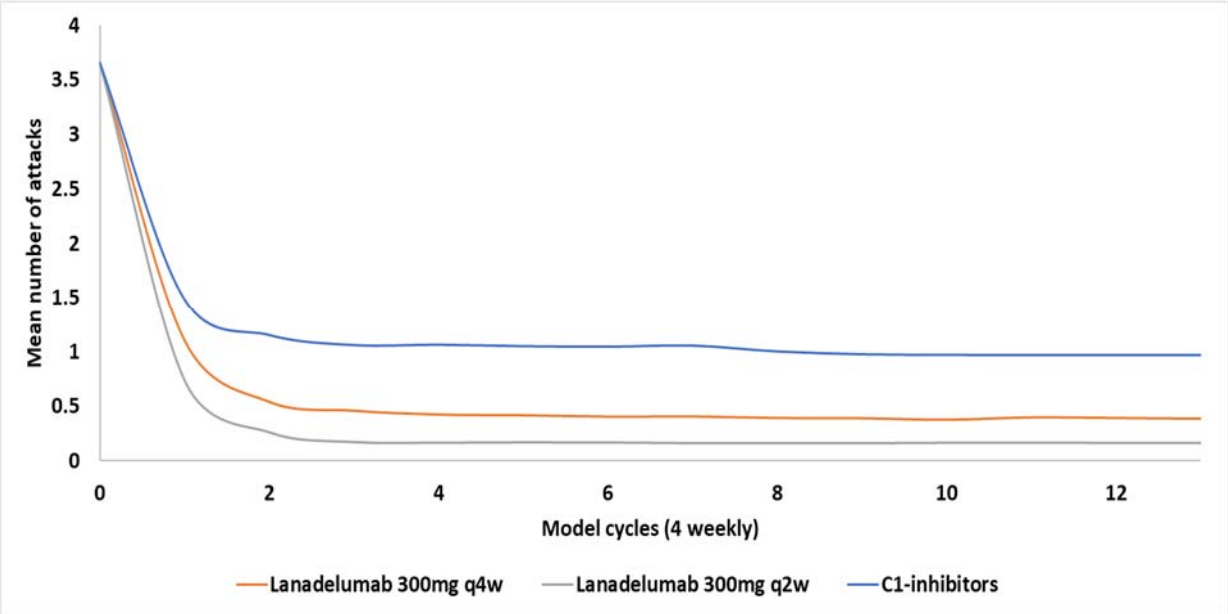
Patients in CHANGE received Cinryze IV at a dose of 1,000IU twice per week. However, feedback from UK clinical experts noted that a sizeable proportion of patients in clinical practice would receive Berinert IV at a dose of [redacted] and that patients treated with C1-INH may also be [redacted]. Given the uncertainty around the effectiveness of higher-dose C1-INH, a threshold analysis has also been presented, which demonstrates how the results of the analysis changed as the rate ratio of C1-INH is varied. This was to overcome any potential issues of treatment costs and efficacy failing to align.

Figure 21 presents the predicted number of attacks over time for all treatments included in the cost-effectiveness model.

Figure 21: Attack estimates over time for all treatments



Key: q4w, every 4 weeks; q2w, every 2 weeks.

Attack severity and duration

Following the calculation of the mean number of attacks experienced in each cycle, the number of attacks considered to be mild, moderate or severe were estimated. The proportions of attacks assumed to be mild, moderate or severe were estimated from the pooled attack data from HELP-03 trial data (Table 39). Therefore, once a patient experienced an attack, attack severity was assumed to be equal between lanadelumab and C1-INH.

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Mild, moderate and severe attacks were defined in the HELP-03 trial as:

- Mild: transient or mild discomfort
- Moderate: mild to moderate limitation in activity – some assistance needed
- Severe: marked limitation in activity – assistance required

These definitions of severity are consistent with the HAARP criteria. For further details of HAARP please refer to the HELP-03 clinical trial protocol (specifically Amendment 3.0, Appendix 4).[67]

One additional scenario relaxes the assumption that the severity of attacks is equal between treatments and instead the attack severity for lanadelumab 300mg q4w and 300mg q2w was based on treatment-arm-specific data from HELP-03, with an alternative study conducted by Riedl (2016) utilised for C1-INH. This was a multicentre observational study conducted between 2010 and 2014 at 30 US and seven European sites. The aim was to obtain prospective and retrospective safety and usage data on patients receiving C1-INH primarily as a treatment for acute attacks.[90] This study estimated that a greater proportion of attacks are classified as severe compared to that observed in HELP-03; however, it is unclear whether this increase is a result of the treatment patients are receiving or the differences in the definition of attack severity between the studies.

Table 39: Attack severity data

Attack severity	HELP-03 (Pooled)	Placebo	150mg q4w	300mg q4w	300mg q2w	Riedl (2016)
Mild	324 (40%)	249 (44%)	21 (25%)	43 (41%)	11 (24%)	3,748 (37%)
Moderate	418 (52%)	272 (48%)	57 (68%)	57 (54%	32 (70%)	4,734 (46%)
Severe	65 (8%)	51 (9%)	6 (7%)	5 (5%)	3 (7%)	1,764 (17%)
Total	807	572	84	105	46	10,246
Key: q4w, every 4 weeks; q2w, every 2 weeks.						

Data on the mean duration of each attack experienced were collected in HELP-03 and CHANGE. These results, presented in Table 40, demonstrate that both treatments reduced the average attack duration compared to placebo. The attack

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durations reported in CHANGE for both the C1-INH and placebo arm are higher than the durations reported in HELP-03 across all treatment arms. This may be due to differences in reporting between trials or improvements in the treatment of acute attacks reducing the length of attacks. Therefore, the mean attack duration applied in the model across both treatments was assumed to be equal to the duration for lanadelumab 300 q4w as it was the lowest value and therefore provided the most conservative approach.

Table 40: Average attack duration

HELP-03		CHANGE	
Treatment	**Attack duration: mean days (SD)**	**Treatment**	**Attack duration: mean days (SD)**
Lanadelumab 300 q4w	[redacted]	C1-INH	2.10 (1.13)
Lanadelumab 300 q2w	[redacted]		
Placebo	[redacted]	Placebo	3.40 (1.39)
Key: q4w, every 4 weeks; q2w, every 2 weeks; SD, standard deviation.			

Mortality

No disease-specific mortality was considered within the cost-effectiveness model. Instead, age-specific general population mortality rates based on UK national life tables from 2015 to 2017 were applied in each cycle.[91]

As highlighted in Section B.1.3, limited robust data exist on HAE-related mortality due to the rarity of the disease. However, the Office of National Statistics reported that five patients died from angioedema (hereditary and acquired) in 2017 in England and Wales.[19]

A survey conducted by Zanichelli (2015) reported that in a cohort of approximately 1,000 patients diagnosed with HAE Type I or II in Italy, who were followed between 1973 and 2013, there were five deaths from asphyxiation due to laryngeal attacks in patients who received on-demand therapy.[20] Utilising this data would equate to a monthly probability of death from a laryngeal attack of 0.0019%. Given the improvements in clinical practice over time, this mortality risk is likely to be lower in current UK practice. Therefore, given the lack of robust data on the mortality risk in UK clinical practice, only general population mortality was applied in the economic analysis. This is likely a conservative assumption, given that lanadelumab is

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estimated to reduce the absolute number of attacks that patients experience versus C1-INH.

Treatment discontinuation

Of the 125 patients in HELP-03, eleven withdrew from treatment across all study arms, while one patient was lost to follow-up. Of the 84 patients enrolled onto one of the three lanadelumab dosing regimens in HELP-03, five patients withdrew from treatment (6.0%), while six of the forty-one patients enrolled on the placebo arm in HELP-03 withdrew (14.6%). In comparison, of the 24 patients enrolled in the CHANGE trial, two patients discontinued treatment while receiving C1-INH, and two discontinued treatment while receiving placebo therapy.[59, 84]

Given these results, the small number of events observed across HELP-03 and CHANGE, and the strong safety profile of lanadelumab and C1-INH reported in the RCTs, discontinuation was assumed to be equal between each treatment.

The rate of treatment discontinuation in each cycle applied in the model was estimated utilising data from all treatment arms in the HELP-03 trial, where it was found that 91.2% of patients completed the treatment period in the trial. This proportion of patients in both treatment arms were assumed to continue receiving treatment over the remaining model time horizon, and therefore continue to accrue treatment costs.

B.3.4. Measurement and valuation of health effects

Patients with HAE have a chronic disease that has a substantial and indefinite impact on quality of life. As outlined in detail in Section B.1.3, HAE attacks are disabling and can impair daily living. Besides the physical impact, the unpredictability of the disease has a significant psychological impact on the patient.

HAE attacks involve painful, non-pruritic, non-inflammatory swelling, which can occur in several locations across the body. In addition to swelling, HAE attacks may be accompanied by a range of symptoms, depending on the attack location.[92] In a UK audit study of patients with HAE, patients were asked to rate the impact of HAE on their quality of life. Of the 223 adults questioned, 37% rated the impact as moderate or severe.[15]

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Depression and anxiety are particular issues in patients with HAE, resulting from fear of attacks because of their unpredictable nature (severity, location and triggers are often unknown), pain, disfigurement, and the impact of attacks on daily activities.[31, 37] Physical functioning is greatly impacted in patients with HAE, especially during attacks themselves, and this has a subsequent effect on the patients' daily activities and ability to work.[14, 15, 31, 38]

In addition to the impact of the disease itself, patients with HAE also experience a burden in terms of treatment administration. Patients in current clinical practice receiving C1-INH receive IV administration up to 3–4 times/week. Studies have reported on the issues associated with IV preparations in HAE; 62% of patients with HAE who used a peripheral vein to administer treatment reported difficulties in finding a usable vein or getting the infusion to work properly.[39] Furthermore, frequent administration is not only inconvenient for patients (and potentially carers) but is also associated with a high frequency of injection-related side effects (e.g. rash/erythema, infusion site pain).[41]

Alongside the significant impacts on patients themselves, carers and the families of patients with HAE are also greatly affected by the condition due to the assistance often required to treat attacks and anxiety associated with the unpredictability of the disease.

The sections below present the HRQL data considered and used in the economic model.

Health-related quality-of-life data from clinical trials

In the HELP-03 trial, HRQL was measured using the EQ-5D-5L. Data were collected at three time points during the trial: Days 0, 98 and 182.

Mapping

EQ-5D-5L data collected in HELP-03 were analysed using the crosswalk algorithm by van Hout (2012)[93] to map the individual dimensions of the EQ-5D-5L onto an EQ-5D-3L equivalent continuous utility score in line with NICE DSU guidance.[94]

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Health-related quality-of-life studies

The full details of the HRQL data SLR are presented in Appendix H. Two studies were identified that provided relevant utility values for potential use in the economic model:

- Nordenfelt (2014)[32] – based on a retrospective registry study of Swedish patients with HAE captured by the Sweha-Reg census. Patients completed EQ-5D-5L questionnaires for both the attack-free state, and the last HAE attack
- Aygören-Pürsün (2016)[33] – based on the HAE-BIOS-Europe study which included patients from Germany, Denmark and Spain. EQ-5D utilities were computed for each respondent in the HAE-BOIS-Europe survey for acute attacks and between attacks

A full description of these studies is outlined in the sections below.

Adverse reactions

No impact of adverse reactions on HRQL was modelled as this was similar across treatment arms and very few treatment-related AEs were experienced within HELP-03 (results presented in Section B.2.10) or CHANGE.

C1-INHs are administered more frequently than lanadelumab and are therefore associated with a higher frequency of injection-related side effects. However, as a utility increment was applied to lanadelumab patients in the model as a result of its preferential method of treatment administration (see 'Treatment administration' below), no HRQL impact associated with these side effects was included in the model to avoid the risk of double counting.

Health-related quality-of-life data used in the cost-effectiveness analysis

Although HRQL data were collected as part of the HELP-03 trial, these data have significant limitations. Table 41 presents a summary of the average EQ-5D-5L index values by treatment arm and observation, and Table 42 presents the results for change in EQ-5D-5L over the treatment period. No statistically significant differences were observed either over time or across the three lanadelumab treatment arms and placebo arm.

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Table 41: HELP-03 EQ-5D-5L index summary data

Treatment	Day 0	Day 98	Day 182
Pooled treatments	0.874 (n=124)	0.891 (n=117)	0.876 (n=115)
Lanadelumab 150mg q4w	0.839 (n=28)	0.869 (n=27)	0.889 (n=26)
Lanadelumab 300mg q4w	0.870 (n=28)	0.908 (n=28)	0.869 (n=28)
Lanadelumab 300mg q2w	0.888 (n=27)	0.914 (n=25)	0.874 (n=25)
Placebo	0.890 (n=41)	0.878 (n=37)	0.874 (n=36)
Key: q4w, every 4 weeks; q2w, every 2 weeks.			

Table 42: ANCOVA results for change in EQ-5D-5L scores from Day 0 to Day 182 by treatment arm, adjusted for baseline scores: ITT population

Treatment arm	EQ-5D-5L least square mean change (SD)
	Utility/index
Placebo	-0.01 (0.13)
Lanadelumab 300mg q2w	0.0 (0.13)
Lanadelumab 300mg q4w	-0.01 (0.13)
Lanadelumab 150mg q4w	0.03 (0.13)
F value	1.34
Lanadelumab total versus placebo: least square mean change (SD)	
Placebo	-0.01 (0.13)
Lanadelumab total	0.01 (0.13)
F value	0.98
Key: ANCOVA, analysis of covariance; CI, confidence interval; EQ-5D-5L, EuroQol 5-dimensional 5-level descriptive system; ITT, intent-to-treat; q2w, every 2 weeks; q4w, every 2 weeks; SD, standard deviation. **Source:** HELP-03 CSR[59]	

The utility data in HELP-03 were insufficient to represent the attacks that are characteristic of the disease and to appropriately represent the disease within the cost-effectiveness model. This was due to the limited timepoints of data collection (Days, 0, 98 and 182) and very few observations having been collected (only two out of 807 attacks in study) while patients were experiencing an attack. These data were therefore deemed unsuitable for representing the HRQL benefit associated with the prevention of attacks, as these events represent the main HRQL burden for patients.

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Other HRQL data, such as the AE-QoL, were collected at more frequent timepoints within HELP-03. These data demonstrated improvements in HRQL across the lanadelumab treatment arms versus placebo (as outlined in Section B.2.6). As there is no validated method available to map the AE-QoL to EQ-5D, these data could not be used in the model.

Alternative sources of HRQL data, identified by the utilities SLR, which did collect information on the impact of acute attacks, were therefore utilised in the cost-effectiveness model.[32, 33] A summary of the SLR HRQL findings are presented in Appendix H. Details of the methods used in each of the relevant studies identified and how they are applied in the economic analyses are presented below.

Nordenfelt (2014)

This study was based on a retrospective registry study of Swedish patients with HAE captured by the Sweha-Reg census. Patients completed EQ-5D-5L questionnaires for both the attack-free state (EQ-5D today) and the last HAE attack (EQ-5D attack). Questions related to each patient's age and sex, and other variables such as attack location and severity were included to better understand the burden of HAE.[32]

A total of 103 responses were analysed from 139 questionnaires (74% response rate). One hundred and one reported an EQ-5D today score and 78 reported an EQ-5D attack score, with significant differences between the two states ($p<0.0001$). The study provided attack-free utilities for patients with HAE and attack utilities (by average attack or split by severity). Attack severity was defined as the following:

- Mild: noticeable symptoms but they did not impact activities of daily living. For example, your hand was swollen but you could still hold a pencil or grip a utensil
- Moderate: wanted intervention for symptoms during your attack or your activities of daily living were affected. For example, if your hands were swollen and you could not button your shirt, or your feet were swollen and wearing shoes was uncomfortable
- Severe: treatment or intervention was required, or you were unable to perform activities of daily living. For example, if your throat was swollen and you were having difficulty breathing, or your lips were swollen, and you could not eat

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The study also estimated a difference in utility based on the number of attacks experienced; that is, patients with a higher number of attacks appeared to have a lower average utility while not experiencing an attack.

Patient EQ-5D-5L scores were valued using a community-based sample, with the UK crosswalk value set from the EQ-5D-3L to the EQ-5D-5L used to derive the utility scores.[93] The estimated mean ± standard error EQ-5D today (i.e. 'attack-free') utility score was 0.825 ± 0.207. Increasing attack frequency (-0.0043 per attack, $p<0.001$) and greater age (-0.02205 per 10 years of age, $p<0.001$) had significant effects on the EQ-5D today score. The relevant utility values of the data are presented in Table 43.

Aygören-Pürsün (2016)

This study was based on a HAE-BIOS-Europe survey that included 111 patients from Germany, Denmark and Spain. In this study, utilities were derived by manually crosswalking survey items that overlapped conceptually with the EQ-5D domains (pain/discomfort, mobility, self-care, usual activities, and anxiety/depression) to the corresponding UK population base EQ-5D utility weights. EQ-5D utilities were computed for each respondent in the HAE-BOIS-Europe survey for acute attacks and between attacks – self-care and mobility were assumed not to be impacted between attacks, and self-care was also not considered to be impacted during an attack.

This study used an unvalidated approach in mapping to EQ-5D in which the self-care and mobility domains were assumed to not be affected. The study reported everyday utilities for patients with HAE and utilities were split by severity. The relevant utility values are presented in Table 43.

Treatment administration

As highlighted in Section B.1.3, current treatment with C1-INH IV therapy places a significant burden on patients due to the method of treatment administration and the frequency with which the treatment is administered. Lanadelumab comparatively reduces that burden on patients, and as a result improves patients HRQL in two key areas:

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- Lanadelumab is administered subcutaneously rather than intravenously. Studies have demonstrated that patients with HAE treated with IV therapy can experience issues finding a usable vein to administer treatment, or with getting the infusion to work properly.[39] Additionally, multiple studies across a range of disease areas have demonstrated patients' preference for SC treatments over IV therapies
- Lanadelumab is administered every 2–4 weeks as a low volume injection (2 ml) compared to C1-INHs which are typically administered twice a week at a higher volume (at least 10 ml). A higher frequency of administration is not only inconvenient for patients but also for carers, who can often be involved in supporting the administration of treatment. More frequent administration is also associated with a higher frequency of injection-related side effects (e.g. rash/erythema, infusion site pain)[41]

Although studies have highlighted issues with IV therapy and patients' preference for less invasive and less frequent administrations, no such HRQL benefits have been quantified in patients with HAE. However, studies have been conducted that have valued HRQL benefits related to treatment administration in a range of other disease areas. Studies have reported HRQL benefits in terms of reducing the frequency and changing the route of administration from IV to SC.

A targeted literature review was conducted to find specific utility increments or decrements associated with the route and frequency of treatment administration. The review identified nine relevant studies that compare SC and IV therapy, and also different frequencies of administration, which are summarised in Appendix S.

Three of the studies identified were utilised in the model, one in the base-case analysis and two in scenario analysis. Jørgensen (2017)[85, 95] conducted a time-trade-off (TTO) study in 1,645 adult respondents from the UK general population who were recruited through a representative internet-based survey panel. The study presented participants with eight health states that varied the route of treatment administration (SC injection/IV infusion), frequency (every 1/2/4/8/12 weeks), and location (hospital/home) to correspond with treatment regimens for a number of commonly used biological compounds. The resulting utility values demonstrated a clear HRQL benefit for SC therapy over IV therapy, and improvements related to a reduction in the frequency of administration.

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Holko (2018)[96] conducted a TTO study in patients with inflammatory bowel disease. The study asked 127 patients to value health states for: once-daily oral, every 2 weeks SC and every 8 weeks IV administration of biological therapy treatment for inflammatory bowel disease. The process utility of the once-daily oral state adjusted for confounders was estimated at 0.147 (95% CI: 0.087, 0.208) and 0.164 (95% CI: 0.096, 0.233) in comparison with SC and IV states, respectively, demonstrating a HRQL benefit for patients treated with SC over IV therapy.

Evans (2013)[97] conducted a TTO study in patients in the UK, Canada and Sweden, including 2,465 respondents from the general population, 274 people with Type I diabetes and 417 people with Type II diabetes. Participants evaluated diabetes related health states were patients were assumed to receive either basal or basal-bolus regimens once-daily with a flexible time, once daily at a fixed time, or twice-daily at fixed times. Health states which specified a reduced dosing frequency and greater flexibility in the timings of those doses were valued more highly than other health states.

The other studies identified reported HRQL benefits of a similar magnitude in a range of disease areas including diabetes and cancer. Therefore, there is a variety of evidence in the published literature demonstrating HRQL benefits associated with treating patients subcutaneously rather than intravenously and with less frequent treatment administration.

Application of utility data in the economic model

The study conducted by Nordenfelt (2014)[32] was selected for use in the base-case analysis. This study was selected as it was deemed to provide the most robust utility estimates when patients were attack-free or experiencing an attack.

The study by Aygören-Pürsün (2016)[33] utilised an unvalidated method for deriving utilities that does not meet the NICE reference case and was therefore only used in scenario analysis. This is because utilities were derived by manually crosswalking survey items that overlapped conceptually with the EQ-5D domains to the corresponding UK population base EQ-5D utility weights, with self-care and mobility assumed not to be impacted between attacks, and self-care not considered to be impacted during an attack.

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A summary of the values from these two studies is presented in Table 43. The utility values from Nordenfelt (2014) presented in Table 43 most closely match the EQ-5D values estimated from HELP-03 as presented in Table 41. In addition, the Nordenfelt (2014) study was utilised in the evidence report that was published by the Institute for Clinical and Economic Review in the US, investigating prophylaxis for HAE with lanadelumab and C1-INH.[86]

The utility value for patients not experiencing an attack was estimated by utilising the formula from Nordenfelt (2014) presented in Figure 22.

Figure 22: Attack-free utility formula

$$Attack\ free\ utility = 0.825 - 0.02205 * age - 0.0043 * no.of\ attacks\ in\ previous\ cycle$$

In the base-case analysis, utilities applied during an attack were applied based on the values for an average attack, rather than utility values estimated by attack severity. This was to overcome any potential issues with differences in the definition of attack severity between HELP-03, CHANGE and Nordenfelt (2014). The utility values based on attack severity were applied in scenario analysis. For this scenario, the proportions of patients experiencing mild, moderate or severe attacks were estimated as outlined in Section B.3.3.

The average per-cycle utility value was estimated by weighting the attack-free utility and the attack utility by the average number of attacks experienced in that cycle and the assumed duration of those attacks.

Scenario analyses are presented utilising the values from Aygören-Pürsün (2016).[33]

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Table 43: Attack utility values applied in the cost-effectiveness model

Health state	Base case: Nordenfelt[32] Mean (SD)	Scenario analysis: Aygören-Pürsün[33] Mean (SD)
Attack-free	0.825 (0.207)	0.722 (0.230)
Mild attack	Decrement: -0.070 (0.350)	0.613 (0.260)
Moderate attack	Decrement: -0.369 (0.500)	0.467 (0.270)
Severe attack	Decrement: -0.486 (0.550)	0.080 (0.080)
Average attack utility	0.512 (0.299)	0.444 (0.300)
Age (per year)	-0.02205	N/A
Previous number of attacks	-0.0043	N/A

In addition to these utility values, the model applies a utility increment to patients treated with lanadelumab based on the preferential administration of treatment compared to patients receiving C1-INH. This was applied as an increment as it represents an additional benefit of lanadelumab over the current standard of care. In the base-case analysis the model utilised values from Jørgensen (2017)[85] as this study was not disease specific, included a large sample of participants from the UK general population, and valued health states based on both the route of administration and the frequency of dosing. In addition, the range of utility values in this study was broadly consistent with the utility values in HELP-03 and Nordenfelt (2014)[32]. The health state utility values selected from this study to estimate the utility increment were:

- SC therapy administered every 8 weeks at hospital: 0.860
- IV therapy given every 4 weeks at hospital: 0.836

The difference between these values resulted in an increment of 0.024, which was applied in the lanadelumab treatment arm in each model cycle.

These health states did not align precisely with the dosing regimens of interest (lanadelumab SC therapy administered at home every 2–4 weeks versus C1-INH IV therapy administered at home twice a week) but these differences likely result in an underestimation of the HRQL benefit of lanadelumab. Firstly, although the health states are hospital rather than home based, this assumption was consistent across both the health states, resulting in the only factors driving differences in HRQL

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between the health states being the route and frequency of administration. Secondly, the health states present a scenario where IV therapy is administered twice as frequently as SC therapy (every 8 weeks vs every 4 weeks), whereas C1-INHs are administered at least 4–8 times more frequently than lanadelumab depending on the treatment regimen given. These factors should therefore result in the increment leading to a conservative estimate of the HRQL benefit.

To test the robustness of the results to a range of different utility increments, values of 0.017 and 0.039 estimated from Holko (2018)[96] and Evans (2013)[97], respectively, were applied in scenario analysis. A summary of the values applied in the model is presented in Table 44.

Table 44: Treatment administration utility values applied in the cost-effectiveness model

Study	SC health state	IV health state	Increment
Jørgensen (2017)[85]	SC every 8 weeks at hospital: 0.860	IV every 4 weeks at hospital: 0.836	0.024
Holko, Przemyslaw (2018)[96]	Oral vs SC every 2 weeks: 0.147	Oral vs IV every 8 weeks: 0.0164	0.017
Evans (2013)[97]	NR	NR	0.039 (one vs two fixed injections)
Key: IV, intravenous; NR, not reported; SC, subcutaneous**.**			

B.3.5. Cost and healthcare resource use identification, measurement and valuation

The cost and resource use SLR did not identify studies which were relevant for inclusion within the cost-effectiveness model. However, the studies highlighted the high cost and resource use associated with the acute treatment of attacks. The findings of the SLR are reported in Appendix I.

NHS Reference Costs and Monthly Index of Medical Specialities (MIMS) were used to inform costs in the model.[98, 99]

Intervention and comparators' costs and resource use

Costs for prophylactic treatments were obtained from MIMS. Drug posology and pack costs for lanadelumab and its comparators are presented in

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Table 45. A confidential PAS has been submitted and is expected to be approved prior to the first appraisal committee meeting. This arrangement provides lanadelumab to NHS patients at a [redacted] discount on list price. A list price of £12,420 per 300 mg vial has been approved by the Department of Health and Social Care, with the PAS subsequently reducing this price to £[redacted].

Table 45: Drug posology, form, administration, unit size, pack size, and pack cost – prophylactic treatments

Treatment	Posology		Unit size	Pack size	Cost per pack
	Units	Admin/frequency			
Lanadelumab	300mg	SC/28 days SC/14 days	300mg	1	[redacted]
C1-INH	1,000IU (Cinryze IV)[88]	IV/3.5 days[a]	500IU	2	£1,336
	[redacted] (Berinert IV)[100]	IV/3.5 days[a]	1500IU	1	£1,650
			500IU	1	£550

Key: IU, international units; IV, intravenous; SC, subcutaneous.

Note: [a]Administered every 3 or 4 days; 3.5 days used as midpoint to allow for variation between administrations every 3 or 4 days.

In calculating the drug costs in each cycle for lanadelumab, a weighted average of the per cycle costs for lanadelumab 300 q4w and q2w was estimated utilising the proportions of patients assumed to be treated on each dosing regimen at each time point outlined in Section B.3.2.

Both Cinryze IV and Berinert IV are administered every 3–4 days, with patients treated with Cinryze IV receiving 1000IUat each dose[88], while patients on Berinert IV typically receive an average initial dose of approximately [redacted] based on clinical expert opinion.[46] This was a conservative assumption as clinical experts also indicated that the [redacted], while we assumed constant dosing regimen within the base case.

In calculating the drug costs per cycle for C1-INH, a dose of 1,000IU per dose was assumed for Cinryze IV consistent with its licence[88], with patients assumed to use two 500IU vials per administration. It was assumed that patients treated with Berinert IV receive an average dose of approximately [redacted], based on clinical expert opinion.[46] A weighted average of the per cycle costs for Cinryze IV and Berinert IV

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was estimated in each cycle based on the proportions of patients assumed to be treated with each treatment outlined in Section B.3.2.

Vial wastage was applied in the base case for Berinert IV as this is a weight-based IV treatment. Given the rare nature of HAE, the frequency of self-administration at home and the issues with storing vials, it is assumed no vial sharing or storage would occur, and the cost of the full vial was applied even when the vial was not fully used. The method of moments was used to determine the average dose across the patient population when this varied with patient characteristics. In the method of moments, first a log-normal distribution is derived for the patient weight within the trial based upon the mean and standard deviation of the weight.[101] The simplifying assumption is made that the average weight of patients remains constant over time. The log-normal distribution is then used to predict what proportion of patients require each number of vials to administer the required dose. This method assumes that patients only receive whole vials (no vial sharing) and thus accounts for drug wastage.

The average weight ([redacted]), calculated as a weighted average of the average weight of females and males, and the ratio of females to males (70.4% versus 29.6%) as reported in the HELP-03 trial, was used to inform the dosing and costing for Berinert IV.[59]

The per-cycle (28 day) cost calculations applied in the model are shown in Table 46 and were calculated based on per-mg/per-IU costs.

Table 46: Per-cycle prophylaxis drug costs

Treatment	Dose	Administrations per cycle (28 days)	Per-cycle costs
Lanadelumab	300mg every 4 weeks	1	[redacted]
	300mg every 2 weeks	2	[redacted]
C1-INH	1000IU every 3.5 days[a] (Cinryze IV)	8	£10,688
	[redacted] every 3.5 days[a] (Berinert IV)	8	£[redacted]

Key: IU, international units; IV, intravenous; SC, subcutaneous.

Notes: [a]Administered every 3 or 4 days; 3.5 days used as midpoint to allow for variation between administrations every 3 or 4 days.

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Lanadelumab is administered subcutaneously, whereas C1-INHs are IV treatments. Administration costs were not included in the model base case. In fact, based on clinical feedback,[46] [redacted]. Shire offers a homecare service for patients treated with Cinryze which [redacted] This assumption was varied for C1-INH in a scenario analysis given issues with administering IV therapies makes hospital administration more likely for some patients. In this scenario, costs were taken from the Unit Costs for Health and Social Care 2017, assuming a 30-minute appointment with a hospital specialist nurse for IV administration.[102] The costs are presented in Table 47.

Table 47: Drug administration costs

Administration	**NHS reference costs[102]**	
	Code/description	**Cost**
	Hospital specialist nurse £110 per hour of patient contact. Assumed 30-minute appointment.	£55
IV		
Key: GP, General practitioner; IV, intravenous; SC, subcutaneous.		

Health-state unit costs and resource use

It is expected that not all the acute attacks will require acute treatment. Based on the HELP-03 trial data pooled across treatment arms, 85% of the attacks experienced were assumed to be treated for both patients receiving lanadelumab or C1-INH as their prophylactic therapy as no equivalent data were available from the CHANGE trial. This figure was estimating by dividing the number of attacks reported in HELP-03 that required on-demand medication use (686) by the total number of attacks reported in HELP-03 (807).

When attacks require acute treatment, this could vary and expert opinion indicated the most commonly used treatments are [redacted]. [46]

As data on the acute treatments received in CHANGE were not available, it was assumed that [redacted] based on feedback from clinical

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experts.[46] This is probably a conservative estimate as clinical experts indicated that for some patients it [redacted]. This additional cost has not been included in the model. As lanadelumab is not licensed as an acute treatment, patients receiving lanadelumab as a prophylactic therapy were assumed to receive acute treatments based on the proportions observed in the HELP-03 trial. The proportions of each of the acute treatments received for the lanadelumab arms were calculated using the distribution sourced from the HELP-03 study CSR. The HELP-03 study included Kalbitor® as an acute attack treatment. However, this treatment is not available in the UK and the distribution of acute treatments for lanadelumab was therefore re-normalised to exclude Kalbitor®.[46] The distribution of treatments received for acute attacks for each prophylactic treatment is given in Table 49. The percentages given in Table 49 sum to 100%; these were multiplied by the proportion of patients receiving acute treatment for an attack (85%) before being applied in the model.

Costs for the acute treatments were taken from MIMS and are presented in Table 48.

Table 48: Drug posology, form, administration, unit size, pack size, and pack cost – acute attack treatments

Treatment	Posology	Unit size	Pack size	Cost per pack
Cinryze[88]	IV 1000IU/day	500IU	2	£1,336
Firazyr[103]	SC 30mg/day	30mg	1	£1,395
Ruconest[104]	IV 50IU/kg/day	2100IU	1	£750
Berinert IV[100]	[redacted]	1500IU	1	£1,650
		500IU	1	£550
Key: IV, intravenous; IU, international units; SC, subcutaneous.				

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Table 49: Acute treatments received by prophylactic treatment

	Percent of patients receiving acute treatments				
Prophylactic treatment	**Icatibant (Firazyr)**	**Recombinant C1-INH (Ruconest)**	**Cinryze IV**	**Berinert IV**	**Cost per attack**
Lanadelumab (all arms)	[redacted]	[redacted]	[redacted]	[redacted]	1,382.21
C1-INH	0.00%	0.00%	[redacted]	[redacted]	[redacted]

Key: C1-INH, C1-inhibitor; IV, intravenous.

In addition to the treatment costs associated with an attack, patients may also require an accident and emergency (A&E) visit or hospitalisation depending on the severity and location of the attack. The percentage of patients requiring an A&E visit or hospitalisation was assumed to be the same across prophylactic treatments in the base case because the severity and location of attacks experienced by patients appeared to be broadly consistent regardless of the treatment arm within the HELP-03 trial, as highlighted in Table 39, and data were not available from the CHANGE trial.

The proportion of attacks requiring an A&E visit or an inpatient hospital stay, and the average length of each hospital stay was estimated from data presented in Helbert (2013).[105] This study presents the mean number of hospital visits and mean number of bed days per patient per year for HAE patients and a control sample of non-HAE patients in the UK. It was estimated that the mean number of hospital visits per patient per year was higher in the HAE group compared to the control group (1.85 vs 0.33), as was the mean number of bed days per patient per year (3.02 vs 0.95).

To calculate the percentage of attacks requiring an A&E or hospital stay, the difference in hospital visits between the HAE and control patients was estimated (1.52), and this figure was then divided by the average number of attacks patients were assumed to experience each year. The average annual attack rate estimated from the C1-INH arm in the economic model (12.6 attacks per year) was used as a proxy for the average number of attacks patients experience in practice per year. Dividing these values resulted in an estimate of 11.9% of attacks requiring an A&E visit and an inpatient hospital stay.

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To estimate the average length of each hospital stay, the difference in the number of bed days per patient per year between the HAE and control groups (2.07) was divided by the difference in the number of hospital visits between the HAE patients and the control patients (1.52), to estimate an average stay of 1.36 days. The figures utilised in the analysis are presented in Table 50. These values are consistent with UK clinical expert opinion.[46] In scenario analysis, values were utilised from a US study conducted by Wilson (2010) in order to test the robustness of the results to changes in these values.[106] Utilising the values presented in this study resulted in estimates of 10.3% and 17.4% for the percentage of attacks requiring a hospital stay and an A&E visit respectively. It was also estimated that 10.7% of attacks resulted in an additional GP visit.

Table 50: Attack resource use

Percentage of HAE attacks requiring hospitalisation	11.9%
Average duration of hospitalisation	1.38 days
Percentage of HAE attacks requiring A&E visit	11.9%
Key: A&E, accident and emergency; GP. General practitioner; HAE, hereditary angioedema.	

Self-administration of treatment for acute attacks was not assumed to be associated with an administration cost. The cost of (self-)administration for the acute treatment of attacks was assumed to be captured in the application of GP, A&E and hospitalisation visit costs; therefore, no additional administration cost was applied in the acute treatment setting.

Costs for hospitalisation and A&E visit costs were obtained from the NHS National Schedule of Reference Costs (2017–2018).[98]

The hospitalisation costs applied in the model are weighted averages (based on activity) of the following:

- KC04A: Inborn Errors of Metabolism with Complication and Comorbidity Score 3+
- KC04B: Inborn Errors of Metabolism with Complication and Comorbidity Score 0–2 – non-elective inpatient

A&E visit costs were a weighted average (based on activity) of the following:

- WF01B: Non-Admitted Face-to-Face Attendance, First, Consultant Led.
- WF01B: Non-Admitted Face-to-Face Attendance, First, Non-Consultant Led.

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Costs for GP visits were taken from the Personal Social Services Research Unit 2017, and were based on a cost per patient contact consultation lasting 9.22 minutes.[102]

Table 51: Costs for medical attention

Reference cost code/details	Description	Cost as stated in reference	Activity	Cost used in model[a]
KC04A Inborn Errors of Metabolism with CC Score 3+	Hospitalisation	£3367.62	1,097	£2,961
KC04B Inborn Errors of Metabolism with CC Score 0–2	Hospitalisation	£803.48	207	
WF01B - Non-Admitted Face-to-Face Attendance, First, Consultant Led	A&E	£143	127,674	£139
WF01B - Non-Admitted Face-to-Face Attendance, First. Non-Consultant Led	A&E	£105	12,227	
GP/per patient contact lasting 9.22 minutes	GP visit	£38.00	N/A	£38

Key: A&E, accident and emergency; CC, complication and comorbidity; GP, general practitioner; N/A, not applicable.
Note: [a], Weighted averages were calculated based on activity.

Adverse events unit costs and resource use

AEs and the associated costs are presented in Table 53. Only Grade ≥3 treatment-emergent AEs, excluding events reported as HAE attacks, occurring in >2% of patients in any treatment arm were included in the economic analysis. AEs for lanadelumab were informed by the HELP-03 trial, and the CHANGE trial informed the number of AEs for C1-INH.[59, 84] The frequency of events assumed to occur in each model cycle was estimated by first dividing the number of events recorded during the trial by the number of patients in each treatment arm, and then converting these values into per cycle rates by adjusting them by the length of the trial. The data utilised in the model are presented in Table 52.

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Table 52: Adverse event frequency per cycle

Adverse event	Lanadelumab 300mg q4w	Lanadelumab 300mg q2w	C1-INH
Increased liver enzymes	1.09%	0.00%	0.00%
Chest discomfort	0.00%	0.00%	1.41%
Key: q4w, every 4 weeks; q2w, every 2 weeks			

Costs associated with these AEs and their treatment were taken from the Unit Costs for Health and Social Care 2017.[102] The simplifying assumption was made that these AEs would be treated by a GP.

Table 53: Adverse event costs

AE	UK	
	Code/description	**Cost**
Increased liver enzymes	General practitioner – per patient contact lasting 9.22 minutes, including direct care staff costs, with qualification costs	£38.00
Chest discomfort		
Key: AE, adverse event; HCUP, Healthcare Cost and Utilization Project.		

Miscellaneous unit costs and resource use

Monitoring costs were not included in the base case. Excluding monitoring costs was based on clinical opinion: patients on C1-INH require very few and infrequent monitoring visits/tests and these would be similar across all HAE treatments. Monitoring costs were therefore not expected to have an impact on the results.

B.3.6. Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

A summary of the variables and distributions applied in the economic model is presented in Appendix R, including references to the corresponding sections in the submission where each is explained in more detail.

Summary of model assumptions

Table 54 details the key assumptions used in the economic model and provides a justification for each one, as well as the references to the corresponding sections in the submission where each is explained in more detail.

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Table 54: Base case assumptions in the economic model

Assumption	Justification	Reference in submission
Population		
Efficacy data utilised in the model is applicable to patients whose condition is not adequately controlled with oral prophylactic treatment and those for whom oral prophylactic treatment is not suitable	Lanadelumab is expected to be prescribed for patients with HAE that is not adequately controlled with oral prophylactic treatment or for whom oral prophylactic treatment is not suitable. As only 8% of patients in HELP-03 and 14% of patients in CHANGE received oral therapy prior to trial enrolment, it was not feasible to specifically address efficacy in the decision problem population. However, as there were no statistically significant differences in efficacy between patients with and without prior prophylactic therapy in HELP-03, and based on feedback from clinical experts, the population investigated in the model appears to be broadly consistent with the decision problem.	Section B.3.2
Intervention and comparators		
44.4% of patients will switch to a lanadelumab dose of 300mg q4w in UK clinical practice after the first 6 months of treatment; at 12 months 76.9% of patients will switch to this dose	This proportion is based on clinical expert opinion and the time to first attack data from the HELP-03 trial. These data demonstrate that by the end of the trial period 44.4% of patients treated with a dosing regimen of 300mg q2w were attack-free. The time to first attack analysis conducted from Day 70 onwards (corresponding to the achievement of steady state of lanadelumab plasma concentration) also demonstrated that 76.9% of patients were attack-free during this period. The assumption that a proportion of patients would receive the lower dose in clinical practice [redacted].[46] To ensure that the treatment effect was not overestimated in these patients, the Poisson regression coefficients for the 300mg q4w dose were applied to this proportion of patients at the point of switch.	Section B.3.3
The most relevant comparator is C1-INH, a weighted comparator of [redacted] of patients receiving Cinryze IV 1,000IU and [redacted] receiving Berinert IV [redacted]	These figures were based on Hospital Pharmacy Audit data which estimated the use of each treatment in UK clinical practice.[87] The figures applied in the model were calculated by estimating the ratio between the number of vials of Berinert IV and Cinryze IV that were used over the last 3 months of reported data. These proportions were varied in scenario analyses.	Section B.3.2
Efficacy		

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Assumption	Justification	Reference in submission
All C1-INHs included in the model have the same effectiveness	Given the absence of robust clinical effectiveness data for Berinert IV, the rate ratio derived for Cinryze IV was also applied for patients treated with Berinert IV. Given the uncertainty around its effectiveness, a threshold analysis is also presented which demonstrates how the results of the analysis change as the rate ratio of Berinert IV is varied.	Section B.3.3
The heterogeneity between the HELP-03 and CHANGE trials is reasonable and allows for a robust comparison between lanadelumab and C1-INH	A comparison of the patient characteristics and the inclusion criteria from each of these studies demonstrates consistency between the two patient populations, with similarities in terms of age, sex and the percentage of patients with Type I or Type II HAE. Some differences exist in the inclusion criteria for the baseline attack rate (one per month in HELP-03 versus two attacks per month in CHANGE), and the percentage of patients receiving prior long-term prophylactic therapy (56% in HELP-03 versus 14% in CHANGE). However, a subgroup analysis from the HELP-03 trial demonstrated that there were no statistically significant differences in efficacy outcomes between patients with differing levels of baseline attack risk, or between patients with and without prior prophylactic therapy, providing no evidence that these characteristics are treatment effect modifiers. Therefore, the population presented in the cost-effectiveness model is consistent with the decision problem.	Section B.3.2
Once a patient's attack rate has stabilised it remains stable across all treatment arms	The output of the Poisson regression predicted that the number of attacks patients experience declines from baseline, before plateauing and remaining at a constant rate in the longer term. This is consistent with the exploratory Day 70 analysis in HELP-03 presented in Section B.2.6, which indicated that over time, treatment became more effective when lanadelumab concentration appeared to reach a steady state. In addition, the 6-month HELP extension study highlighted how the attack rate remained constant beyond the HELP-03 trial period (as highlighted in B.3.10).	Section B.3.3
The Poisson regression method is appropriate to predict the number of attacks patients experience over time	A Poisson regression analysis was selected as the most appropriate method to estimate the average number of attacks per cycle given its suitability to model count	Section B.3.2

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Assumption	Justification	Reference in submission
	data, as it is concerned with the number of events within a given time-period e.g. each model cycle. Other regression techniques such as the negative binomial were considered, but the Poisson regression provided a good fit to the observed trial data and was therefore selected.	
Health-related quality-of-life		
Nordenfelt (2014)[32] and Jørgensen (2017)[85] provide the most appropriate sources of utility data for application in the model	HRQL data from the HELP-03 trial were collected at limited timepoints (Days 0, 98 and 182). Only two questionnaires were completed while patients were experiencing an attack. These data were therefore deemed unsuitable for inclusion in the analysis. Utility values from Nordenfelt (2014)[32] were selected in the base case. An alternative utility source was identified but this utilised an unvalidated method to derive utility values. The attack-free utility values from Nordenfelt (2014) also most closely matched the EQ-5D values estimated from HELP-03 and these values were also utilised in the evidence report that was published by the Institute for Clinical and Economic Review. In addition, a targeted literature review indicated that lanadelumab has the potential to reduce the burden of treatment administration on patients because it is administered subcutaneously rather than intravenously and is administered less frequently than its comparators. Jørgensen (2017)[85] conducted a time trade-off study in 1,645 adult respondents from the UK general population. The study asked participants to value health states for subcutaneous and intravenous therapies given at different frequencies. A utility increment estimated from this study was applied in the base case analysis to patients treated with lanadelumab.	Section B.3.4
Costs		
There are no differences in treatment discontinuation between lanadelumab and C1-INH	Given the small proportion of patients who discontinued treatment in HELP-03 and CHANGE, the small number of events observed across both trials and the strong safety profile of lanadelumab and C1-INH reported in the RCTs, discontinuation was assumed to be equal between each treatment.	Section B.3.3
Attack severity and medical resource use associated with an attack is equal across treatment arms	Given that the differences in attack severity between each treatment are small, the proportions of attacks assumed to be mild, moderate or severe were estimated utilising the pooled attack data from HELP-03. Therefore, once a patient experienced an	Section B.3.3

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Assumption	Justification	Reference in submission
	attack, the probability of having a mild, moderate or severe attack was comparable across treatments.	
No administration costs are incurred when patients are treated	Self-administration was allowed for all treatments. Based on clinical feedback, [redacted].	Section B.3.5
Vial sharing or storage is not possible for IV treatments	This was deemed to be a reasonable assumption given the rarity of the disease and the fact that patients tend to self-administer at home, making it unlikely any vial sharing would occur in practice.	Section B.3.5
Key: IV, intravenous; q4w, every 4 weeks.		

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B.3.7. Base-case results

Base-case incremental cost-effectiveness analysis results

As detailed in Section B.3.5, a confidential PAS has been submitted and is expected to be approved prior to the first appraisal committee meeting. This arrangement provides lanadelumab to NHS patients at a [redacted] discount on list price. Therefore, this PAS has been applied and the results presented reflect this discount.

The key results of the base-case analysis are presented in Table 55 and a summary of all costs captured in the model is presented in Table 56. The results demonstrate that lanadelumab is a cost-effective use of NHS resources for the routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older. Not only does lanadelumab result in a QALY gain but it is also a cost-saving treatment, based on both prophylactic drug acquisition costs and savings from reducing the need for the acute treatment of attacks.

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Table 55: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	NMB
C1-INH	[redacted]	21.48	[redacted]					
Lanadelumab	[redacted]	21.48	[redacted]	[redacted]	0.00	[redacted]	Dominant	£470,031

Key: C1-INH, C1 esterase inhibitor; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALY, quality-adjusted life year.

Table 56: Base-case cost breakdown

Component	Costs: lanadelumab	Costs: C1-INH IV	Incremental costs	Absolute	% Proportion
Prophylaxis costs					
Drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attack-related costs					
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A&E visit costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GP visit costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; A&E, accident and emergency; C1-INH, C1 esterase inhibitor; ER, emergency room; IV, intravenous.

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B.3.8. Sensitivity analyses

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted in which all inputs were varied simultaneously over 1,000 iterations, based upon their distributional information.

To determine the number of patients required to run through the Poisson regression for PSA, convergence testing was conducted. A convergence criterion of NMB within £10 of the previous Poisson regression run was set. The number of patients at which this criterion was met was recorded by running the model starting with 1 patient and increasing the number of patients running through the regression by 1 each time until convergence. Convergence was achieved at 88 patients and therefore for the PSA, 90 patients were used for each PSA run within the Poisson regression.

The results are summarised in Table 57 and are also presented on a cost-effectiveness plane in Figure 23. The results are consistent with the deterministic analysis and show that lanadelumab is a cost-effective use of NHS resources.

Table 57: Mean probabilistic sensitivity analysis results

Technology	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NMB
C1-INH	[redacted]	[redacted]				
Lanadelumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£469,369

Key: C1-INH, C1 esterase inhibitor; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.

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Figure 23: Cost-effectiveness plane

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

The cost effectiveness acceptability curve for the comparison of lanadelumab versus C1-INH suggests that there is a 100% likelihood that lanadelumab is cost effective at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained.

Deterministic sensitivity analysis

A series of one-way sensitivity analyses was performed to evaluate the sensitivity of the model ICER to individual inputs, holding all else constant. In the deterministic sensitivity analysis, the lower and upper bounds of a parameter were taken from the 95% confidence intervals if these were available from the data source. If only the standard error was reported, then the lower and upper bounds were set to ±1.96*standard error (SE) of the base case value (or mean). However, when such information was not available, the upper and lower bounds were assumed to be within ±10% of the base-case value. In a few cases, variation of a model parameter in deterministic sensitivity analysis was performed as per specific NICE guidelines (e.g. 0% and 5% for discount rate).

A summary of the variables and distributions applied in the economic model is presented in Appendix R, including references to the corresponding sections in the submission where each is explained in more detail.

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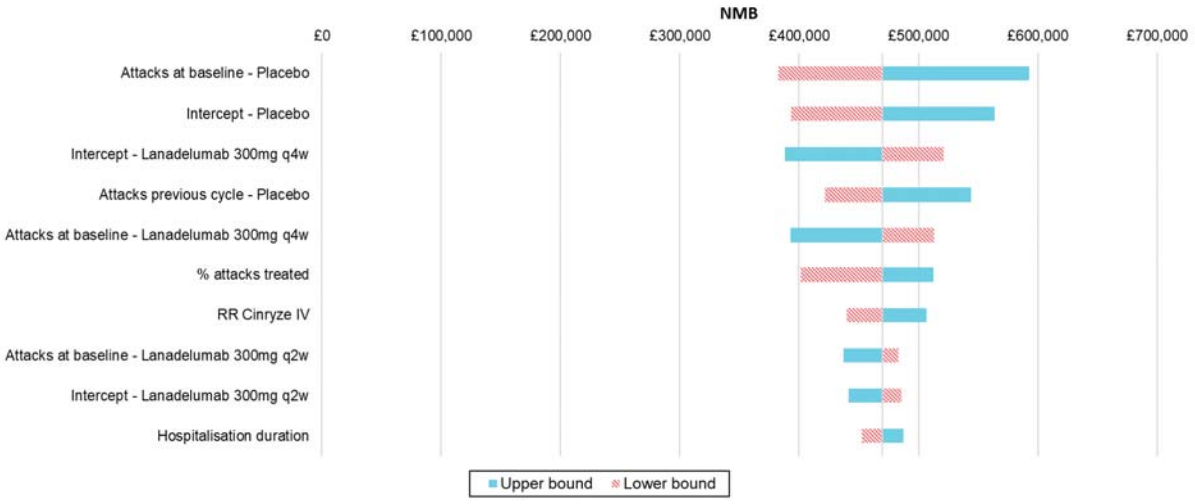
Each value was varied based on its uncertainty parameters. Figure 24 presents the tornado diagram for lanadelumab versus C1-INH with parameters shown in descending order of ICER sensitivity.

These results demonstrate that the model is relatively insensitive to the majority of parameters, with lanadelumab providing a significantly positive net monetary benefit at a willingness-to-pay threshold of £30,000 per QALY for variations in each parameter.

Figure 24: Results of one-way sensitivity analysis



Key: IV, intravenous; q4w, every 4 weeks; q2w, every 2 weeks; NMB, net monetary benefit; RR, rate ratio; SC, subcutaneous.

Scenario analysis

The scenarios explored in the model are presented in Table 58. The results were relatively insensitive in most of these analyses with lanadelumab remaining dominant in all scenarios. The scenarios that resulted in the largest impact on the results were firstly the time horizon, however, lanadelumab remained cost effective even as the time horizon was reduced from 60 to 10 years. Additionally, [redacted] in line with the opinion of some UK clinical experts who noted that C1-INHs are often up-dosed in clinical practice,[46] led to a substantial increase in the net monetary benefit.

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Table 58: Scenario analysis results

Model assumption	Base-case	Scenario	ICER (£/QALY)	NMB (£)
Base case			**Dominant**	**£470,031**
Probabilistic			**Dominant**	**£471,928**
Time horizon	Lifetime (60 years)	10 years	Dominant	£113,087
		20 years	Dominant	£247,023
		40 years	Dominant	£412,481
C1-INH distribution	Based on hospital dispensing data: [redacted] Cinryze IV: [redacted] Berinert IV	[redacted] Cinryze IV: [redacted] Berinert IV	Dominant	£568,400
		[redacted] Cinryze IV: [redacted] Berinert IV	Dominant	£408,136
C1-INH frequency	Administered twice per week	Administered [redacted]	Dominant	£743,269
Attack utility settings	Apply average attack disutility	Apply disutilities by attack severity	Dominant	£469,557
	Attack severity based on pooled HELP-03 data across all treatments	Apply disutilities by attack severity. Attack severity for lanadelumab based on data from treatment arms in HELP-03 and C1-INH based on Riedl (2016)[90]	Dominant	£469,982
	Apply Nordenfelt (2014) values	Apply Aygören-Pürsün (2016)[33] utility values	Dominant	£468,159
Treatment administration utility benefit	Increment: 0.024 (Jørgensen [2017])	Apply no utility benefit	Dominant	£454,565
		Increment: 0.017 (Holko, Przemyslaw [2018])[96]	Dominant	£465,520
		Increment: 0.039 (Evans [2013])[97]	Dominant	£479,696
Lanadelumab efficacy	Efficacy estimated using Poisson regression coefficient	Lanadelumab efficacy estimated by applying rate ratio from NMA to the placebo estimates	Dominant	£393,793
Self-administration	100% of patients assumed to self-administer	90% of C1-INH patients assumed to self-administer (100% for lanadelumab)	Dominant	£481,286
Treatment discontinuation	Treatment discontinuation from HELP-03 applied	No treatment discontinuation applied	Dominant	£478,533
Attack resource use	Values applied calculated from Helbert (2013)[105]	Values applied calculated from Wilson (2010)[106]	Dominant	£460,174

Key: C1-INH, C1 esterase inhibitor; ICER, incremental cost-effectiveness ratio; IV, intravenous; NMA, network meta-analysis; NMB, net monetary benefit.

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Threshold analysis

As highlighted in Section B.3.3, in the absence of robust clinical effectiveness data on C1-INH at a dose of [redacted], the efficacy of a dose of 1,000IU was also assumed to be applicable to the weight-based dose of Berinert IV. This is a simplifying and restrictive assumption in the analysis, as it is unclear whether the rate ratio for C1-INH at a dose of 1,000IU versus placebo (0.492) would also apply in this instance.

Limited data exists on the efficacy of higher doses of C1-INH. A single-arm study conducted by Bernstein (2014)[107] investigated the impact of escalating doses of C1-INH in sequence, with patients initially considered to be uncontrolled on treatment with a dose of 1,000IU receiving an increased dose of 1,500IU. Patients then subsequently received doses of 2,000 and 2,500IU if they were later considered to be uncontrolled on higher doses. The average monthly attack rate was estimated for each patient on each dose, with the results presented in Figure 25.

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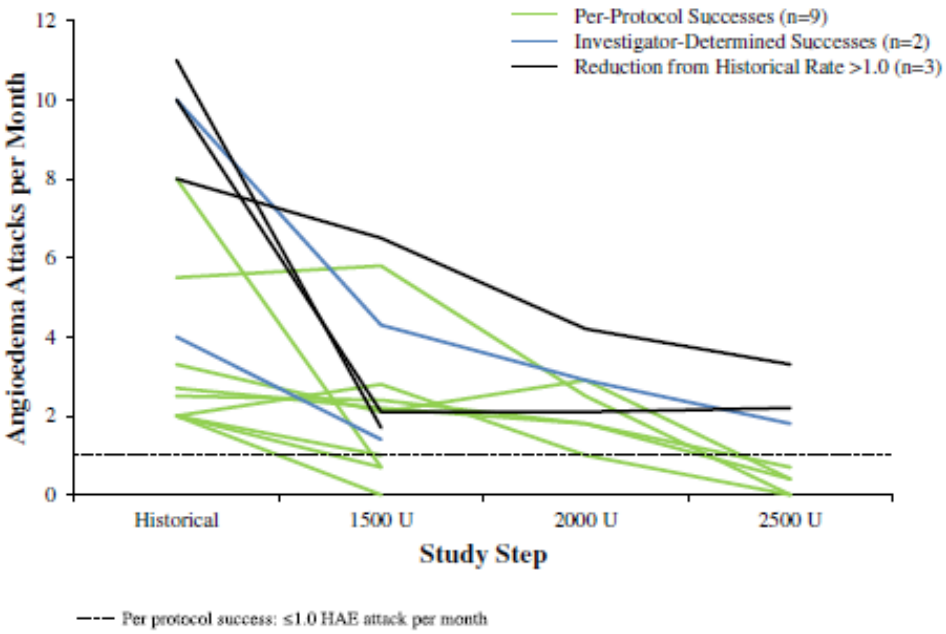
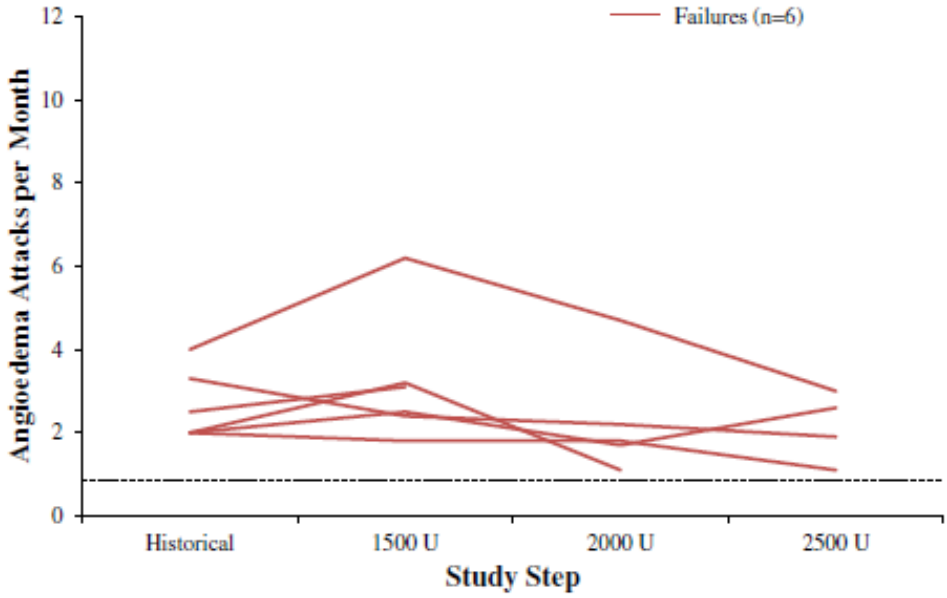
Figure 25: Results of Bernstein (2014)





Digitisation of these curves allowed for the estimation of the percentage reduction in the attack rate at each dose relative to baseline (C1-INH at a dose of 1,000IU). The average attack rate at each dose was first estimated for each patient and an average was taken of these values. The results are presented below in Table 59.

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Table 59: Attack rate with higher doses of C1-INH

Dose in units (n)	Average monthly attack rate	Percentage reduction
1,000	4.44	
1,500 (n=20)	2.64	40%
2,000 (n=13)	2.36	47%
2,500 (n=12)	1.44	67%
Key: ICER, incremental cost-effectiveness ratio, NMB, net monetary benefit.		

This study provides an indication of the potential impact of higher doses of C1-INH in reducing the frequency of HAE attacks. However, the study is restrictive in its ability to estimate effectiveness estimates for C1-INH IV at a dose of [redacted] given it is a single arm trial, has a small sample size and adopts a specific sequencing approach.

As a result, in order to test the robustness of the model results to changes in the effectiveness of C1-INH IV at a dose of [redacted], a threshold analysis was conducted, varying the rate ratio of this dose of C1-INH vs placebo by increments of 0.1. The results of the analysis presented in Table 60 demonstrate that lanadelumab is still the dominant treatment option when the confidential PAS is applied even as the rate ratio was lowered to 0.1, which is lower than the rate ratio estimated for lanadelumab 300mg q2w (0.131).

Table 60: Threshold analysis – rate ratio of Berinert IV [redacted]

Rate ratio vs placebo	ICER	NMB
Base case (0.492)	Dominant	£470,031
0.1	Dominant	£209,038
0.2	Dominant	£282,835
0.3	Dominant	£350,091
0.4	Dominant	£413,697
0.5	Dominant	£475,059
0.6	Dominant	£534,943
0.7	Dominant	£593,800
0.8	Dominant	£651,916
0.9	Dominant	£709,478
1.0	Dominant	£766,615
Key: ICER, incremental cost-effectiveness ratio, NMB, net monetary benefit.		

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Summary of sensitivity analyses results

The results were robust to changes in the parameters and the key model assumptions. The one-way sensitivity analyses highlight that lanadelumab provides a significantly positive net monetary benefit even with variations in each parameter, and the scenario and threshold analyses highlight that the model is also robust to changes in key modelling assumptions.

B.3.9. Subgroup analysis

The NICE scope stated that 'if the evidence allows, the following subgroups will be considered':

- Severity of angioedema attacks
- Frequency of angioedema attacks

Based on the subgroup analysis presented from HELP-03 (discussed in B.3.2), there were no statistically significant differences in the efficacy of lanadelumab between any key subgroups (presented in Appendix E). Additionally, the sizes of the clinical trials limit the ability to perform a robust assessment of subgroups. Therefore, no subgroups were considered in this submission.

B.3.10. Validation

Validation of cost-effectiveness analysis

The model was finalised before being validated by internal and external modellers. A programmer (other than the one who built the model) reviewed all formulae and labelling in the model. Following this first validation step, an extreme value analysis was conducted. This involved inputting sensible upper and lower bounds (e.g. £0 for costs, but not negative costs) into the model, one parameter at a time, and observing the corresponding changes in the results. Where it was not sensible to vary only one parameter or the expected effect on the results was not straightforward, a related group of parameters was varied simultaneously. The results were checked against their expected impact or the predicted direction of change for the varied parameter(s). For example, setting all AE costs to zero would result in £0 for AE

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management across all treatment arms. An academic health economist also validated the model and critiqued the modelling strategy and methodology.

A number of the parameters and assumptions included in the model were validated by UK clinical experts.[46]

HELP-04

As outlined in Section B.2.3, patients in HELP-03 were enrolled onto the HELP-04 extension study with results collected after 6 months presented in Section B.2.6. There were 212 patients enrolled onto the study; 109 who rolled over from HELP-03 and 103 non-rollover patients. All patients went on to receive the lanadelumab dose of 300mg every 2 weeks regardless of their prior therapy.

Table 20 presents a comparison of the mean attack rates per month from HELP-03 and HELP-04, separated by which treatment patients received in HELP-03. The results demonstrate that as patients switched onto the 300 q2w dosing regimen, the attack rate fell regardless of the treatment patients switched from. The results also demonstrate that the attack rate in patients who received 300mg q2w over both studies was sustained into the future, and even fell from [redacted]. This validates the attack rate extrapolations for each treatment presented in Figure 20, and is in line with the expectations of clinical expert experts. It also validates the assumption that when patients switch between different lanadelumab dosing regimens that they experience a response to treatment consistent with the response observed in the HELP-03 trial, regardless of their prior treatment. Table 21 presents the attack rate for the non-rollover patients based on their prior therapy. Again, the results demonstrate that regardless of the treatment patients received previously, the fall in attack rate was consistent across all patient groups. This validates the assumption that the efficacy data utilised in the model is applicable to patients whose condition is not adequately controlled with oral attenuated androgens and those for whom oral attenuated androgens are not an option.

The Institute for Clinical and Economic Review

The Institute for Clinical and Economic Review in the US (US ICER review) recently published a report investigating prophylaxis for HAE with lanadelumab and C1-INH.[86] This review presents evidence from a US perspective, including comparing

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lanadelumab, Cinryze IV and Haegarda (a treatment currently unavailable in UK clinical practice) to no prophylactic treatment in a health outcome-based model. For the comparison of lanadelumab and Cinryze IV to no prophylaxis, consistent with this submission, the analysis utilised findings from HELP-03 and CHANGE to inform the clinical-effectiveness parameters, as well as utility estimates for attacks from Nordenfelt (2014).[32]

A comparison of the QALY and LY results from the US ICER review with this submission is presented in Table 61. For this comparison the settings in the cost-effectiveness model were set to align with the assumptions made in the review. This involved setting the discount rates for health outcomes to 3% and only including utilities based on attacks. The results demonstrate consistency between the two analyses, with the incremental QALYs equalling [redacted] in the cost-effectiveness model compared to 0.45 in the review. Additionally, the cost-effectiveness model predicts that lanadelumab will reduce the number of attacks experienced by 354 while the review predicts a reduction of 620, over a lifetime horizon. These findings highlight that the findings of the CE model are broadly consistent with the health outcome findings of the review and are also conservative.

Table 61: Comparison of health outcome results: cost-effectiveness model vs review report

		Cost-effectiveness model	Review
Lanadelumab	LYs	23.29	23.55
	QALYs	[redacted]	18.66
	No. of attacks	172	223
C1-INH IV	LYs	23.29	23.55
	QALYs	[redacted]	18.21
	No. of attacks	526	843
Key: C1-INH, C1 esterase inhibitor; LY, life year; No., number; QALY, quality adjusted life year.			

B.3.11. Interpretation and conclusions of economic evidence

Patients with HAE and their carers experience a significant impact on their quality of life as a result of the effect of disabling HAE attacks, and current treatment regimens which place a significant burden on patients due to the method and frequency of

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treatment administration. Additionally, acute treatment of attacks is costly, placing a significant burden on NHS resources.

Prophylactic treatment with lanadelumab has been shown to reduce the number of attacks that patients experience compared to currently available C1-INH. This reduction in attack frequency results in a significant improvement in HRQL and a large reduction in resource use. Additionally, as lanadelumab is administered subcutaneously rather than intravenously, and is given less frequently than C1-INH (every 2–4 weeks vs twice a week), this also results in significant HRQL benefits.

Lanadelumab is associated with an incremental gain of [redacted] QALYs per patient and reduces total costs by £[redacted] due to its lower drug acquisition cost and the reduction in attack frequency, reducing the need for acute treatment. These results indicate that lanadelumab is a dominant treatment option as it both increases QALYs and lowers costs. In addition, the probability of lanadelumab being a cost-effective treatment option versus C1-INH is 100% at willingness-to-pay thresholds of £20,000 or £30,000 per QALY.

The ICER was largely insensitive to parameters and assumptions tested in one-way sensitivity analyses and scenario analysis, with lanadelumab remaining a cost-effective treatment in all instances. The assumptions implemented in the base-case analysis have been validated by both the clinical trial data and UK clinical expert opinion.

Some limitations of the analysis included the use of data which has been estimated from small patient numbers due to the rare nature of the disease and the lack of longer-term clinical evidence. Additional limitations included the lack of clinical evidence for higher doses of C1-INH for prophylactic use and the potential mismatch between the patient population presented in the model and the population of interest (patients for whom androgens are unsuitable). In addition, there was a lack of robust EQ-5D data available from the HELP-03 trial assessing the impact of acute attacks on HRQL. However, validation of the long-term validity of the clinical-effectiveness results from clinical experts and the HELP-04 study, the results of the higher dose threshold analysis, and the subgroup analysis presented in HELP-03, all highlight the robustness of the analysis despite these limitations.

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In conclusion, these results show that lanadelumab is a cost-effective use of NHS resources which not only results in improvements in HRQL but also reductions in both prophylactic and acute treatment costs.

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B.5. Appendices

Appendix C: Summary of product characteristics (SPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Clinical guidelines and policy documents for the management of hereditary angioedema

Appendix M: Sensitivity analyses of the primary endpoint

Appendix N: Exploratory analyses

Appendix O: Additional adverse event data

Appendix P: Phase 1b study summary

Appendix Q: Targeted literature review

Appendix R: Summary of base-case analysis inputs

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

Clarification questions

January 2019

File name	Version	Contains confidential information	Date
To PM for company	Final for company	Yes	28.01.2019

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Decision problem

A1. Company submission (CS), document A, section A5, table 2 (page 10) and document B, section B.1.1, table 1 (page 11). Table 2 in document A contains a row for "Perspectives for outcomes." The NICE final scope refers to "All direct health effects, whether for patients or, when relevant, carers" while the company refers to "All direct health effects for patients". Please provide the rationale for not including health effects for carers in their decision problem. This row and associated information is missing from table 2 in document B.

There is evidence to suggest that HAE and the currently available treatment options in UK clinical practice can have a detrimental impact on not only the quality of life of patients, but also carers as highlighted in document B, section B.1.3 (pages 22-23). Caregivers are frequently required to assist patients with their prophylactic therapy or the treatment of acute attacks, and in one study reported caregivers missing days of work/leisure time during an attack, and in another noted the emotional impact that the unpredictability of attacks can have on their daily lives.[1-3] Additionally, given that robust evidence exists to demonstrate that lanadelumab reduces the number of attacks patients experience, results in a greater proportion of patients remaining

attack free, and provides a preferential method for treatment administration compared to C1-INH, it is likely that lanadelumab will result in improvements in the quality of life of caregivers.

However, as no utility data exists which seeks to quantify the impact of HAE on caregivers, or how treatment with lanadelumab may lead to improvements in their quality of life, it was not possible to formally capture this as part of the analysis. This will lead to the economic model predicting conservative estimates of the incremental QALY gains for lanadelumab.

A2. The submission indicates that lanadelumab would be self-administered by patients at home. Please clarify that it is not necessary for lanadelumab to be administered in a clinical setting.

There is no requirement for lanadelumab to be administered in a clinical setting and, in accordance with the SPC, it should be initiated by a physician experienced in the management of patients with HAE and can be self-administered after training in subcutaneous injection by a healthcare professional.[4]

Identification and selection of relevant studies

A3. CS, document B, section B.2.1 (page 34). The company state "Non-RCT evidence identified in the SLR were not used for comparative effectiveness". Please clarify why the non-RCT evidence was not used for the studies presented in table 9 on pages 16 to 19 in appendix D and why non-RCT data from these studies are not presented in the submission.

Given we have higher quality RCT evidence for the only relevant comparator, C1-INH intravenous (C1-INH IV; as described in section B1.3 [page 25]),[5] that was used to inform the NMA (Section B.2.9), the non-RCT evidence was considered not to be required.

A4. CS, document B, last paragraph section B.2.2 (page 37). The results of the DX-2930-02 study were not included because the pivotal phase III Help-03 study superseded it. Please expand further on this, explaining the decision to exclude.

The DX-2930-02 study was a Phase Ib, 120-day dose finding study, which included just five patients on the approved 300mg dose of lanadelumab every two weeks (q2w) and no patients treated every four weeks. All other patients (n=19) receiving lanadelumab in study DX-2930-02 received non-approved doses of lanadelumab and were therefore, not relevant to the decision problem. Therefore, longer-term data from the Phase III, 180-day, HELP-03 RCT, which included greater numbers of patients on the approved 300mg q2w dose (n=27) and 300mg q4w dose (n=29) and provides higher quality data due to the more robust trial design (i.e., randomised, double-blind, placebo-controlled parallel-group), supersedes data from the multiple ascending dose study, DX-2930-02.

Adverse events (AE)

A5. CS, document B, tables 24 to 32. Some of the AE tables report n (%) m, where 'm' indicates the number of adverse events. For completeness, please provide 'm' in all other similar tables (e.g. Tables 31 and 32 of document B).

Question A5 should refer to Table 30 and Table 32 of the original submission; Table 31 already includes these 'm' numbers.

The updated versions of Table 30 and Table 32, now including the number of adverse events, in addition to numbers of patients, are presented in Table 1 and Table 2, respectively. Please note, in Table 30 of the original submission, data for 150mg q4w and 300mg q2w were presented the wrong way around, this has been corrected below (Table 1). This error does not impact the observed low levels of anti-drug antibody (ADA) developed against lanadelumab.

Table 1: Summary of immunogenicity responses of patients in the HELP-03 trial – Safety population

Event, n (%), m	Placebo (n=41)	Lanadelumab			
		300mg q2w (n=28)	300mg q4w (n=29)	150mg q4w (n=27)	Total (n=84)
ADA prevalence[a]	3 (7.3) 3	4 (14.8) 6	3 (10.3) 5	5 (17.9) 10	12 (14.3) 21
ADA incidence[b]	2 (4.9) 2	2 (7.4) 4	3 (10.3) 4	5 (17.9) 10	10 (11.9) 18
Pre-existing ADA[c]	1 (2.4) 1	2 (7.4) 2	1 (3.4) 1	0 (0.0) 0	3 (3.6) 3
Treatment-induced[d]	2 (4.9) 2	2 (7.4) 4	2 (6.9) 4	5 (17.9) 10	9 (10.7) 18
Treatment-boosted[e]	0 (0.0) 0	0 (0.0) 0	1 (3.4)[f] 1	0 (0.0) 0	1 (1.2) 1
Non-neutralising ADA	3 (7.3) 3	4 (14.8) 6	3 (10.3) 5	3 (10.7) 6	10 (11.9) 17
Neutralising ADA	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	2 (7.1) 4	2 (2.4) 4

Key: ADA, antidrug antibody; m, Number of events; n, Number of patients experiencing the event, q2w, every 2 weeks; q4w, every 2 weeks.
Notes: Percentages are based on all patients in the Safety Population.
[a] Prevalence is defined as the proportion of study population having drug-reactive antibodies (including pre-existing antibodies) at any time point.
[b] Incidence is defined as the proportion of study population found to have seroconverted or boosted their pre-existing ADA during the study period.
[c] Pre-existing ADA refers to a signal detected prior to treatment.
[d] Treatment-induced responses are characterised by a negative pre-treatment sample with at least one positive sample at a subsequent timepoint.
[e] Treatment-boosted responses are characterized by a positive pre-treatment sample that are boosted to a higher level following drug administration.
[f] One additional patient with pre-existing ADA had a positive sample post-dose, however since the titre was the same as the pretreatment sample it was not considered to be “treatment-boosted”.
Source: HELP-03 CSR[6]; Banerji et al. 2018.[7]

Table 2: Common TEAEs (≥5% of patients) and related TEAEs in long term extension study HELP-04

Event, n (%), m	Rollover Patients	Non-rollover Patients	Total
	n=109	n=103	N=212
Common TEAEs			
Injection site pain	34 (31.2) 275	42 (40.8) 319	76 (35.8) 594
Viral upper respiratory tract infection	26 (23.9) 33	18 (17.5) 20	44 (20.8) 53
Headache	17 (15.6) 34	16 (15.5) 25	33 (15.6) 59
Injection site erythema	12 (11.0) 22	14 (13.6) 48	26 (12.3) 70

Event, n (%), m	Rollover Patients	Non-rollover Patients	Total
	n=109	n=103	N=212
Upper respiratory tract infection	13 (11.9) 18	13 (12.6) 18	26 (12.3) 36
Injection site bruising	4 (3.7) 9	12 (11.7) 33	16 (7.5) 42
Arthralgia	4 (3.7) 9	8 (7.8) 8	12 (5.7) 17
Back pain	10 (9.2) 12	2 (1.9) 2	12 (5.7) 14
Urinary tract infection	5 (4.6) 5	6 (5.8) 8	11 (5.2) 13
Nausea	6 (5.5) 7	5 (4.9) 8	11 (5.2) 15
Injection site swelling	3 (2.8) 14	7 (6.8) 12	10 (4.7) 26
Abdominal pain	3 (2.8) 4	6 (5.8) 6	9 (4.2) 10
Pain in extremity	6 (5.5) 7	2 (1.9) 2	8 (3.8) 9
Common treatment-related TEAE			
Injection site pain	31 (28.4) 237	36 (35.0) 289	67 (31.6) 526
Injection site erythema	11 (10.1) 21	14 (13.6) 48	25 (11.8) 69
Injection site bruising	2 (1.8) 2	10 (9.7) 31	12 (5.7) 33

Key: HAE, hereditary angioedema; TEAE, treatment emergent adverse event.
Notes: Data are from an interim analysis. Excludes HAE attack-reported events
Source: Lanadelumab AMPC dossier[4]; Riedl et al. 2018[5]

A6. PRIORITY QUESTION. CS, document B (page 104 onwards). Multiple events of the same AE occurring in the same patient (i.e. 'm') are not analysed. This may affect the economic model so please justify this decision.

In the clinical interpretation of the safety data, the focus was on the number and percentage of patients with an AE, rather than the total number of events. There are mainly two reasons for this approach:

1. Analyses on number of events are more heavily influenced by outliers, i.e., patients with large number of the AEs. Therefore, to accurately identify safety signals and provide an interpretation for the overall safety population, the number and percentage of patients with an AE are preferred.

2. For a study that is not randomised 1:1 (treated vs. placebo) ratio, such as the HELP-03 study (which was randomised in a 2:1 ratio, lanadelumab: placebo), the number of events cannot support a fair comparison between the treatment groups. Whereas, the number and percentage of patients with an AE provides a fair comparison between treatment groups.

The adverse event incidence rates utilised in the economic model were calculated from the reported “m” values in Table 26 in document B. Utilising the number of events rather than the number of patients was considered a more appropriate approach to estimate the incidence of each event.

A7. CS, document B, tables 24 to 32 (pages 107 to121). Lanadelumab 150mg q4w has been included in the overall totals in all the adverse events tables and subsequently compared with control groups. However, the company initially stated they would disregard this dose in HELP-03 because it is not expected to be included in the marketing authorisation and will not be available (see document B, section B.2.6, page 63). Therefore, the rationale for including it here it is unclear. Please provide additional totals for document B tables 24 to 32, without this arm.

Question A7 should only refer to Table 24 to Table 30 of the original submission; as Table 31 and Table 32 relate to HELP-04 only.

The updated versions of Table 24 to Table 30, now including the lanadelumab total for the lanadelumab 300mg q2w and 300mg q4w arms only, are presented in Table 3 to Table 9. As mentioned in the response to question A5, data for 150mg q4w and 300mg q2w were presented the wrong way around in Table 30 of the original submission, this has been corrected below (Table 9). This error does not impact the observed low levels of ADA developed against lanadelumab.

Table 3: Summary of TEAEs during the treatment period by treatment group- safety population

		Lanadelumab		
Event, n (%) m	**Placebo (n=41)**	**300mg q2w (n=27)**	**300mg q4w (n=29)**	**Total (N=56)**
Any TEAE	31 (75.6) 231	26 (96.3) 235	25 (86.2) 182	51 (91.1) 417
Any treatment-related TEAE	14 (34.1) 85	19 (70.4) 131	14 (48.3) 121	33 (58.9) 252
Any serious TEAE	0 (0.0) 0	1 (3.7) 1	3 (10.3) 3	4 (7.1) 4
Any related serious TEAE	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Any severe TEAE	4 (9.8) 7	2 (7.4) 2	4 (13.8) 6	6 (10.7) 8

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (N=56)
Any related severe TEAE	1 (2.4) 4	0 (0.0) 0	1 (3.4) 2	1 (1.8) 2
Any investigator-reported AESI	0 (0.0) 0	3 (11.1) 4	1 (3.4) 2	4 (7.1) 6
Deaths due to TEAE	0 (0.0) -	0 (0.0) -	0 (0.0) -	0 (0.0) -
Hospitalisation due to TEAE	0 (0.0) 0	1 (3.7) 1	3 (10.3) 3	4 (7.1) 4
Discontinuation due to TEAE	1 (2.4) -	0 (0.0) -	1 (3.4) -	1 (1.8) -

Key: AESI, adverse event of special interest; EDC, electronic data capture; HAE, hereditary angioedema; n, number of patients experiencing the event, NE, non-estimated; m, number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.
Notes: Percentages are based on all patients in the safety population. Patients were counted once per category per treatment. TEAEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. Related TEAEs are TEAEs classified as related to study drug by the investigator; severe TEAEs are TEAEs classified as severe (Grade 3) or life threatening (Grade 4) by the investigator; Non-HAE attack reported AEs include the subset of AEs identified in EDC as not a reported HAE attack. 95% CI for relative risk is calculated by exact method.
Source: HELP-03 CSR[6];

Table 4: Most common TEAEs (≥5% in any treatment arm) during the treatment period by treatment group and preferred term

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (N=56)
Any TEAE				
Injection site pain				
Viral upper respiratory tract infection				
Headache				
Injection site erythema				
Procedural pain				
Back pain				
Migraine				
Injection site haematoma				
Diarrhoea				
Upper respiratory tract infection				
Rash				
Abdominal pain upper				
Oropharyngeal pain				
Rhinitis				
Urinary tract infection				
Injection site bruising				
Injection site haemorrhage				
Sinusitis				
Neck pain				
Pain in extremity				
Dizziness				
Abdominal discomfort				
Vomiting				
Fatigue				
Arthralgia				
Toothache				
Myalgia				
Injection site discomfort				

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (N=56)
Injection site pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis contact	[redacted]	[redacted]	[redacted]	[redacted]
Injection site paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]
Paraesthesia oral	[redacted]	[redacted]	[redacted]	[redacted]
Hordeolum	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]

Key: Adverse events, AEs; n, Number of patients experiencing the event, NE, non-estimated; m, Number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.
Notes: Percentages are based on all patients in the Safety Population; patients were counted once per system organ class and once per preferred term. TEAEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. Non-HAE-attack-reported AEs include the subset of AEs identified in electronic data capture as not a reported HAE attack.
Source: HELP-03 CSR[6]; Banerji et al. 2018.[7]

Table 5: Grade 3 or higher (severe) TEAEs (>2% in any treatment arm) during the treatment period by treatment group and preferred term – Safety population

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (N=56)
Any severe TEAE	4 (9.8) 7	2 (7.4) 2	4 (13.8) 6	6 (10.7) 8
Alanine aminotransferase increased	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	1 (1.8) 1
Aspartate aminotransferase increased	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	1 (1.8) 1
Bipolar II disorder	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	1 (1.8) 1
Catheter site infection	0 (0.0) 0	1 (3.7) 1	0 (0.0) 0	1 (1.8) 1
Cervical radiculopathy	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	1 (1.8) 1
Fibula fracture	0 (0.0) 0	1 (3.7) 1	0 (0.0) 0	1 (1.8) 1
Musculoskeletal pain	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	1 (1.8) 1
Pyelonephritis	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	1 (1.8) 1
Retinal detachment	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Upper limb fracture	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Cellulitis	1 (2.4) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Injection site pain	1 (2.4) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Nephrolithiasis	1 (2.4) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Tonsillitis	1 (2.4) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0

Key: AEs, adverse events; EDC, electronic data capture; n, Number of patients experiencing the event, NE, non-estimated; m, Number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.
Notes: Percentages are based on all patients in the Safety Population. Adverse events were classified into preferred term using Version 20.0 of MedDRA. Patients were counted once per preferred term. TEAEs are defined as AEs with onset at the time of or following the start of treatment with study; medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. Severe AEs are AEs classified as severe (Grade 3) or life threatening (Grade 4) by the investigator. Non-HAE-attack-reported AEs include the subset of AEs identified in EDC as not a reported HAE attack.
Source: HELP-03 CSR.[6]

Table 6: Treatment related TEAEs (≥5% of safety population) during the treatment period by treatment group and preferred term – Safety population

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (n=56)
Any related TEAE				
Injection site pain				
Injection site erythema				
Headache				
Injection site bruising				
Injection site discomfort				
Injection site haemorrhage				
Injection site pruritus				
Injection site swelling				
Dysgeusia				
Injection site haematoma				
Injection site induration				
Injection site paraesthesia				
Injection site reaction				
Injection site warmth				
Alanine aminotransferase increased				
Aspartate aminotransferase increased				
Dizziness				
Hypersensitivity				
Injection site oedema				
Injection site rash				
Malaise				
Myalgia				
Paraesthesia				
Paraesthesia oral				
Rash maculo-papular				
Somnolence				

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (n=56)
Prothrombin time prolonged	[redacted]	[redacted]	[redacted]	[redacted]
Tension headache	[redacted]	[redacted]	[redacted]	[redacted]

Key: AEs, adverse events; n, Number of patients experiencing the event, NE, non-estimated; m, Number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.
Notes: Percentages are based on all patients in the Safety Population; patients were counted once per system organ class and once per preferred term. TEAEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. Related TEAEs are TEAEs classified as related to study drug by the investigator. Non-HAE-attack-reported AEs include the subset of AEs identified in electronic data capture as not a reported HAE attack.
Source: HELP-03 CSR.[6]; Banerji et al. 2018.[7]

Table 7: Grade 3 or higher (severe) treatment-related TEAEs during the treatment period by treatment group and preferred term – Safety population

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (n=56)
Any related severe TEAE	1 (2.4) 4	0 (0.0) 0	1 (3.4) 2	1 (1.8) 2
Injection site pain	1 (2.4) 4	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
ALT increased	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	1 (1.8) 1
AST increased	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	1 (1.8) 1

Key: AEs, adverse events; ALT, alanine transaminase; AST, aspartate transaminase; EDC, electronic data capture; n, Number of patients experiencing the event, NE, non-estimated; m, Number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.
Notes: Percentages are based on all patients in the Safety Population; patients were counted once per preferred term. Adverse events were classified into preferred term using Version 20.0 of MedDRA; TEAEs are defined as AEs with onset at the time of or following the start of treatment with study. Medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment; Severe AEs are AEs classified as severe (Grade 3) or life threatening (Grade 4) by the investigator. Non-HAE-attack-reported AEs include the subset of AEs identified in EDC as not a reported HAE attack.
Source: HELP-03 CSR.[6]

Table 8: Serious treatment emergent adverse events during the treatment period by treatment group, and preferred term – Safety population

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (n=84)
Any serious TEAE	0 (0.0) 0	1 (3.7) 1	3 (10.3) 3	4 (7.1) 4
Catheter site infection	0 (0.0) 0	1 (3.7) 1	0 (0.0) 0	1 (1.8) 1
Pyelonephritis	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	1 (1.8) 1
Meniscus injury	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	1 (1.8) 1
Bipolar II disorder	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	1 (1.8) 1

Key: AEs, adverse events; EDC, electronic data capture; n, Number of patients experiencing the event, NE, non-estimated; m, Number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.
Notes: Percentages are based on all patients in the Safety Population; patients were counted once per system organ class and once per preferred term. AEs were classified into system organ class and preferred term using Version 20.0 of MedDRA; TEAEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. Non-HAE-attack-reported AEs include the subset of AEs identified in EDC as not a reported HAE attack.
Source: HELP-03 CSR.[6]; Banerji et al. 2018.[7]

Table 9: Summary of immunogenicity responses of patients in the HELP-03 trial – Safety population

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=28)	300mg q4w (n=29)	Total (n=56)
ADA prevalence[a]	3 (7.3) 3	4 (14.8) 6	3 (10.3) 5	7 (12.5) 11
ADA incidence[b]	2 (4.9) 2	2 (7.4) 4	3 (10.3) 4	5 (8.9) 8
Pre-existing ADA[c]	1 (2.4) 1	2 (7.4) 2	1 (3.4) 1	3 (5.4) 3
Treatment-induced[d]	2 (4.9) 2	2 (7.4) 4	2 (6.9) 4	4 (7.1) 8
Treatment-boosted[e]	0 (0.0) 0	0 (0.0) 0	1 (3.4)[f] 1	1 (1.8) 1
Non-neutralising ADA	3 (7.3) 3	4 (14.8) 6	3 (10.3) 5	7 (12.5) 11

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=28)	300mg q4w (n=29)	Total (n=56)
Neutralising ADA	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0

Key: ADA, antidrug antibody; m, Number of events; n, Number of patients experiencing the event, q2w, every 2 weeks; q4w, every 2 weeks.
Notes: Percentages are based on all patients in the Safety Population.
[a] Prevalence is defined as the proportion of study population having drug-reactive antibodies (including pre-existing antibodies) at any time point.
[b] Incidence is defined as the proportion of study population found to have seroconverted or boosted their pre-existing ADA during the study period.
[c] Pre-existing ADA refers to a signal detected prior to treatment.
[d] Treatment-induced responses are characterised by a negative pre-treatment sample with at least one positive sample at a subsequent timepoint.
[e] Treatment-boosted responses are characterized by a positive pre-treatment sample that are boosted to a higher level following drug administration.
[f] One additional patient with pre-existing ADA had a positive sample post-dose, however since the titre was the same as the pretreatment sample it was not considered to be "treatment-boosted".
Source: HELP-03 CSR[6]; Banerji et al. 2018.[7]

Help-03 study

A8. CS, document A, tables 4 and 5 (pages 17 and 19) specifies a Poisson model. The various documentation supplied (e.g. document B, page 132) all infer that the only adjusters were 'baseline' attack rate and offset time. Please explain the decision for not including other covariates, specifically age and sex as possible adjusters – there are slight baseline differences in HELP-03 for sex (document B, table 8, page 51) and for age in HELP-04 (see A9 below). If possible, please incorporate these into the model(s). Age could be included as a continuous variable thus avoiding the small counts issue.

The covariates utilised in the Poisson regression analysis were selected with the aim of choosing variables which helped address the decision problem of this appraisal. This was achieved by generating a regression that provided a good visual fit to the clinical trial data and a feasible prediction of the number of attacks experienced in each model cycle. A covariate for the number of attacks experienced in the previous cycle was required to allow for the model to predict the future attack rate, and the inclusion of a baseline attack risk covariate allows for the potential to explore higher or lower risk groups.

Additional covariates such as age and sex were not considered for inclusion in the regression for a number of reasons. Firstly, given the limited sample size within the HELP-03 trial, a simple model which provided a good fit to the observed trial data was considered appropriate to minimise any potential risks of overfitting the regression. As Figure 19 of document B demonstrates, the regression including baseline attack risk and the number of attacks in the previous cycle as covariates provides a good fit to the observed data, and therefore the addition of more covariates was judged to be of limited merit. Secondly, subgroup analysis results presented from the HELP-03 trial did not indicate other factors such as age and sex being key drivers of the treatment effect.[6] Taking these results together, there was judged to be little merit in adding variables such as age and sex as covariates in the model as it was unclear how their addition would help in further addressing the decision problem.

Help-04 study

A9. CS, document B, table 9, page 55. The <18 years category in the rollover group is smaller than that in the non-rollover group. Would this potentially affect the results (see A8 above)? Please provide additional comments on this.

The percentage of patients who were under 18 in the rollover group was 7.3% while the percentage in the non-rollover group was 12.6%, with a mean age of 41.9 and 39.5 years in each group respectively. These differences are minimal and therefore are unlikely to result in any meaningful variations in the results. Given the small proportion of patients in the HELP-03 and HELP-04 studies who were less than 18 years of age, it would not be feasible to present a robust sub-group analysis from the Poisson regression in this age group. In addition, subgroup analysis results presented from the HELP-03 trial did not identify age as being a key driver of the treatment effect, indicating that any differences in the efficacy results for younger patients would be minimal.

A10. CS, document B, table 9 (page 55). Please note that 35/103 (non-rollover male patients) is not 44%, please provide corrected values.

This is a typographical error. The correct percentage of patients who were male in the non-rollover group was 34% (35/103).

Efficacy endpoints

A11. PRIORITY QUESTION. CS, document B, figure 5 and 6 (pages 71 to 72) and figures 44/45 in Appendix N. Please provide data for time to first investigator-confirmed attack/day so that these curves may be reproduced for time to first attack based on 0 to 182 & 70 to 182 days.

To be added

A12. CS, document B, table 11, page 60. Please provide a justification for using a generalised estimating equations (GEE) method (rather than for example a multilevel model) in the sensitivity analysis for the number of HAE attacks day 14 to 182.

The sensitivity analysis using GEE method to analyse number of HAE attacks Day 14-182 was the primary endpoint defined in the original version of the protocol for study DX2930-03.[10] After Shire acquired Dyax and the then ongoing study DX2930-03, Shire team considered the GEE method not the preferred method to analyse count data collected in the study and changed the primary endpoint analysis method to a generalized linear model for count data assuming a Poisson distribution in protocol amendment 1.0.[11] However, the GEE model approach was kept as a sensitivity analysis for consistency and transparency purposes.

The GEE model was not the preferred method to analyse the study data because it requires artificially dividing the total number of attacks into the 26 weeks of the treatment period, such that the repeated measurement scheme for the GEE method can be applied. However, for this study, subjects did not follow a weekly reporting schedule. Attacks occurred randomly and were reported within 72 hours after the occurrence. Therefore, it was deemed unnecessary to subset attack data and perform analysis using the GEE method. Instead, a generalized linear model on count data, assuming a Poisson distribution, was more appropriate and used as the model analysing the primary and secondary endpoints.

Network meta-analysis (NMA)

A13. PRIORITY QUESTION. CS, document B (pages 30 and 92) and Appendix D.1 (from page 26). HELP-03 (lanadelumab 2 doses versus placebo) is

compared indirectly with the CHANGE study, which assessed C1-inh IV 1000IU versus placebo twice weekly. However, CHANGE is a crossover trial thus will have smaller standard errors (SEs) between the treatment and placebo groups compared with HELP-03. Please comment on how the non-independent groups in the CHANGE trial have been accounted for - Document B (page 30) briefly suggests the use of '…the normalised attack rate'. Please expand on this so that it may be replicated by the ERG in the NMA and provide a justification for its use in the NMA.

The normalised attack rate in the CHANGE study refers to the fact that the number of attacks of angioedema during each treatment period was normalized for the number of days the subject participated in that period.[12] The analysis of the number of attacks of angioedema during each treatment period in the CHANGE study was based on a Poisson assumption using generalised estimating equations (GEE) including terms for both treatment period and treatment sequence. The effects for both treatment and sequence were not statistically significant.[12] Since each treatment period lasted 12 weeks, the mean number of attacks estimated from the GEE represents the attack rate per 12 weeks.

To calculate the log rate ratio required for the NMA we took the difference of log attack rate per 12 weeks for C1-INH minus log attack rate per 12 weeks for placebo. To calculate the standard error of the log rate ratio we calculated the standard error of the difference in log rates (see above) to be the square root of the sum of the variance for the log rate in each treatment arm.

The variance in each arm was derived based on the fact that the mean number of attacks in each treatment period was derived from the Poisson GEE. Since the outcome follows a Poisson distribution, the mean is equal to the variance. The original analysis of the trial used a Poisson GEE that included terms for treatment sequence and treatment period to account for the crossover design of the trial.

As noted elsewhere, while we recognise the limitations of the CHANGE study as a source of evidence for C1-INH, this study represents the only RCT evidence available. Therefore, despite the limitations, this NMA represents the best available estimate of the relative treatment effects for lanadelumab compared to C1-INH.

A14. CS, document B (page 104). The submission indicates that CHANGE and HELP-03 have different endpoints. Please define the endpoints used and clarify whether CHANGE is a good comparator study in this case.

Both CHANGE and HELP-03 evaluated the frequency of HAE attacks during the study period as a main endpoint; the difference being the time at which the endpoint was assessed. The outcome was reported for each interval of 12 weeks in the CHANGE study and between Day 0 to 182, Day 14 to 182, and 70 to 182 in the HELP-03 study. Both studies assessed the outcome from day 0 to the end of the trial period (in addition to the post-hoc time points in HELP-03) so remain comparable in this respect.

There is difference regarding the analysis of time to first attack endpoints. NMAs were conducted on time to first attack after day 0 and time to first attack after day 70. These endpoints were reported for the HELP-03 study but were not reported directly for the CHANGE study. The CHANGE study reported the proportion of patients who were attack free over the entire follow up period in that study.

The binary data from the CHANGE study were combined with the hazard ratios for time to first attack after day 0 and time to first attack after day 70 in separate NMAs using the method of Woods et al. 2010[13] as described in document B p97 and appendix D1. The proportion of patients attack free in the CHANGE study is measured over the full study period which includes the period from day 0 to day 70. Attacks which occurred in the period from day 0 to day 70 in the HELP-03 study would not be included in the measurement of time to first attack after day 70. The follow-up period in the CHANGE study was also shorter than the follow up period in the HELP-03 study. While we recognise that there are limitations in the NMA, in practice, the CHANGE study was the only appropriate source of evidence available for C1-INH to include in this comparative analysis. Therefore, despite the limitations, we believe the comparison with the CHANGE study represents the best available estimate of the relative treatment effects.

A15. PRIORITY QUESTION. The company used lanadelumab 300q4w and lanadelumab 150q4w with placebo to find SE for placebo to link to the CHANGE study - as per Woods et al. (2010). However, the 150mg arm should not be the focus here (see document B, section B.2.6, page 63). Was this arm

used because of the decision to investigate attack rate over 4 weeks? This would not affect the hazard ratios (HRs). Is it possible to use the 300 q4w/300 q2w/placebo network triangle instead? To allow us to replicate the original NMA and investigate this other network 'triangle', please provide the original HRs for attack rate in the table below.

The estimation procedure described by the ERG in the question refers to the approach used for the time to first attack endpoints. The analysis of the attack rate was based on rate ratios as documented in appendix D.1 of the CS (p27-30). The input data were taken from the CSR of the HELP-03 trial. As stated on page 30 of appendix D.1 "The SE of the log rate of placebo in the HELP-03 trial was also required as a comparison with the other treatments. This value was taken from the CSR of the HELP-03 trial."

This value was based on the original analysis of the trial data using a Poisson GEE as reported in the HELP-03 CSR (Table 14.2.2.1). Therefore, the stated value of the standard error for the log rate (SE = 0.13) is not based on the other arms of the trial since this was the reference arm in the GEE.

A16. PRIORITY QUESTION. CS, document B, section B.2.9. Random effects models were used despite the small sample sizes. The three priors considered were U(0,3), U(0,5) and half normal (0,2). Please justify the priors particularly the parameter choice(s) for each distribution (see key point 4 in Spiegelhalter, Abrams and Myles 'Bayesian Approaches to Clinical Trials and Health-Care evaluation', Wiley, Statistics in Practice series, 2007, page 176, section 5.9).

The use of three alternative priors on the random effect parameter, the between trial standard deviation, was done to assess the sensitivity of the results to alternative prior distributions. In the absence of data to support a reasonable choice of an informative prior, all three choices were chosen to be vague/uninformative in line with the guidance documented in NICE TSD 2.

Uniform distributions on the range 0-3 or 0-5 indicate that values of the between trial standard deviation from 0 to 3 or 0 to 5 are equally likely. These distributions were based on the examples presented in NICE TSD2. The half normal (0,2) distribution represents the positive part of a normal distribution with a mean of 0 and variance of 2. This distribution implies that large values of the between trials standard deviation

are possible but that smaller values, nearer to zero are more likely. Half normal distributions are cited as an option by Higgins et al 2009[14] based on earlier work by Gelman 2006[15] in situations where there are small number of studies available for the meta-analysis such as the evidence base available here. In this situation, uniform distributions were anticipated to lead to implausibly large estimates of the between trial standard deviation. The half-normal distribution represents a compromise where some variation between studies is considered but the range of this variation is constrained.

A17. CS, appendix D, (page 29). Please clarify that *mean rate*^{2} == *mean4*^{2} and that *variance rate* == V(X)

We confirm that *mean rate*^{2} == *mean4*^{2} and that *variance rate* == V(X)

A18. CS, document B (page 97). Continuity correction of 1 was used rather than 0.5. It is more conservative, but apart from maintaining whole numbers, is there any other rationale?

A continuity correction of 1 was used to maintain whole numbers of patients.

Section B: Clarification on cost-effectiveness data

Comparator

B1. PRIORITY QUESTION. CS, document B (page 183). The submission refers to the 2016 NHS England Commissioning Policy for C1-esterase inhibitor use as prophylaxis (document B, reference 18). Important features of this policy are as follows:

- The criteria for starting C1-esterase inhibitor prophylaxis – on oral prophylaxis, NHSE specify the patient must have had 2 or more clinically significant attacks per week over 56 days (8 weeks).
- Being contraindicated to oral prophylaxis as a criterion for starting C1-esterase inhibitor prophylaxis.
- Consider reducing the dosing frequency after 6 months if attacks have reduced sufficiently.
- Consider discontinuing C1 if less than 2 clinically significant attacks per week on a once weekly prophylaxis dose

- Stop treatment with C1-esterase inhibitor after two months if the attack frequency has not adequately reduced.

Please clarify how these informed your assumptions in the modelling of C1-esterase inhibitor prophylaxis and provide a sensitivity analysis where C1-esterase inhibitor prophylaxis reflects the NHSE commissioning policy.

We are aware there are criteria within the Commissioning Policy that determine which patients should be considered for C1-INH prophylaxis and that these criteria do not necessarily overlap with the population covered by the clinical evidence.[16] The average number of attacks at baseline in the HELP-03 trial was 3.7 and patients were not required any contraindication to oral therapy, therefore our submission focused on the entirety of the trial population, which aligns with the NICE scope.[17]

We are also aware that clinical experts are not supportive of the current criteria and when this issue was raised by the experts participating at the scoping workshop, it was concluded that the Commissioning Policy may be reviewed following this technology appraisal.

We appreciate that, for the clarity of this submission, it may be useful to specify that lanadelumab is expected to be used in patients who would otherwise be considered for treatment with C1-INH prophylaxis. This would avoid any confusion should the Commissioning Policy be revised and reduces uncertainty over the position of lanadelumab within the treatment pathway.

While a sensitivity analysis could potentially be conducted that takes into account an attack rate at baseline equal to 2 per week, we believe this would not be representative of the population currently considered for C1-INH prophylaxis as this includes patients that are contraindicated for oral prophylaxis who do not have to meet a specific attack threshold. Furthermore, as only few patients in the clinical trials had more than 2 attacks per week at baseline, a sub-group analysis on those patients may not lead to meaningful results. However, we provide the results of the analyses where the baseline rate is increased to show the trend of the results. This analysis is conducted by excluding patients from the Poisson regression analysis who did not meet the specified baseline attack risk. As reported in Table 10 below,

when the baseline number of attacks is increased, lanadelumab provides a more cost-effective option for HAE patients.

Table 10: Results by baseline attack risk

Baseline attack risk (per 28 day cycle)	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB (£)
≥ 1 attack	[redacted]	[redacted]	Dominant	£408,206
≥ 2 attack	[redacted]	[redacted]	Dominant	£447,432
≥ 3 attack	[redacted]	[redacted]	Dominant	£489,232
≥ 4 attack	[redacted]	[redacted]	Dominant	£495,161
≥ 5 attack	[redacted]	[redacted]	Dominant	£543,225
≥ 6 attack	[redacted]	[redacted]	Dominant	£640,106
≥ 7 attack	[redacted]	[redacted]	Dominant	£766,649
≥ 8 attack	[redacted]	[redacted]	Dominant	£856,445

Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality adjusted life years,

Finally, while the Commissioning Policy lists some options for considering treatment discontinuation, clinical experts, including those interviewed for the purpose of this submission, indicated that if patients are still experiencing breakthrough attacks they are more likely to receive an increase in administration frequency,, while if they are successfully controlled, i.e. they are experiencing no attacks or few of them, treatment is rarely discontinued; this is still in line with the Commissioning Policy which provides some flexibility to clinicians in their consideration of treatment discontinuation. Therefore, sensitivity analyses where a discontinuation, for either lack of effectiveness or sustained effectiveness is implemented, would not be representative of current practice as this rarely happens.

B2. CS, document B, table 55. Please provide cost-effectiveness results using the placebo arm of the RCTs as the comparator rather than C1-esterase inhibitor or lanadelumab prophylaxis.

We believe these results would not be meaningful for this submission and, as we have suggested above, for the clarity of this submission, it may be useful to specify that lanadelumab is expected to be used in patients who would otherwise be

considered for treatment with C1-INH prophylaxis. As such, comparing lanadelumab to placebo/no treatment is not relevant for this decision problem.

B3. CS, document B, page 143. The company acknowledge that the posology of Cinryze in the CHANGE RCT does not fully match clinical practice in England and Wales, and that the added efficacy from increasing the dose and/or frequency is not easily quantified (document B, page 143, first paragraph). A threshold analysis is presented, which gives the ICER for each level of Cinryze efficacy (document B, table 60, page 177). The Bernstein study (reference 107) is provided to support this and is summarised in Table 59. Please clarify the link between Tables 59 and 60. Is it correct to state that the base case rate ratio is 0.492 at a dose of 1,000IU and if this were increased to 1500IU, the reduction in Table 59 is 40%, so 60% of 0.492 is 0.295? Therefore, if the Bernstein data were interpreted in this way the base case would be shown by the row where the rate ratio is 0.3?

No appropriate data was identified in order to model the efficacy of higher doses of C1-INH, resulting in the presentation of a threshold analysis to demonstrate how the results are impacted as the efficacy of Berinert IV at a dose of [redacted] is increased in increments. The Bernstein (2014)[18] study does not provide robust data to inform the efficacy of higher doses of C1-INH. This is firstly because the study does not provide a head-to-head comparison of the different doses of Cinryze (1,000, 1,500, 2,000 and 2,500 units), but instead increases the dose received by one cohort of patients over time. Additionally, patients received a higher dose only if they met the specified response criteria in the study protocol, with only 13 of the 20 patients in the study going on to receive a dose of 2,000 units and 12 of the 20 going on to receive a dose of 2,500 units. This means that the estimates are subject to significant selection bias.

Table 59 of document B presents the average attack rate while patients were receiving each dose, and the percentage reduction presented simply demonstrates the difference between the average attack rate at a 1,000 unit dose and each alternative dose given. Therefore, this data does not allow for the estimation of rate ratios for each dose, but the figures are instead presented in order to provide a sense of the magnitude of benefit patients could accrue if they were to receive a

higher dose of C1-INH. This therefore helps indicate which of the rate ratios presented in the threshold analysis are plausible for a dose of [redacted].

B4. CS, document B. In the submission, lanadelumab is positioned for use after oral prophylaxis, instead of IV C1-esterase inhibitor prophylaxis (e.g. page 130 of document B). However, some patients will previously have tried IV C1-esterase inhibitor prophylaxis and either had inadequate control or are unable to tolerate it. Please clarify: i) what the company would regard as the comparator in this circumstance; ii) what the company estimate the cost-effectiveness of lanadelumab to be in this circumstance.

As we indicated in our response to B1, most patients who receive C1-INH that experience inadequate control [redacted]. As such, this is explored in a scenario analysis by [redacted], which shows increased cost-effectiveness of lanadelumab in this patient population.

Clinical expert advice confirmed that only a negligible number of patients, if any, would not tolerate C1-INH. Due to the rarity of this event (expert estimates indicate less than 5%), the lack of an identifiable group of patients within the trial evidence, and the uncertainty regarding what treatment they would be receiving, estimating the cost-effectiveness of lanadelumab in this circumstance is unfeasible. We are aware that some patients cannot tolerate IV infusion; in these instances, off-label subcutaneous infusion [redacted] may be considered, which would increase the costs under the comparator treatment, therefore not including this analysis is a conservative assumption. Furthermore, since in the UK this is currently a very small population, we have not included this in our submission.

Treatment effectiveness

B5. CS, document B, page 146. Please clarify what assumptions have been made about treatment and effectiveness when lanadelumab is discontinued and when C1-esterase inhibitors are discontinued.

Patients are assumed to discontinue both lanadelumab and C1-INH at an equal rate in the first six months of the model consistent with the discontinuation rate observed in HELP-03. This was due to the similarity between the discontinuation rates in

HELP-03 and CHANGE.[6, 12] No additional treatment discontinuation was assumed in the long-term due to the lack of data available to inform long-term predictions and because of the strong safety profile of lanadelumab and C1-INH reported in the RCTs.

The attack rate data from HELP-03 which informed the Poisson regression analysis adjusts the number of attacks patients experienced in each cycle for treatment discontinuation. The attack rate was calculated as the number of attacks occurring during the period divided by the number of days the patient contributed to the period multiplied by 28 days. This method accounted for patients withdrawing from the trial and aligned with the method applied in the HELP-03 CSR.[6]

Patients who discontinued therapy on either arm were assumed to accrue no prophylactic treatment costs. This was a simplifying assumption given the uncertainty regarding which subsequent treatment patients would typically go on to receive in practice, and because the assumption of equal discontinuation and survival rates between the arms means that any subsequent therapy costs would, in all likelihood be equal between the treatment arms.

The results of a scenario analysis where no treatment discontinuation was assumed are presented in Table 58 of document B. This scenario demonstrated the robustness of the results to changes in this assumption with the net monetary benefit (NMB) increasing from £470,031 in the base-case analysis to £478,533 in this scenario were no discontinuation was assumed.

B6. The model assumes no waning of the treatment effect over time for lanadelumab. Please clarify your rationale for this, given that treatment is predicted to last a lifetime and anti-bodies may develop. Please provide a sensitivity analysis where the increased effectiveness in terms of reduced attacks wanes after 5, 10 and 20 years.

There is no data on the durability or waning of lanadelumab effectiveness beyond those reported to date in the clinical trial programme comprising the HELP-03 study and the open label extension, HELP-04. For this reason, we have provided a scenario analysis accounting for the possibility of a reduction in treatment effect at some point in time, however this is subject to a high degree of uncertainty. The

scenario assumes that at 5, 10 or 20 years lanadelumab loses effectiveness at preventing angioedema attacks and therefore treatment is discontinued for all patients. The model has the functionality to assume that patients who discontinue lanadelumab due to treatment waning go on to receive either subsequent C1-INH or no prophylactic treatment, with their costs and efficacy adjusted accordingly. The results of this scenario analysis are presented below in Table 18.

The assumption that 100% of patients will experience an instant reduction in their treatment effect at one specified time point is a simplifying assumption. However, given there is no data to inform how the treatment effect may change over time and how many patients this could impact, this scenario is implemented simply to highlight the robustness of the results for changes in assumptions around the continuation of the treatment effect. The assumption that 100% of patients experience a reduction in their treatment effect is an extremely conservative scenario given that in HELP-03 the overall incidence of anti-drug antibodies (ADAs) in treated subjects was just 9.6% (12/125); 11.9% (10/84) of lanadelumab-treated subjects and 4.9% (2/41) of placebo-treated subjects had at least 1 treatment-emergent ADA-positive sample. For this reason, we believe assuming that 100% of patients will experience treatment effect waning after only 5 years is extremely unlikely and the 5-year scenario should be considered unrealistic.

While we recognize the development of ADAs could occur in a population treated with lanadelumab, in both HELP-03 and HELP-04 studies, no subject discontinued treatment with lanadelumab due to the presence of ADA or reported an adverse event (AE) indicative of a hypersensitivity reaction due to the presence of ADA, with the majority of patients in the HELP-03 study electing to rollover and participate in the open-label study. In addition, antibody-positive subjects had no apparent difference in efficacy profiles compared to antibody-negative subjects. Therefore, while some patients developed ADAs, this did not have an impact on treatment efficacy and did not result in discontinuation.

Furthermore, there is some evidence showing that ADAs production was transient, as ADA response was transient in 2 of 10 lanadelumab-treated subjects in the HELP-03 study and in 6 of 19 subjects in the HELP-04 study.

Modelling of attacks

B7. CS, document B, table 36, page 137. Two factors identified as being significant are presented in table 36 and are described as co-variates, but this does not show which other factors were tested or the goodness of fit of the equation. Please provide these additional data.

As outlined in the response to question A8, the covariates utilised in the Poisson regression analysis were selected with the aim of choosing covariates which helped meet the decision problem for this appraisal by providing a good fit to the clinical trial data and an accurate prediction of the number of attacks experienced in each model cycle. A covariate for the number of attacks experienced in the previous cycle was required to allow for the model to predict the future attack rate, and the inclusion of a baseline attack risk covariate allows for the potential to explore higher or lower risk groups.

As Figure 19 of document B demonstrates, the regression including baseline attack risk and the number of attacks in the previous cycle as covariates provides a good fit to the observed data, and therefore the addition of more covariates was judged to be of limited merit. As part of the step-wise selection process, models were also fitted, including just the baseline risk, and the number of attacks experienced in the previous cycle covariates. As the Poisson regression analysis utilises data on a patient's attack rate, rather than the absolute number of attacks experienced in each cycle, this prevented the estimation of AIC values for the measure of statistical fit due to the presence of non-integer values.

However, AIC values have been estimated for each of the models utilising the absolute number of attacks patients experienced in each cycle which are presented in Table 11. These estimates demonstrate that, overall the inclusion of both terms leads to a reduction in the total AIC values across all treatment arms and therefore improves the model fit.

Table 11: Measures of statistical fit: AIC values by treatment arm

Model	AIC by treatment			
	Lanadelumab 300mg q4w	**Lanadelumab 300mg q2w**	**Placebo**	**Total AIC**
Full model	325.11	217.94	776.08	1319.13
Baseline risk only	373.22	236.57	811.18	1420.97
No. of attacks in previous cycle only	325.02	216.16	780.96	1322.14
Key: AIC, akaike information criterion; q2w, every two weeks; q4w, every 4 weeks.				

B8. CS, document B, table 36, page 137. In the equation for the Poisson regression, the baseline attack rate is a significant predictor of attacks in future cycles, based on data from the HELP-03. By using the same rates over the lifetime of the patients, this means the rate in the baseline period is assumed to still be playing the same role in predicting attacks many years later. Please clarify the basis for this assumption.

Patients baseline attack risk was considered as a relevant covariate within the Poisson regression, firstly because it was deemed to be a potentially relevant clinical indicator of a patient's future attack risk, but secondly because its inclusion allows for the potential to explore higher or lower risk patient groups.

During the step-wise selection process to determine the final regression model, a patient's baseline attack risk was found to be a statistically significant covariate in univariate analysis presented in Table 36 of document B. Additionally, the statistical fit values produced for each regression model presented in Table 11 demonstrated that the best fitting regression was the model including the baseline attack covariate. Therefore, the full model including both covariates for baseline attack risk and number of attacks experienced in the previous cycle was considered to be the most relevant for the analysis.

B9. The 2016 NHS England Commissioning Policy defines an attack as being clinically significant if it is potentially life-threatening (on the head or neck) or if causes pain/disability such that usual activities cannot continue. Please clarify how this relates to the three levels of severity of attack considered in

the cost-effectiveness model. Please provide a scenario analysis only including attacks defined as clinically significant by NHS England.

The severity of the attacks in the model are consistent with the definition used in the HELP-03 trial as the occurrence data in the model are based on the same trial.

Scenario analyses utilising the definition from the Commissioning Policy cannot be performed because data on occurrence of these specific events in the RCTs and on the associated quality of life are not available; therefore, it would not be possible to estimate how many of these events occurred during the trial period and their impact on quality of life. Furthermore, the definition used in the Commissioning Policy would probably include the majority of attacks experienced by patients as, based on discussion with clinicians and patient groups, most attacks impair usual activities.

Dose switching

B10. CS, document B, section B.3.3. When patients switch from lanadelumab every 2 weeks (q2w) to every 4 weeks (q4w) in the model, estimates based on the q4w arm of the HELP-03 trial are applied. However, the q4w arm of this RCT was in patients previously naïve to lanadelumab. It is unclear whether the RCT experience with q4w reflects the likely experience when switching patients whose disease is controlled with q2w to q4w. Is there any other evidence about the effectiveness of a switching policy as in the model? If so, please provide details.

While there is no evidence yet on the effectiveness of a switching policy, we believe the approach in the economic model is most reflective of the label and conservative as patients switch to the q4w regimen when they are stably attack free and lanadelumab has reached the steady state, while at the point of switching, the effectiveness of the q4w arm is applied, assuming lanadelumab still has to reach its steady state after the switch.

B11. CS, document B, section B3.3 (p141 to 142). The submission explains that, based on the observed time to first attack presented in Figure 5, 44.4% of the lanadelumab cohort are assumed to switch to the lower dose (300mg q4w) at six months. This seems reasonably well justified. However, it is then assumed that 76.9% of the cohort will be on the lower dose from 12 months

onwards in the model. This is based on the proportion of the q2w cohort that remain attack free from day 70 to day 182 (a period of 112 days ~3.7 months). Given the assumed [redacted] assessment schedule, this may overestimate the proportion of the cohort who remain attack free between 6 months and 12 months – and hence may overestimate the proportion of the cohort on the lower does in the long-term. To overcome the mismatch between the observed time period and the [redacted] assessment schedule, it would be useful to extrapolate the observed time to first attack between day 70 and day 182, out to a period of [redacted], and use the projected attack free rate at this time point in a scenario analysis.

A higher percentage of patients were assumed to be attack free in the six months preceding a patient's second assessment compared to the first assessment. This is based on an analysis of the HELP-03 data from Day 70 onwards which indicates that treatment becomes more effective when lanadelumab concentration reaches a steady state, which is anticipated to be after 70 days from initiation of treatment.[6] The analysis, presented in Section B.2.6 of document B and Appendix M, showed that not only did the attack rate fall across patients treated with a dosing regimen of 300mg every 2 weeks, but also that 76.9% of patients were attack-free between Day 70 and Day 182.

Although this figure of 76.9% was only estimated between day 70 and day 182, a period of just under four months as opposed to six months, this data was deemed to be the most appropriate value for inclusion in the model given the absence of data beyond day 182. Although an extrapolation of the data may provide an estimate for the relevant six-month period, it is worth noting that this estimate will be subject to some uncertainty.

However, an analysis has been conducted in order to extrapolate this data beyond the trial period. In accordance with the NICE DSU TSD 14 guidance on survival analyses, a range of standard parametric distributions (exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma) were explored in the extrapolation of the KM data.[19] Survival models, utilising treatment arm as a covariate were utilised in order to make efficient use of the trial data. These curves each generally produced poor visual fits to the KM data from the trial as is

demonstrated in Figure 1, and therefore spline models were fitted in order to address this issue.

Figure 1: Extrapolated day 70 time to first attack analysis (lanadelumab 300mg q2w): standard parametric distributions

Key: q2w, every two weeks.

Proportional hazards spline models were considered as a more flexible alternative. We explored the use of different numbers of internal knots in the model to identify whether increasing this number enhanced the fit of the model. Utilising these models allowed for greater flexibility to capture any changes in hazards as the concentration of lanadelumab continued to reach steady state. Figure 2 presents the extrapolated curves, which provide a better visual fit to the observed trial data when compared to the standard parametric distributions.

Figure 2: Extrapolated day 70 time to first attack analysis (lanadelumab 300mg q2w): spline models

Key: K, knot.

Table 12 summarises the findings of the analysis and their impact on the results of the model. Firstly, an assessment of the AIC/BIC values demonstrate that the spline model with one internal knot provided a curve with the best statistical fit. The addition of further internal knots did not substantially improve the fit of the model. Secondly, estimates of the percentage of patients predicted to be attack free after a six-month period demonstrate that the results from each curve are consistent, with the four best fitting curves producing the most consistent results. Finally, the results from the model demonstrate that lanadelumab remains the dominant treatment option for each predicted value, highlighting the robustness of the results to changes in this assumption.

Table 12: Scenario analysis for the percentage of patients assumed attack free at the second clinical assessment point

	AIC	BIC	% attack free at second assessment	ICER (£/QALY)	NMB (£)
Base-case model	N/A	N/A	76.9%	Dominant	£470,031
Spline model with 1 internal knot	704.98	721.7		Dominant	£346,998
Spline model with 2 internal knots	706.8	726.32		Dominant	£355,200
Gompertz	707.13	721.07		Dominant	£415,349
Spline model with 3 internal knots	708.66	730.96		Dominant	£360,668
Log-normal	718.22	732.16		£75,297	-£33,035
Log-logistic	719.63	733.57		Dominant	£92,731
Generalised-gamma	719.7	736.43		Dominant	£46,252
Weibull	721.22	735.15		Dominant	£204,827
Exponential	728.03	739.18		Dominant	£100,933

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit.

Utility values

B12. CS, document B, section B.3.4. When applying utility values, the company make the reasonable point that the EQ-5D data in the RCT did not capture the utility loss of attacks because so few patients completed this instrument at the time of an attack. Therefore, a literature search is conducted to identify values to use during an attack. However, having identified utility decrements from the literature search, these are also applied to utility values for 'alive, attack-free'. The NICE Methods Guide supports the use of EQ-5D measured in a clinical study of the treatment when possible, and while a case is made for attacks, it is not clear why utility values from the RCT data for the 'no attack' state were not used. Please provide a rationale for the approach set out in the base case. In line with DSU recommendations (TSD 12 The use of health state utility

values in decision models), it may be preferable to calculate an age adjusted utility multiplier for 'attack' relative to 'attack-free', and apply this multiplicatively to an age adjusted attack free utility.

Given that the utility values applied in the model for when patients are experiencing an attack are sourced from Nordenfelt (2014)[20], values from this study were also applied while patients were not experiencing an attack for consistency. This study provides attack-free utility values broken down by age allowing for adjustments to be made over the time horizon of the model. Additionally, this study also included a utility decrement that could be applied based on the number of attacks patients had experienced in previous cycles to capture this additional impact on HRQL for higher-risk patients.

However, two additional scenarios have been incorporated into the model related to the application of utilities. The first allows for the application of HELP-03 utility values for patients who are not actively experiencing an attack. Firstly, a regression was conducted with age included as a covariate to allow for the utility values to be adjusted over time. As the attack-free and attack utilities are taken from different sources when this scenario is utilised, the multiplier approach presented in NICE DSU TSD12[21] is adopted to adjust the attack utility for differences between both populations using the formulae outlined in Figure 3.

Figure 3: Utility adjustment formulae

$$Attack\ utility\ value * \frac{HELP\ 03\ attack\ free\ utility\ value}{Nordenfelt\ attack\ free\ utility\ value}$$

The second adjustment made to the application of utilities involved converting the average attack utility value sourced from Nordenfelt (2014)[20] into a utility decrement. The application of an absolute utility value rather than a utility decrement in the submitted model does not allow for the impact of attacks to be adjusted over time as patients' age. Therefore, the attack-free utility value declines over time as the average age of patients increases, but the attack utility remains constant over time, resulting in an assumption that the HRQL impact of an attack declines over time. Therefore, a more appropriate approach has been adopted which involved estimating the utility decrement of an attack by subtracting the average attack-free

utility value from Nordenfelt (2014)[20] from the average attack utility value and applying this decrement to the attack-free utility value in each cycle.

The impact of these scenarios on incremental QALYs and NMB, both individually and combined is presented in Table 13. Changes made to the application of utility values results in minimal changes to the results.

Table 13: Scenario analysis for changes in the application of utility values

Scenario	Incremental QALYs	NMB (£)
Base-case	[redacted]	£470,031
1. Age-adjusted attack-free utility values from HELP-03	[redacted]	£468,580
2. Average attack utility value applied as a decrement	[redacted]	£470,540
Scenarios 1 & 2	[redacted]	£469,137
Key: NMB, net monetary benefit; QALY, quality-adjusted life year		

B13. CS, document B, page 143. In the cost-effectiveness modelling, attacks are categorised as mild, moderate and severe. The company do not consider where on the body the swelling occurred but this seems likely to affect the disutility and hence potentially the propensity to seek health care. Please clarify any discussions that were had with patients or representative groups on the factors influencing the utility loss from an attack. Please present a sensitivity analysis where the location of the swelling is considered as a factor.

Discussions with clinical experts and patient groups highlighted that the location of attacks does not necessarily correlate with impact on quality of life; other factors seem to be more important such as discomfort and impact on daily activities.

It is not possible to present scenario analyses where the location of the swelling is a factor influencing utilities because these data are not available.

Resource use and costs

B14. CS, document B, page 134 and 135. The submission states that the most common C1-esterase inhibitor used in NHS practice is Cinryze in some cases and Berinert in others. The company estimated the proportion using each

medicine and provide some sensitivity analyses. However, the range of alternative scenarios considered is limited. Please provide a sensitivity analysis showing the results i) where 100% of C1-esterase inhibitor use is Cinryze and 0% Berinert and ii) where 0% is Cinryze and 100% Berinert.

On page 134 and 135, the submission states that Cinryze IV and Berinert IV are the most common C1-INH used in UK clinical practice and it reports data on Hospital Pharmacy Audit data to estimate the actual distribution within HAE patients. The proposed ranges of 100% and 0% do not reflect actual prescription data and current practice; as the data show and clinical experts have confirmed, both drugs are used to treat the HAE population in the UK.

We have considered the distribution of Cinryze and Berinert use for each month in the past 3 years from the Hospital Pharmacy Audit data and the ranges are [redacted] for Berinert and [redacted] for Cinryze.[22] As an alternative, we have reported below the cost-effectiveness results of the scenarios where the broader ranges have been considered, including also a scenario where [redacted] patients are prescribed Cinryze than Berinert. The results of these additional scenarios are reported in Table 14. This analysis demonstrates that the results are robust even as these proportions are varied over large ranges.

Table 14: Scenario analysis for changes in the percentage of patients receiving Cinryze/Berinert IV

Proportions	ICER (£/QALY)	NMB (£)
Base-case ([redacted] Cinryze IV: [redacted] Berinert IV)		
([redacted] Cinryze IV: [redacted] Berinert IV)	Dominant	£568,400
([redacted] Cinryze IV: [redacted] Berinert IV)	Dominant	£408,136
([redacted] Cinryze IV: [redacted] Berinert IV)	Dominant	£247,873
([redacted]Cinryze IV: [redacted] Berinert IV)	Dominant	£87,609
Key: IV, intravenous; QALY, quality-adjusted life year		

B15. CS, document B, figure 24 (page 173). The percentage of attacks as reported in the clinical studies that would require treatment in an NHS setting

is uncertain, and a sensitivity analysis is provided in the submission. Please re-present these data as a table showing the effect on the ICER assuming the proportion treated is 85% as in the base case, and also include 90%, 80%, 70%, 60%, 50%.

The value for the proportion of attacks that were assumed to be treated was taken from the HELP-03 estimating the ratio between all attacks that were treated (686) and the total number of attacks experienced in the trial (807). Given this proportion is estimated from a large sample of events, the figure inputted into the model provides a robust estimate. Additionally, this figure has been varied in one-way sensitivity analysis, with a lower bound of 65% and an upper bound of 97%, demonstrating that the results remain robust for variations in this value (NMB ranging from £401,365 to £512,330).

The majority of patients in UK clinical practice are assumed to administer their acute treatment at home consistent with the administration of prophylactic therapies, with the exception of the more severe attacks. Patients in the HELP-03 trial did not change the manner in which they treated their acute attacks prior to enrolment in the study.[6] Therefore, there is no reason to suggest that the value for the proportion of attacks that are treated, estimated from the trial will not be reflective of UK clinical practice. However, the results of this scenario are presented in Table 16 to demonstrate the robustness of the results to changes in this assumption.

B16. CS, document B, page 162. Considering the cost of hospital treatment for an attack: please clarify why the NHS Reference Cost HRG code KRC04 is used for the cost of an admission? For an assumed hospital stay of 1.38 days (document B, table 50, page 162), a cost of £2,961 seems high - please clarify if the NHS Reference Cost includes the costs of medicines (which the company have costed separately)? When conducting the sensitivity analysis requested in B15 for the proportion of attacks requiring treatment, please combine it in a table with a cost per hospital admission of £2,500, £2,000 and £1,500, as well as the company's base case value.

The daily hospitalisation cost of £2,961 applied in the model was estimated as a weighted average of two NHS reference costs presented in Table 15. Given the

uncertainty around which was the more relevant cost, the weighting was based on the activity reported in the NHS reference cost data set.[23]

Table 15: Summary of NHS reference costs for hospitalisation

NHS ref cost 2017/18	Currency	Currency Description	Activity	% activity	Unit Cost	Weighted average cost
Total HRG codes	KC04A	Inborn Errors of Metabolism with CC Score 3+	1097	84.13%	£3,367.62	£2,961
Total HRG codes	KC04B	Inborn Errors of Metabolism with CC Score 0-2	207	15.87%	£803.48	
Key: HRG, healthcare resource group						

It is not clear from the whether these codes include the cost of medicines, but this uncertainty is addressed in the submission by including these cost parameters in One-way sensitivity analysis. However, Table 16 presents the estimated NMB from the model for changes in both the percentage of attacks that are assumed to be treated and the hospitalisation cost per day to further test how the results of the model change as this cost is varied. This scenario analysis demonstrates that the results of the model are robust, even when extreme estimates are applied.

Table 16: Results for changes in the proportion of attacks assumed to be treated and the hospitalisation cost per day (NMB)

% of attacks treated	Hospitalisation cost per day			
	£2,961 (base-case)	£2,500	£2,000	£1,500
Base-case (85%)	£470,031	£456,183	£441,150	£426,117
90%	£487,153	£473,305	£458,272	£443,239
80%	£452,866	£439,018	£423,985	£408,952
70%	£418,579	£404,731	£389,698	£374,665
60%	£384,292	£370,444	£355,411	£340,378
50%	£350,005	£336,157	£321,124	£306,092

B17. CS, document B, table 56, page 170. In the results section, a breakdown of the differences in costs between treatments into sub-headings is provided. Please also provide a table breaking down the differences in QALYs between the treatments.

As the model only includes health states for “alive” and “dead” no further breakdown of QALYs was provided in the submission. However, the functionality has now been added to the model to breakdown the incremental QALY gains that due to either: the reduction in the frequency of attacks, and the improvements in treatment administration predicted with lanadelumab. The results of this breakdown for the base-case analysis are presented in Table 17.

Table 17: Incremental QALY breakdown

Category	QALYs lanadelumab	QALYs C1-INH	Incremental QALYs
Attack free			
During attacks			
Treatment administration			
Total			

Key: C1-INH, C1 esterase inhibitor; QALY, quality-adjusted life year.

HELP-04 study

B18. CS, document B, section B 3.10, page 178. In terms of validating the model predictions, the company use the HELP-04 study, referring to table 20 on page 87 of document B. Please clarify what duration of data follow-up is available from the HELP-04 extension study. In addition, the company state that table 20 validates the assumption that when patients switch treatments in the model, the results from HELP-03 for the relevant treatment that the patients were assumed to switch to should apply. As the patients in the model switch from q2w to q4w but HELP-04 switched to q2w, it is not clear how relevant this is. Please clarify the basis for your statement.

As reported in section B.2.6, page 86 of CS, the available duration of data follow-up in the HELP-04 study is 6 months (182 days).

We acknowledge no data are available on the observed effectiveness of patients switching from q2w to q4w; the data from the HELP-04 extension study reported in

table 20 of the CS show that the effectiveness of the q2w regimen was similar irrespective of the previous treatment received (placebo, 300mg q2w, or 300mg q4w). This supports the general assumption that when patients are switched to a different regimen, the previous treatment received should not affect the effectiveness of the new regimen. We do appreciate this conclusion comes from patients switching to the q2w regimen, however we do not have reason to believe this would not be applicable to patients switching to the q4w regimen.

B19. HELP-04 offers some data beyond Day 182 on the rate of attacks with lanadelumab. However, there are no comparable validation data for C1 esterase inhibitors. Please clarify what steps have been undertaken to test the 5- and 10-year predictions for patients in the model treated with C1-esterase inhibitors as prophylaxis.

Clinical expert opinion was used to model the use and effectiveness of C1-esterase inhibitors in the long-term.

Firstly, clinical experts advised that only a negligible number of patients would not tolerate treatment with C1-esterase inhibitors, therefore discontinuation with C1-esterase inhibitors due to intolerance would be considered negligible; this is however incorporated into the model based on trial data.

Furthermore, if the standard dose was not effective at adequately controlling the occurrence of attacks, treatment would not be discontinued according to expert opinion, and instead treatment would be administered more frequently. This scenario is covered by an additional analysis provided in the CS, where a proportion of patients receive a slightly more frequent dose administration with C1-esterase inhibitors. By not including this in the base case model, the cost-effectiveness analysis is being conservative as it assumes that patients are controlled with the recommended starting dose throughout their lifetime.

For the long-term effectiveness of C1-esterase inhibitors, the model conservatively assumes sustained effectiveness over time in the absence of data demonstrating any waning of treatment effect.

Model issues

B20. PRIORITY QUESTION. It appears that the attack rates applied in the model are not adjusted for the proportion of patients who discontinue the alternative treatments. The ERG's clinical advisor maintains that patients who discontinue lanadelumab may switch to a C1INH, whilst those who discontinue on C1INH may incur an attack rate in line with the placebo arm of HELP-03. In order to provide greater flexibility, and to address questions B1 to B3 above, please revise the model so that attack rates can be adjusted for discontinuation and treatment switching from lanadelumab to C1INH or standard of care (SoC) without C1INH, and from C1INH to SoC without C1INH. Similarly, the costs for those that discontinue their treatment should also reflect the subsequent treatment they receive.

As noted in the response to question B5, patients are assumed to discontinue both lanadelumab and C1-INH at an equal rate in the first six months of the model consistent with the discontinuation rate observed in HELP-03. The attack rate data from HELP-03 utilised for the Poisson regression adjusts the number of attacks patients experienced in each cycle for treatment discontinuation, and patients who discontinued therapy on either arm were assumed to accrue no prophylactic treatment costs. This was a simplifying assumption given the uncertainty regarding which subsequent treatment patients would typically go on to receive in practice, and because the assumption of equal discontinuation and survival between the arms means that any subsequent therapy costs would, in all likelihood be equal between the treatment arms.

However, it would be reasonable to assume that patients who discontinue treatment would experience a different attack rate than if they had continued to receive ongoing treatment with lanadelumab. Likewise, patients assumed to discontinue will not accrue the utility increment applied to patients receiving lanadelumab which captures the HRQL benefits associated with receiving a lower frequent subcutaneous dose compared to the more frequent intravenous administration with C1-INHs. Therefore, the model has been amended to assume that patients who discontinue treatment with lanadelumab experience a different attack rate and no longer accrue any HRQL benefits associated with treatment administration.

The treatment that patients will receive following discontinuation from lanadelumab is uncertain. However, it is plausible as the ERG has suggested that patients could receive C1-INH following treatment with lanadelumab. Therefore, the functionality has been included to allow for patients who discontinue lanadelumab to receive treatment with either C1-INH or no prophylactic treatment, with their attack rates and costs adjusted accordingly. The results of this scenario analysis are presented below in Table 18.

B21. PRIORITY QUESTION. Related to B20 above, the ERG's clinical advice suggests that uncertainty exists regarding the longer-term efficacy and continuation of treatment with lanadelumab – given a potential loss of efficacy over time due to the production of antibodies against it. For this reason, the ERG believe the model should be adapted to allow for different longer-term discontinuation rates for lanadelumab and C1INH, and switching to subsequent treatment as described in B20 above. Please revise the model accordingly.

As explained in our response to question B6, there is no data on the durability or waning of lanadelumab effectiveness beyond those reported to date in the clinical trial programme comprising the HELP-03 study and the open label extension, HELP-04.

For this reason, we have provided a scenario analysis accounting for the possibility of a reduction in treatment effect at some point in time, however this is subject to a high degree of uncertainty. The scenario assumes that lanadelumab loses effectiveness at preventing angioedema attacks at 5, 10 or 20 years and therefore treatment is discontinued for all patients. The model has the functionality to assume that patients who discontinue lanadelumab due to treatment waning go on to receive either subsequent C1-INH or no prophylactic treatment, with their costs and efficacy adjusted accordingly.

While we recognize the development of ADAs could occur in a population treated with lanadelumab, in both HELP-03 and HELP-04 studies, no subject discontinued treatment with lanadelumab due to the presence of ADA or reported an AE indicative of a hypersensitivity reaction due to the presence of ADA, with the majority of patients in the HELP-03 study electing to rollover and participate in the open-label

study. In addition, antibody-positive subjects had no apparent difference in efficacy profiles compared to antibody-negative subjects. Therefore, while some patients developed ADAs, this did not have an impact on treatment efficacy and did not result in discontinuation.

Furthermore, there is some evidence showing that ADAs production was transient as ADA response was transient in 2 of 10 lanadelumab-treated subjects in the HELP-03 study and in 6 of 19 subjects in the HELP-04 study.

C1-INH are a plasma-derived replacement therapy and therefore treatment waning due to the production of ADAs is not expected to be an issue for this treatment. As we have explained in responses to questions B1 and B5, if patients are still experiencing breakthrough attacks while treated with C1-INH as their prophylactic treatment, they are more likely to receive an increase in administration frequency. The required increase in frequency with C1-INH is not due to a decrease effectiveness over time but to the natural fluctuations of the disease. This practice by clinicians to adjust the dose of patients receiving C1-INH may partially be a result of the absence of alternative treatment options available to these patients. Furthermore, C1-1NH have been now used for several years and from discussions with clinical experts we had not been told of any case where a gradual and sustained decrease in effectiveness have been observed. Therefore, a sensitivity analysis where discontinuation for lack of effectiveness is implemented would not be representative of current practice as this rarely happens.

Table 18: Treatment waning and discontinuation scenarios

Waning	Waning time	Discontinuation	Inc. costs	Inc. QALYs	ICER (£/QALY)	NMB (£)
I) No treatment waning	N/A	A) No treatment following lanadelumab and C1-INH	[redacted]	[redacted]	Dominant	£447,838
		B) C1-INH following lanadelumab & no treatment after C1-INH	[redacted]	[redacted]	Dominant	£127,377
II) Lanadelumab waning	5 years	A) No treatment following lanadelumab and C1-INH	[redacted]	[redacted]	Less costly / Less effective	£3,183,367
	10 years		[redacted]	[redacted]	Dominant	£2,567,684
	20 years		[redacted]	[redacted]	Dominant	£1,632,262
	5 years	B) C1-INH following lanadelumab & no treatment after C1-INH	[redacted]	[redacted]	Dominant	£37,326
	10 years		[redacted]	[redacted]	Dominant	£57,966
	20 years		[redacted]	[redacted]	Dominant	£89,093
Key: *To apply these scenarios in the model first adjust the attack rate and utility values for discontinuation by setting cells E128 and E140 on the Controls sheet to "Yes"*						

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

Clarification questions

January 2019

File name	Version	Contains confidential information	Date
To PM for company	Final for company	Yes	14.01.2019

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Decision problem

A1. Company submission (CS), document A, section A5, table 2 (page 10) and document B, section B.1.1, table 1 (page 11). Table 2 in document A contains a row for "Perspectives for outcomes." The NICE final scope refers to "All direct health effects, whether for patients or, when relevant, carers" while the company refers to "All direct health effects for patients". Please provide the rationale for not including health effects for carers in their decision problem. This row and associated information is missing from table 2 in document B.

[Company: please enter your answer to this question here]

A2. The submission indicates that lanadelumab would be self-administered by patients at home. Please clarify that it is not necessary for lanadelumab to be administered in a clinical setting.

[Company: please enter your answer to this question here]

Identification and selection of relevant studies

A3. CS, document B, section B.2.1 (page 34). The company state "Non-RCT evidence identified in the SLR were not used for comparative effectiveness". Please clarify why the non-RCT evidence was not used for the studies presented in table 9 on pages 16 to 19 in appendix D and why non-RCT data from these studies are not presented in the submission.

[Company: please enter your answer to this question here]

A4. CS, document B, last paragraph section B.2.2 (page 37). The results of the DX-2930-02 study were not included because the pivotal phase III Help-03 study superseded it. Please expand further on this, explaining the decision to exclude.

[Company: please enter your answer to this question here]

Adverse events (AE)

A5. CS, document B, tables 24 to 32. Some of the AE tables report n (%) m, where 'm' indicates the number of adverse events. For completeness, please provide 'm' in all other similar tables (e.g. Tables 31 and 32 of document B).

[Company: please enter your answer to this question here]

A6. PRIORITY QUESTION. CS, document B (page 104 onwards). Multiple events of the same AE occurring in the same patient (i.e. 'm') are not analysed. This may affect the economic model so please justify this decision.

[Company: please enter your answer to this question here]

A7. CS, document B, tables 24 to 32 (pages 107 to121). Lanadelumab 150mg q4w has been included in the overall totals in all the adverse events tables and subsequently compared with control groups. However, the company initially stated they would disregard this dose in HELP-03 because it is not expected to be included in the marketing authorisation and will not be available (see document B, section B.2.6, page 63). Therefore, the rationale for including it

here it is unclear. Please provide additional totals for document B tables 24 to 32, without this arm.

[Company: please enter your answer to this question here]

Help-03 study

A8. CS, document A, tables 4 and 5 (pages 17 and 19) specifies a Poisson model. The various documentation supplied (e.g. document B, page 132) all infer that the only adjusters were 'baseline' attack rate and offset time. Please explain the decision for not including other covariates, specifically age and sex as possible adjusters – there are slight baseline differences in HELP-03 for sex (document B, table 8, page 51) and for age in HELP-04 (see A9 below). If possible, please incorporate these into the model(s). Age could be included as a continuous variable thus avoiding the small counts issue.

[Company: please enter your answer to this question here]

Help-04 study

A9. CS, document B, table 9, page 55. The <18 years category in the rollover group is smaller than that in the non-rollover group. Would this potentially affect the results (see A8 above)? Please provide additional comments on this.

[Company: please enter your answer to this question here]

A10. CS, document B, table 9 (page 55). Please note that 35/103 (non-rollover male patients) is not 44%, please provide corrected values.

[Company: please enter your answer to this question here]

Efficacy endpoints

A11. PRIORITY QUESTION. CS, document B, figure 5 and 6 (pages 71 to 72) and figures 44/45 in Appendix N. Please provide data for time to first investigator-confirmed attack/day so that these curves may be reproduced for time to first attack based on 0 to 182 & 70 to 182 days.

[Company: please enter your answer to this question here]

A12. CS, document B, table 11, page 60. Please provide a justification for using a generalised estimating equations (GEE) method (rather than for example a multilevel model) in the sensitivity analysis for the number of HAE attacks day 14 to 182.

[Company: please enter your answer to this question here]

Network meta-analysis (NMA)

A13. PRIORITY QUESTION. CS, document B (pages 30 and 92) and Appendix D.1 (from page 26). HELP-03 (lanadelumab 2 doses versus placebo) is compared indirectly with the CHANGE study, which assessed C1-inh IV 1000IU versus placebo twice weekly. However, CHANGE is a crossover trial thus will have smaller standard errors (SEs) between the treatment and placebo groups compared with HELP-03. Please comment on how the non-independent groups in the CHANGE trial have been accounted for - Document B (page 30) briefly suggests the use of '…the normalised attack rate'. Please expand on this so that it may be replicated by the ERG in the NMA and provide a justification for its use in the NMA.

[Company: please enter your answer to this question here]

A14. CS, document B (page 104). The submission indicates that CHANGE and HELP-03 have different endpoints. Please define the endpoints used and clarify whether CHANGE is a good comparator study in this case.

[Company: please enter your answer to this question here]

A15. PRIORITY QUESTION. The company used lanadelumab 300q4w and lanadelumab 150q4w with placebo to find SE for placebo to link to the CHANGE study - as per Woods et al. (2010). However, the 150mg arm should not be the focus here (see document B, section B.2.6, page 63). Was this arm used because of the decision to investigate attack rate over 4 weeks? This would not affect the hazard ratios (HRs). Is it possible to use the 300 q4w/300 q2w/placebo network triangle instead? To allow us to replicate the original

NMA and investigate this other network 'triangle', please provide the original HRs for attack rate in the table below.

Study	Treatment	Base	HR	HR_{LCI}	HR_{UCI}
HELP-03	DX150mg/ 4wk	placebo			
	DX300mg/ 4wk	placebo			
	DX300mg/ 4wk	DX150mg /4wk			
	DX300mg/ 4wk	DX300mg /2wk			

[Company: please enter your answer to this question here]

A16. PRIORITY QUESTION. CS, document B, section B.2.9. Random effects models were used despite the small sample sizes. The three priors considered were U(0,3), U(0,5) and half normal (0,2). Please justify the priors particularly the parameter choice(s) for each distribution (see key point 4 in Spiegelhalter, Abrams and Myles 'Bayesian Approaches to Clinical Trials and Health-Care evaluation', Wiley, Statistics in Practice series, 2007, page 176, section 5.9).

[Company: please enter your answer to this question here]

A17. CS, appendix D, (page 29). Please clarify that *mean rate*^{2} == *mean4*^{2} and that *variance rate* == V(X)

[Company: please enter your answer to this question here]

A18. CS, document B (page 97). Continuity correction of 1 was used rather than 0.5. It is more conservative, but apart from maintaining whole numbers, is there any other rationale?

[Company: please enter your answer to this question here]

Section B: Clarification on cost-effectiveness data

Comparator

B1. PRIORITY QUESTION. CS, document B (page 183). The submission refers to the 2016 NHS England Commissioning Policy for C1-esterase inhibitor use

as prophylaxis (document B, reference 18). Important features of this policy are as follows:

- The criteria for starting C1-esterase inhibitor prophylaxis – on oral prophylaxis, NHSE specify the patient must have had 2 or more clinically significant attacks per week over 56 days (8 weeks).
- Being contraindicated to oral prophylaxis as a criterion for starting C1-esterase inhibitor prophylaxis.
- Consider reducing the dosing frequency after 6 months if attacks have reduced sufficiently.
- Consider discontinuing C1 if less than 2 clinically significant attacks per week on a once weekly prophylaxis dose
- Stop treatment with C1-esterase inhibitor after two months if the attack frequency has not adequately reduced.

Please clarify how these informed your assumptions in the modelling of C1-esterase inhibitor prophylaxis and provide a sensitivity analysis where C1-esterase inhibitor prophylaxis reflects the NHSE commissioning policy.

[Company: please enter your answer to this question here]

B2. CS, document B, table 55. Please provide cost-effectiveness results using the placebo arm of the RCTs as the comparator rather than C1-esterase inhibitor or lanadelumab prophylaxis.

[Company: please enter your answer to this question here]

B3. CS, document B, page 143. The company acknowledge that the posology of Cinryze in the CHANGE RCT does not fully match clinical practice in England and Wales, and that the added efficacy from increasing the dose and/or frequency is not easily quantified (document B, page 143, first paragraph). A threshold analysis is presented, which gives the ICER for each level of Cinryze efficacy (document B, table 60, page 177). The Bernstein study (reference 107) is provided to support this and is summarised in Table 59. Please clarify the link between Tables 59 and 60. Is it correct to state that the base case rate ratio is 0.492 at a dose of 1,000IU and if this were increased to 1500IU, the reduction in Table 59 is 40%, so 60% of 0.492 is 0.295? Therefore, if

the Bernstein data were interpreted in this way the base case would be shown by the row where the rate ratio is 0.3?

[Company: please enter your answer to this question here]

B4. CS, document B. In the submission, lanadelumab is positioned for use after oral prophylaxis, instead of IV C1-esterase inhibitor prophylaxis (e.g. page 130 of document B). However, some patients will previously have tried IV C1-esterase inhibitor prophylaxis and either had inadequate control or are unable to tolerate it. Please clarify: i) what the company would regard as the comparator in this circumstance; ii) what the company estimate the cost-effectiveness of lanadelumab to be in this circumstance.

[Company: please enter your answer to this question here]

Treatment effectiveness

B5. CS, document B, page 146. Please clarify what assumptions have been made about treatment and effectiveness when lanadelumab is discontinued and when C1-esterase inhibitors are discontinued.

[Company: please enter your answer to this question here]

B6. The model assumes no waning of the treatment effect over time for lanadelumab. Please clarify your rationale for this, given that treatment is predicted to last a lifetime and anti-bodies may develop. Please provide a sensitivity analysis where the increased effectiveness in terms of reduced attacks wanes after 5, 10 and 20 years.

[Company: please enter your answer to this question here]

Modelling of attacks

B7. CS, document B, table 36, page 137. Two factors identified as being significant are presented in table 36 and are described as co-variates, but this does not show which other factors were tested or the goodness of fit of the equation. Please provide these additional data.

[Company: please enter your answer to this question here]

B8. CS, document B, table 36, page 137. In the equation for the Poisson regression, the baseline attack rate is a significant predictor of attacks in future cycles, based on data from the HELP-03. By using the same rates over the lifetime of the patients, this means the rate in the baseline period is assumed to still be playing the same role in predicting attacks many years later. Please clarify the basis for this assumption.

[Company: please enter your answer to this question here]

B9. The 2016 NHS England Commissioning Policy defines an attack as being clinically significant if it is potentially life-threatening (on the head or neck) or if causes pain/disability such that usual activities cannot continue. Please clarify how this relates to the three levels of severity of attack considered in the cost-effectiveness model. Please provide a scenario analysis only including attacks defined as clinically significant by NHS England.

[Company: please enter your answer to this question here]

Dose switching

B10. CS, document B, section B.3.3. When patients switch from lanadelumab every 2 weeks (q2w) to every 4 weeks (q4w) in the model, estimates based on the q4w arm of the HELP-03 trial are applied. However, the q4w arm of this RCT was in patients previously naïve to lanadelumab. It is unclear whether the RCT experience with q4w reflects the likely experience when switching patients whose disease is controlled with q2w to q4w. Is there any other evidence about the effectiveness of a switching policy as in the model? If so, please provide details.

[Company: please enter your answer to this question here]

B11. CS, document B, section B3.3 (p141 to 142). The submission explains that, based on the observed time to first attack presented in Figure 5, [redacted] of the lanadelumab cohort are assumed to switch to the lower dose (300mg q4w) at six months. This seems reasonably well justified. However, it is then assumed that [redacted] of the cohort will be on the lower dose from 12 months onwards in the model. This is based on the proportion of the q2w cohort that remain attack free from day 70 to day 182 (a period of 112 days ~3.7 months).

Given the assumed [redacted] assessment schedule, this may overestimate the proportion of the cohort who remain attack free between 6 months and 12 months – and hence may overestimate the proportion of the cohort on the lower does in the long-term. To overcome the mismatch between the observed time period and the [redacted] assessment schedule, it would be useful to extrapolate the observed time to first attack between day 70 and day 182, out to a period of [redacted], and use the projected attack free rate at this time point in a scenario analysis.

[Company: please enter your answer to this question here]

Utility values

B12. CS, document B, section B.3.4. When applying utility values, the company make the reasonable point that the EQ-5D data in the RCT did not capture the utility loss of attacks because so few patients completed this instrument at the time of an attack. Therefore, a literature search is conducted to identify values to use during an attack. However, having identified utility decrements from the literature search, these are also applied to utility values for 'alive, attack-free'. The NICE Methods Guide supports the use of EQ-5D measured in a clinical study of the treatment when possible, and while a case is made for attacks, it is not clear why utility values from the RCT data for the 'no attack' state were not used. Please provide a rationale for the approach set out in the base case. In line with DSU recommendations (TSD 12 The use of health state utility values in decision models), it may be preferable to calculate an age adjusted utility multiplier for 'attack' relative to 'attack-free', and apply this multiplicatively to an age adjusted attack free utility.

[Company: please enter your answer to this question here]

B13. CS, document B, page 143. In the cost-effectiveness modelling, attacks are categorised as mild, moderate and severe. The company do not consider where on the body the swelling occurred but this seems likely to affect the disutility and hence potentially the propensity to seek health care. Please clarify any discussions that were had with patients or representative groups on the factors influencing the utility loss from an attack. Please present a

sensitivity analysis where the location of the swelling is considered as a factor.

[Company: please enter your answer to this question here]

Resource use and costs

B14. CS, document B, page 134 and 135. The submission states that the most common C1-esterase inhibitor used in NHS practice is Cinryze in some cases and Berinert in others. The company estimated the proportion using each medicine and provide some sensitivity analyses. However, the range of alternative scenarios considered is limited. Please provide a sensitivity analysis showing the results i) where 100% of C1-esterase inhibitor use is Cinryze and 0% Berinert and ii) where 0% is Cinryze and 100% Berinert.

[Company: please enter your answer to this question here]

B15. CS, document B, figure 24 (page 173). The percentage of attacks as reported in the clinical studies that would require treatment in an NHS setting is uncertain, and a sensitivity analysis is provided in the submission. Please re-present these data as a table showing the effect on the ICER assuming the proportion treated is 85% as in the base case, and also include 90%, 80%, 70%, 60%, 50%.

[Company: please enter your answer to this question here]

B16. CS, document B, page 162. Considering the cost of hospital treatment for an attack: please clarify why the NHS Reference Cost HRG code KRC04 is used for the cost of an admission? For an assumed hospital stay of 1.38 days (document B, table 50, page 162), a cost of £2,961 seems high - please clarify if the NHS Reference Cost includes the costs of medicines (which the company have costed separately)? When conducting the sensitivity analysis requested in B15 for the proportion of attacks requiring treatment, please combine it in a table with a cost per hospital admission of £2,500, £2,000 and £1,500, as well as the company's base case value.

[Company: please enter your answer to this question here]

B17. CS, document B, table 56, page 170. In the results section, a breakdown of the differences in costs between treatments into sub-headings is provided. Please also provide a table breaking down the differences in QALYs between the treatments.

[Company: please enter your answer to this question here]

HELP-04 study

B18. CS, document B, section B 3.10, page 178. In terms of validating the model predictions, the company use the HELP-04 study, referring to table 20 on page 87 of document B. Please clarify what duration of data follow-up is available from the HELP-04 extension study. In addition, the company state that table 20 validates the assumption that when patients switch treatments in the model, the results from HELP-03 for the relevant treatment that the patients were assumed to switch to should apply. As the patients in the model switch from q2w to q4w but HELP-04 switched to q2w, it is not clear how relevant this is. Please clarify the basis for your statement.

[Company: please enter your answer to this question here]

B19. HELP-04 offers some data beyond Day 182 on the rate of attacks with lanadelumab. However, there are no comparable validation data for C1 esterase inhibitors. Please clarify what steps have been undertaken to test the 5- and 10-year predictions for patients in the model treated with C1-esterase inhibitors as prophylaxis.

[Company: please enter your answer to this question here]

Model issues

B20. PRIORITY QUESTION. It appears that the attack rates applied in the model are not adjusted for the proportion of patients who discontinue the alternative treatments. The ERG's clinical advisor maintains that patients who discontinue lanadelumab may switch to a C1INH, whilst those who discontinue on C1INH may incur an attack rate in line with the placebo arm of HELP-03. In order to provide greater flexibility, and to address questions B1 to B3 above, please revise the model so that attack rates can be adjusted for discontinuation and

treatment switching from lanadelumab to C1INH or standard of care (SoC) without C1INH, and from C1INH to SoC without C1INH. Similarly, the costs for those that discontinue their treatment should also reflect the subsequent treatment they receive.

[Company: please enter your answer to this question here]

B21. PRIORITY QUESTION. Related to B20 above, the ERG's clinical advice suggests that uncertainty exists regarding the longer-term efficacy and continuation of treatment with lanadelumab – given a potential loss of efficacy over time due to the production of antibodies against it. For this reason, the ERG believe the model should be adapted to allow for different longer-term discontinuation rates for lanadelumab and C1INH, and switching to subsequent treatment as described in B20 above. Please revise the model accordingly.

[Company: please enter your answer to this question here]

NICE National Institute for Health and Care Excellence

Patient organisation submission

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	HAE UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	HAE UK is a patient support and advocacy organisation for patients and families affected by Hereditary Angioedema, registered charity 1152591. We also provide support and advice to people affected by Acquired Angioedema (acquired C1-INH deficiency). We have just under 600 members for who we provide (amongst other); 1) Educational and social Patient days with top clinicians providing information about the aetiology of the condition, treatments and research projects 2) Patient and clinician information and training 3) campaigning and lobbying both as individual organisation and as part of Genetic Alliance, Rare Disease UK and The Specialised Health Care Alliance for increased awareness and improved access to treatments 4) Raising awareness of Hereditary Angioedema amongst the general populace and with clinicians 5) Sponsorship of research into management of Hereditary Angioedema, particularly the psychological effects of living with long term, potentially fatal conditions. Also, non-pharmaceutical methods of reducing and/or controlling attacks. HAE UK receives unrestricted charitable grants from Biocryst, CSL Behring, Kalvisa, Pharming and Shire as well as donations from events arranged by members, payroll donation, bequests and other forms of donations.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NONE
5. How did you gather information about the experiences of patients and carers to include in your submission?	**Through patient surveys, personal discussion, discussion with clinicians, attending clinics and patient days, our Facebook page, our website and other forms of communication eg e-mail, letters.** **Real quotes from patients have been put in inverted commas in the following submission and highlighted in purple.** **C1 Esterase Inhibitor has been abbreviated to C1-INH throughout.**

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Hereditary Angioedema is characterised by unpredictable and sporadic attacks of subcutaneous swelling which can attack anywhere and varies from mild to lifethreatening if it affects airways. Historically, it is considered that over 30% of people affected by HAE died from airway obstruction. It is still a major concern to patients. There are no particular triggers for these attacks, as in allergic conditions, but some common triggers emerge, notably hormonal changes, stress and anxiety (eg exams or even 'happy stress ' like family events) invasive procedures such as dentistry, minor surgery, infections such as colds, flue, tooth decay. Sometimes repetitive actions such as painting, even walking can trigger attacks. Attacks can occur in peripheries such as feet, hands and limbs, abdominally, genitally, facially and elsewhere. Swellings reach a very large size in a short time - circa 30-40 minutes - and then take 2 or more days to resolve. Available treatments will stop swelling but will not help it to resolve. HAE swelllings are unresponsive to antihistamines or steroids. It is not unusual for swellings to occur in more than one location in an attack. Some patients suffer such frequent attacks (more than two a week) that they are allowed to use C1-INH as prophylaxis. Most have fewer attacks and treat on demand with C1-INH (replacement therapy) and/or Icatibant (a bradykinin receptor antagonist). Attacks in peripheries such as feet can render the patient unable to wear shoes or to walk. In hands, they cannot use simple equipment for cooking, writing or driving. Abdominal attacks are so painful that they have often been confused with appendicitis or other abdominal conditions and so patients have has unnecessary surgery. The swelling is such that it gives the appearance of late-stage pregnancy. The unpredictable nature of the condition means that patients have heightened levels of anxiety – 'It's always at the back of my mind that I might have an attack' and even patients using prophylaxis treatment will have breakthrough attacks (the rationale/pathway for such attacks is as yet undefined). 'we used to plan family parties or get-togethers and yet never be able to get there' 'my daughter has had to live with the fact that she cannot go on school trips because I may not be able to get there to give her treatment' The condition curtails life to a greater or lesser degree depending on the severity of their condition. Children can suffer from severe limitation to school life and education.

	'Throughout my childhood, I had numerous swellings to the face, hands and feet but when I was taken to the GP's they all brushed it off as an allergic reaction but never tested me for anything. I learnt to live with the swellings even though they were painful and embarrassing as people would stare and other children would tease. When I was 21, I was taken into hospital with excruciating abdominal pain. Doctors told me it was appendicitis and so I had my appendix removed and spent over a week in the hospital recovering as I developed an infection.' Patients are therefore unable to carry out normal day to day tasks and it can affect their work or school lives very badly. As stated previously, there are no discernable triggers as with an allergic condition, but patients are severely affected by stressful situations or infections such as colds, flu, infected teeth etc. Owing to the historic incidence of premature death caused by laryngeal swelling/compromised airways, many patients have a relative who died in this way and it is always in their mind that this could happen to them. Parents with an affected child are particularly conscious of this as they fear the child will not inform them of an attack soon enough. 'Mum was very sick all of her life and passed away in 1969 at the age of 24. Her death was caused by a swelling in her throat, unfortunately medical attention came too late.' 'My grandfather had HAE severely over many years and he died from a throat swelling at the age of 39'
Current treatment of the condition I'n the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Current treatments are effective but still can have problems; 1.Attenuated Androgens; Oral tablets.Stimulate the liver to produce more C1-INH; can be effective prophylaxis for patients but still have breakthough attacks that may require more treatment usually intravenous C1-INH. Some patients suffer extreme side-effects eg masculinisation, weight gain, mood swings. All patients must have regular liver monitoring. 'Never had any issue with danazol and been on it for years' 2. Tranexamic Acid; Tablets or liquid, seems most effective for patients affected by a mutation in the FXII gene. It inhibits plasminogen and so reduces bradykinin production. Only about 1/10 patients find it effective, but those who do, do not report side-effects. Again, breakthrough attacks may require Icatibant or IV C1-INH. It is licensed for use in children. 3. Icatibant; acts by blocking bradykinin receptors. Only licensed for use in attacks, it is best used as early in an attack as possible and is administered by subcutaneous injection. Many patients find it very effective, but it has a

	short half-life and so if there is a prolonged trigger eg an infection there will often be subsequent attacks requiring more use. It is provided as a pre-filled syringe, some patients report unacceptable pain, swelling and irritation at the injection site. Now licensed for use for attacks in children, but syringe not graduated so parent/carer has to measure the syringe and work out how much to give depending on bodyweight of child. Can be held at home. Patients are often only 'allowed' to use one syringe per attack and some clinicians will not permit them to use more than so many a month. Whilst this is unacceptable rationing, it can be argued that patients who have frequent severe attacks should receive different treatment. 'Icatibant is brilliant! I wish this had been available when I was at my worst (in my 30s and 40s)'. 'I self administer Icatabant which works amazingly well and within ten minutes I feel better. This relief can be temporary and if I get a relapse I will have to repeat the Icatabant up to three times. If the problem remains unresolved after three Icatabant injections I need to attend A&E for IV Berinert' 4. Intravenous C1-INH. There are three branded products, two plasma derived and one recombinant. Mode of action is to replace the C1-INH the patient lacks. There is also sub-cutaneous C1-INH available but it is not yet licenced in UK though some patients use it under an IFR as they has insufficiently good venous access to use the IV concentrates. The advantage of recombinant C1-INH is to reduce the risk of infusion transmissible viral contaminants Most patients use C1-INH on an on-demand basis, and have been trained to self-administer, or have a partner/carer/parent who carries out the venepunture. Patients that satisfy the criteria are permitted to use C1-INH as prophylaxis, twice weekly infusions as the C1-INH has a half-life of some 36 hours. However, some patients will still suffer breakthrough swellings which can be more or less disabling. Notwithstanding, the availability of C1-INH through home treatment has revolutionised many peoples' lives as it has greatly reduced anxiety about 'when will my next attack happen?' 'I was a train driver at the time and I couldn't take a chance on things happening once I was in charge of a train. So I told the manager when I got there that I needed to go to the hospital and one of the managers took me there. Fortunately I had my own supply of C1-INH with me. I always carry it with me when I go to work in case of an attack when I am too far from home and that has now proved to be the right thing to do! Despite having the C1-INH and a letter from my immunologist, there was still a bit of fuss about giving me the injections, but taking my own supply definitely sped things up and after about half an hour the C1-INH was being administered.' …….on being finally allowed to keep C1 at home 'This was such a life changing time; I finally had the freedom and confidence to travel away from home and could plan a holiday with my family.

	Although HAE does have a big impact on my day to day activities, I am determined to not let it stop me doing the things I enjoy and leading a full and active life.' 'My life was completely transformed, from that day forward I never had any more upset stomachs or swellings.'
8. Is there an unmet need for patients with this condition?	Whilst the existing treatments are very effective there are several disadvantages. The least severely affected patients can often be managed with oral treatments supported by availability of IV 'rescue'. Very severely affected patients are eligible for prophylaxis or on-demand treatment but the most effective is by IV which any patients find difficult to perform and so rely on an infusion partner. The subcutaneous Icatibant has too short a half-life to be used prophylactically. Prophylactic C1-INH requires venepuncture twice weekly which can result over time in reducing venous access as veins become damaged. And even C1-INH does not prevent breakthough attacks. Therefore there is a real need for a prophylaxis which has a much longer half-life/period of activity, showing superior efficacy to C1-INH or Icatibant (no breakthrough attacks)and with a much easier to manage method of administration.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Method of administration; patients are much quicker to master subcutaneous injections and there will be a considerable reduction in the time spent in instruction by the specialist nurses. Also, the frequency of administration is reduced to twice monthly which is considerably easier for patients to manage with busy family life. Patients who have been on the clinical trial report fewer breakthrough attacks and consequently the efficacy appears much higher than with existing technologies. There is the advantage of it being non-plasma derived, therefore reducing the risks of viral transmission. Recently in 2018 there have been widespread shortages of plasma derived products which has resulted in extreme anxiety amongst patients in case they are no longer to access medication. Therefore they welcome the advent of another non-plasma derived product because it should not suffer the same frequent limitations to supply.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The only concerns I have heard raised have been the theoretical long term safety as the studies have not yet lasted long enough to ascertain this.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	At first sight the patients having long term prophylaxis with C1-INH would appear to be the group that would most benefit from this technology. I would venture to suggest that they would also benefit from still having access to IV C1-INH as they have the facility to infuse it and the clinical trial data would suggest that there is still some tendency for breakthrough swellings although greatly reduced in severity and frequency. There are also patients who fall below the required criteria for C1-INH prophylaxis, but still have frequent disabling attacks and who have to treat 'on demand'. These are a group who will really benefit from this technology, as being rendered more or less attack free with a fortnightly sub cutaneous injection will really expand their lives by allowing them to travel and go abroad, which they previously might have been afraid to do. There is a sub-group of HAE patients who were formerly called 'Type 3' but are described as HAE-with-normal-C1. Because of their blood test results, many clinicians, whilst recognising this as a variant of HAE, will not prescribe C1-INH and so only issue Icatibant. As detailed above, this can be less effective if the 'trigger' lasts longer than the half life. The different mode of action, by reducing bradykinin production through inhibition of kallikrein could be very effective for this group of patients. Students and school children would also benefit from this product as they are at increased risk of stress and anxiety during exam periods, changing schools etc. To be able to access a well tolerated, easily administered and effective treatment once a fortnight, instead of twice or more a week, will greatly increase the chances of such young people, rather than the limitations imposed by the treatments currently available.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**There are still some areas of the country where local decision makers limit access to supply of all HAE medication. It is essential that this product is equally available to all HAE and AAE patients**
Other issues	
13. Are there any other issues that you would like the committee to consider?	HAE UK recognises the huge variety of different presentations of what is essentially the basic condition of Hereditary Angioedema. Family members, siblings and other relatives can express the condition in very many different ways so that one child may have very frequent attacks whilst the sibling will have very few. Consequently, it is our opinion that there should be as wide a choice of medication available to patients and clinicians as possible. There must be a recognition that 'one size does not fit all' and that a patient's condition can vary through their lifetime so that medication can and should be varied accordingly. The availability of all products ultimately is more cost effective to the NHS as appropriate treatment may be targeted to the patient. Therefore, this technology which is shown to be effective, with few side-effects and providing control of symptoms whilst easily administered on a less frequent basis should definitely be available to patients and clinicians in order to determine the most appropriate treatment on a case-by-case basis.

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: • The new technology has been shown to be effective, well-tolerated, easy to administer and long-acting • There are many patients for whom this may prove to be suitable as it will reduce the anxiety of having HAE that is less than well controlled • The new technology will increase choice available to patients and clinicians to make an appropriate choice for their medication • Sub-cut administration is easily taught and ideal for home- treatment • Patients who would otherwise be treating frequently on demand will have fewer, less frequent administration of medication

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted] **on behalf of the Therapy & Guidelines sub-committee**
2. Name of organisation	**British Association of Dermatologists (BAD)**

3. Job title or position	**Consultant Dermatologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the	

condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be	

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator	

treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- **We agree with the final scope and final matrix.**
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Lanadelumab for the long-term prevention of angioedema attacks in hereditary angioedema types I and II [ID1268]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Pathologists**

3. Job title or position	**Consultant immunologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**I work for [redacted] with the largest cohort of patients with hereditary angioedema in the UK. I am representing the Royal College of Pathologists in this technology appraisal**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To prevent attacks that result in swellings that depending on their location can result in debilitation or at worse death.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in the number of attacks.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There are patients who do not respond or have partial response to available medications.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Depending on the frequency or severity of the attacks, patients may be given a management plan for acute attacks or they may be started on prophylaxis. All acute attacks are considered for treatment and treated depending on the site and severity of the attacks. Early treatment is recommended for acute attacks. All attacks that have the potential to cause airway obstruction should be treated. C1 inhibitor replacement or Icatibant are recommended for acute attacks in the UK. Prophylaxis with attenuated androgens or progetogens can be used in some patients. Tranexamic acid is also used but is not successful in most

	patients. C1Inhibitor from human plasma or produced by recombinant technology is also used prophylactically in patients with 2 or more attacks per week..
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. The International WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update Maurer M, Magerl M, Ansotegui I, Aygören-Pürsün E, Betschel S et al. World Allergy Organization Journal 2018; 11:5. doi: 10.1186/s40413-017-0180-1
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The care pathway is well defined. There is some differences of opinion on whether all attacks need to be treated with Icatibant or C1 Inhibitor replacement.
• What impact would the technology have on the current pathway of care?	Depending on the costs, it may affect the prophylactic pathway. It can be used for patients not responding to C1 Inhibitor replacement therapy or if it is cost effective, it may replace the use of regular C1 Inhibitor in patients with high demand for this treatment.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	See above.
• How does healthcare resource use differ	

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No need for new facilities or equipment. No need for extra investment on training if specialist centres used the technology.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
• Do you expect the technology to increase length of life more than current care?	It is expected to reduce the frequency of attacks significantly. As some attacks may involve laryngeal swelling and asphyxiation, it follows that it could prevent morbidity.
• Do you expect the technology to increase health-related quality of	Yes as patients would stay free of attacks for longer periods of time.

life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology should currently only be used in patients with hereditary angioedema type I and II but if shown in future studies it may be effective in other bradykinin mediated angioedema.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	The use of this technology is easier than the intravenous C1 Inhibitor replacement therapy as it is administered subcutaneously.

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	A diagnosis of HAE needs to be established. Failure to respond to treatment with C1 inhibitor replacement, or high demand for C1 Inhibitor (more than the prophylactic dose recommended by the department of health commissioning document) in a patient who has the criteria for C1 Inhibitor prophylaxis should be used as the rule for starting treatment. The rule to stop should be development of unacceptable side effects or adverse events and failure to respond.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes. I can only provide anecdotal support for my view. I look after a patient in their 50's who had never dared to travel abroad because of frequent attacks of swellings until they were started on Lanadelumab. The favourable response to this medication gave the patient the confidence to travel to Malta as their first foreign holiday. It is probably difficult for QALY to capture this aspect of life quality.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	Yes. See above

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes for patients with severe or unresponsive disease. Although, the long term effects of this technology are not known and there is a need for long term post marketing surveillance.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. See above.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are no known side effects that overlap with disease activity and on the whole it is well tolerate at least during the period of the study.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Number of attacks and tolerability which were measured in the trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.

21. How do data on real-world experience compare with the trial data?	Not aware of data on real-world experience In the UK only five patients in were enrolled in the trial our unit (Barts Health NHS Trust), four of whom continued with the open label extension study and are still on treatment.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	I am not aware of any equality issues.
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Novel technology
- Highly efficacious
- Not long enough experience with the technology
- Should be used in patients failing available technology
- Should be initiated in specialist units

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Physicians (RCP)**

3. Job title or position	**RCP registrar**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**Royal College of Physicians funded by members and fellows**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Lanadelumab will be used for prophylaxis to control and prevent angioedema attacks in people with HAE ie to improve both frequency and severity of attacks and thereby improve QoL in patients 12 years of age and older. Lanadelumab is a monoclonal antibody that inhibits plasma kallikrein which is uncontrolled in HAE due to insufficient C1 inhibitor in people with HAE. Lanadelumab is given to patients in a 300 mg dose injected subcutaneously every two weeks and then every four weeks afterward depending on how well the patient responds to treatment after six months. The HELP trial, showed that patients treated with Lanadelumab

or prevent progression or disability.)	experienced an 87% reduction in HAE attack frequency compared to placebo. A post hoc analysis over a 16-week period demonstrated that 77% trial subjects were attack-free compared to 3% on placebo. However there have been no trials comparing efficacy with standard therapies ie danazol or CI-inhibitor.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in frequency and severity of angioedema attacks especially those affecting the larynx or gastroenterological system.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Unmet need for those requiring alternative high cost therpies ie plasma derived and recombinant C1 inhibitor. as these alternatives come at very high cost, may be in short supply and require frequent administration
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	The vast majority are well controlled on danazol and have either no or limited side effects. Furthermore, since the introduction of danazol, deaths due to laryngeal oedema have disappeared. However, an increasing number of patients prescribed danazol continue to experience angioedema and unfortunately because of an inability to monitor compliance with danazol, are switched to Cinryze prophylaxis in line with NHS commissioning policy. This policy has not been audited for effectiveness and it is unclear whether it has resulted in a positive effect on deaths, hospital admissions or ED attendance due to reduction in frequency of attacks. Acute attacks are self-treated with icatibant or the patient attends ED where

	treatment with C1 inhibitor concentrate is administered. Minor attacks do not require treatment. Before surgical or dental procedures an infusion of C1 inhibtor is administered.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There is a requirement for guidelines as the those currently available do not conform to current UK practice and the authors highly conflicted. Therefore, NICE may consider a Clinical guidance to encompass all maintenance and acute therapies rather than TAs for each new HAE drug
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Considerable variation with little agreement over who should continue danazol, who should be prescribed icatibant, for which side effects danazol should be stopped, when to initiate prophylactic C1 inhibitior, and when a patient should self-administer icataibant. Patient groups heavily funded by Shire are conflicted in this regard. This debate will also affect prescribing of landilumab.
• What impact would the technology have on the current pathway of care?	It should replace prophylaxis C1 inhibitor in almost all cases and may lower the threshold at which danazol is replaced with lanadilumab
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Not currently used but if replaces C1 inhibitor then should largely confirm to NHS commissioning policy on C1 concentrate

• How does healthcare resource use differ between the technology and current care?	Not currently used and should be similar to C1 inhibitor concentrate maintenance although there is a danger that almost all HAE patients may “choose” to go onto this therapy and this may be facilitated by their doctors
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics only as this is a high cost therapy but use to monitored to ensure that resource use, rescue therapy and prescribing of other treatments is greatly reduced. Questions about whether icatibant needs to be prescribed in those on lanadilumab must be answered before approval is given otherwise cost effectiveness is not assured
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Allergy depts are already monoclonals for asthma and urticaria and immunology depts already administering SC immunoglobulins and therefore no real investment required unless there is considerable increase in numbers ie 2000 patients in 20 centres receiving SC injections every 2 wks equates to 100 patients treated additionally in each centre ie 50 per wk or 10/ day will then require 2 full time nurses in each centre.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Depending on cost effectiveness and long-term safety profile this technology would be self-administered every two – four weeks and provide effective prophylaxis against angioedema attacks. It is likely that almost all patients with HAE will eventually want to have this treatment because of the unwarranted adverse publicity against Danazol.
• Do you expect the technology to increase length of life more than current care?	Unlikely as there are no longer any deaths from HAE when patients are treated with Danazol

• Do you expect the technology to increase health-related quality of life more than current care?	Very likely as the alternative to using this technology is to use either recombinant or plasma derived C1 inhibitor concentrate which require much more frequent administration and often is in short supply.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This Technology is only licensed for and being considered for HAE types 1 and 2 but may also help those with type 3 disease and those with recurrent idiopathic angioedema
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	For those on danazol who currently take a daily tablet this technology will require considerable increases in resources to train patients in the use of SC injections although some may already have been trained in administration of icatibant which is also administered SC. The long term benefit and safety are not well understood and therefore regular follow-up will continue to be required monitoring for side effects and control of disease.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It is possible that some patients will be less well controlled and compliance with self-administration of a SC injection will need to be monitored. If the attack severity or frequency increases then both compliance and efficacy will need to reviewed and the subject advised to use alternative treatments.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial	This is certainly innovative and represents the first targeted monoclonal therapy for HAE with a treatment interval of up to 4 weekly.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes for the reasons outlined above
• Does the use of the technology address any particular unmet need of the patient population?	In patients that remain uncontrolled or are unable to take anabolic steroids this technology provides a suitable alternative that is more convenient than CI-inhibitor concentrate which is administered 3x weekly.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	It is unclear whether the benefits of danazol which historically has eliminated deaths from HAE will also be seen with lanadelumab – only time will tell
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	No there have been no head to head studies with danazol the standard therapy in UK practice or with C1 - inhibitor administered prophylactically which is given to those with refractory disease
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Frequency and severity of angioedema attacks, use of rescue therapy and additional healthcare resource use – largely covered by the trials
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The trials were too short to predict long term benefits ie reduction in mortality
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not aware of any

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The reduction in mortality and laryngeal angioedema attacks with danazol is not widely appreciated or spoken of. However, before danazol was introduced there was a significant mortality associated with this condition which has been eliminated in countries using danazol.
21. How do data on real-world experience compare with the trial data?	The trials compared this technology with placebo but in the real world this would not be the case where most would be on danazol which would have substantially reduced the frequency and severity of attacks in the control arm.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Patients other than those with HAE types 1 and 2 are also likely to benefit eg those with type 3 HAE and those with idiopathic angioedema which is severe and recurrent are not addressed in this scope and have a disorder which affect quality of life to a similar degree
22b. Consider whether these issues are different from issues with current care and why.	Current care is not effective in those not considered by this technology ie type 3 HAE and those with idiopathic angioedema as these patients rely only on rescue therapy and cannot be given any form of prophylaxis.
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- lanadelumab is an innovative therapy and the first monoclonal for HAE
- Lanadelumab can be administered less frequently than all currently available treatments
- It appears effective compared to placebo with a good safety profile although trials have been of short duration and there are no head to head comparisons with current standard therapies
- There is a danger that the hype with this new treatment will encourage those currently well controlled on danazol to be switched without adequate data on long term cost effectiveness data
- We do not understand whether treatment with lanadelumab will lead to long term reductions in mortality as have been seen with danazol

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Rachel Annals**
2. Are you (please tick all that apply):	☐ / a patient with the condition? ☐ a carer of a patient with the condition? ☐ / a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	HAE UK
4. Did your nominating organisation submit a submission?	☐ / yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ / yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ / I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I have experienced HAE attacks since the age of 2 years. I was only diagnosed at the age of 15 after years of weekly/fortnightly severe abdominal attacks. Having such frequent attacks meant I missed a lot of school and struggled with friendships because I missed a lot of social events and group activities. Before diagnosis my parents took me to see many different consultants and specialist doctors to try and find out what was wrong with me. I tried many different diets, eliminating different foods because the doctors could only assume I had a severe allergy to something, but could never work out what it was. At the age of 15 I saw another new doctor who mentioned HAE and decided to test for it, and I finally had my diagnosis. Because of its hereditary nature, other members of my family were tested, and my sister, brother, father and grandmother were also found to have HAE, although they were largely symptom free at that time. My great grandmother, who had passed away not long before my diagnosis, we believe also

	had HAE because she used to suffer severe facial swellings, but she was always told the swellings were an allergic reaction. Thankfully they never spread to her larynx. After my diagnosis I was prescribed androgens and they worked so well that it enabled me to live a normal life, passing my exams, completing college and securing a full-time job. I had breakthrough attacks every few months, but it was a huge improvement and I felt normal. After 17 years taking androgens, and in consultation with my HAE consultant, I stopped taking them to start a family. My consultant had arranged to have plasma derived C1 available for treatment as and when required. Whilst this treatment was good, the inconvenience it caused by having to have it administered in hospital was huge and it started to impact on my work and social life; I was worried about travelling too far from my local hospital for fear of having an attack and not being able to get back quick enough for treatment. This caused me to become quite anxious and I would regularly cancel social activities for fear of having an attack and being unable to get home. My attacks are mostly abdominal and can come on extremely quickly, sometimes as quick as 10 minutes. After two appeals, in 2014, I was finally accepted to self-administer my C1 at home, and this was a huge life changer for me. My attacks are now approximately every four days but having the medication at home, or on my person, means I can carry on my life as normal. It can be a little inconvenient having to carry medication with me in case of an attack and having to take time out or cancel arrangements at the last minute to enable me to find a quiet place to self-administer, but often it starts to work within 30 minutes and I can continue as normal. Having HAE can cause difficulties and is inconvenient at times, but I now do not let it stop me from enjoying my life, playing sports, managing a busy family and travelling all over the world.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Some find it frustrating because they may not have access to the same treatments as others they know with HAE. Those with access to home therapy feel happy with the treatment but still find it difficult because it can be time consuming, or they treat on demand so are unable to treat until an attack is already present, which by then is affecting their day-to-day activities
10. Is there an unmet need for patients with this condition?	Psychological support. HAE can be a difficult condition to live with and often patients miss out on social activities, holding down a full-time job, feel excluded from peer groups and struggle to maintain a fully normal life when dealing with frequent attacks. Even more so for patients who cannot self-administer acute attack medication themselves and have to attend A&E departments for treatment, as this often involves long waits and having to explain the condition to a doctor who has little or no knowledge of HAE
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	The chance to be attack free, which would highly improve the quality of life of HAE patients, not only physically but also emotionally.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Some patients have a fear of needles so could be worried or fearful of this treatment. Also, the time it takes to be fully in your system and working effectively may mean patients think it isn't working for them.

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	

Key messages
16. In up to 5 bullet points, please summarise the key messages of your statement: • I have personal experience of living with HAE from an early age • I embrace new treatments that may give myself and other HAE patients a better quality of life • This new treatment could improve the quality of life for myself and many HAE patients, allowing us to lead a normal life with less worry of attacks • •

Thank you for your time.

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Lanadelumab for preventing recurrent attacks of hereditary angioedema

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

Andrew walker declares consultancy work for Takeda and SHIRE who make Lanadelumab, but no previous work on this medicine or indication.

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Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contribution of authors

Andrew Walker, Elisabet Jacobsen and Graham Scotland acted as health economists for this appraisal: critiqued the cost-effectiveness evidence, checked the economic model, and conducted further sensitivity analyses. Lorna Aucott acted as statistician: critiqued the statistical methods, checked the numerical results, analyses, tables, and figures related to the review of the clinical effectiveness evidence. Clare Robertson acted as systematic reviewer: critiqued the company's definition of the decision problem, the clinical effectiveness evidence and methods for identifying relevant studies. Richard Herriot acted as clinical advisor: provided clinical advice and general guidance. Miriam Brazzelli acted as lead for the project and with Graham Scotland coordinated the ERG's involvement. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

ADA	Antidrug antibody
AE	Adverse event
AE-QoL	Angioedema Quality of Life Questionnaire
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Asparatate transaminase
C1-INH	C1 esterase inhibitor
CS	Company submission
EMA	European Medicines Agency
EQ-5D-5L	5-level EQ-5D
ERG	Evidence review group
HEA	Hereditary angioedema
HR	Hazard ratio
HRQOL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IOS	Icatibant Outcomes Survey
ITT	Intention-to-treat
IV	Intravenous
LYG	Life-years gained
LTP	Long-term prophylaxis
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Pharmacodynamic
PK	Pharmacokinetic
QALY	Quality adjusted life year
Q2W	Every 2 weeks
Q4W	Every 4 weeks
SAE	Serious adverse event
SC	Subcutaneous
SE	Standard error
SERPIN	Serine protease inhibitor

SPC	Summary of product characteristics
STP	Short-term prophylaxis
TEAE	Treatment-emergent adverse event
TLV	Tandvårds- och läkemedelsförmånsverket

1 Summary

Hereditary angioedema (HAE) is a rare genetic disorder affecting between 1/50,000 and 1/100,000 people in the UK. People with HAE experience angioedema attacks, involving unpredictable tissue swelling and a range of accompanying symptoms depending on the bodily location of the attack. HAE attacks are broadly categorised as laryngeal, abdominal and peripheral (e.g. hands and feet). Laryngeal attacks can be life-threatening due to restricted airway and asphyxiation. Five deaths due to angioedema (hereditary and acquired) were reported in England and Wales by the Office of National Statistics for 2017. Acute HAE attacks have a substantial impact on quality of life and functioning, both in terms of symptoms and ongoing fear of attack. The unpredictable nature of HAE attacks can cause persistent depression and anxiety. Patients may also experience detrimental impacts on their education and careers due to school/work absenteeism and work/activity impairment, which can worsen with increased frequency of attack and/or increased pain associated with attacks. Carers and family members can also be negatively affected by the condition.

People with HAE also experience a quality of life burden associated with treatment, especially intravenous (IV) administration. IV treatments can be required from a minimum of twice a week to a maximum of four times per week. Direct injection-related side effects (e.g. rash/erythema, infusion site pain) are more common with a higher frequency of treatment administration.

1.1 Critique of the decision problem in the company submission

The company's description of the decision problem appears generally accurate and appropriate. The ERG considers also the company's description of current service provision accurate.

1.1.1 Population

The NICE final scope for this appraisal specified the population as people aged 12 years and older with HAE. The company submission (CS) addresses people aged 12 years and older with Type I or II HAE who have at least one angioedema attack every four weeks. The company's rationale for deviating from the final scope is because the

main evidence presented in the CS is from one trial, HELP-03, which was limited to a narrower patient population.

1.1.2 Intervention

The intervention in both the NICE final scope and the CS is lanadelumab (Takhzyro). Lanadelumab is indicated for the routine prevention of HAE attacks and is available as a subcutaneously injectable solution that can be self-administered by patients or caregivers, following training in injection technique by a healthcare professional. Lanadelumab is not intended for the treatment of acute attacks. European Medicines Agency (EMA) marketing authorisation for lanadelumab was approved in November 2018.

1.1.3 Comparator

The comparators in the NICE final scope are C1 esterase inhibitors (C1-INHs), attenuated androgens and anti-fibrinolytics. The comparator addressed in the CS is limited to plasma-derived C1-INHs (Cinryze IV and Berinert IV). The company state that they did not consider subcutaneous (SC) Cinryze as this is not licensed or available in the UK. The company rationale for not considering attenuated androgens and anti-fibrinolytics is that lanadelumab is intended for patients who are not controlled with or who are not suitable for oral prophylactic treatment. Other treatments such as non-plasma derived C1-INH (Ruconest) were also deemed unsuitable by the company due to feedback from clinical experts which indicated [redacted] in the UK at present. The ERG is of the opinion that the comparators considered in the CS are appropriate; however, the ERG clinical advisor notes that the use of Ruconest in clinical practice is likely to increase in the near future.

1.1.4 Outcomes

The company submission included all the outcomes listed in the NICE final scope and reports additional outcomes: time to first attack, high morbidity attacks in the treatment period (severe, hospitalised, haemodynamically significant or laryngeal), proportion of responders with a >50% reduction in attack rate, proportion of responders with a 100% reduction in attack rate and mean attack-free days.

1.1.5 Other relevant factors

The company notes that, unlike attenuated androgens, lanadelumab does not impact on a woman's ability to have children as there is no associated risk of virilisation to the female foetus. The company also note that lanadelumab is not based on human or animal products. Both factors are relevant to direct or indirect discrimination, either on the basis of sex or religion.

1.2 Summary of clinical effectiveness evidence submitted by the company

The main evidence presented by the company for the effectiveness of lanadelumab is from the HELP-03 trial. HELP-03 was an international phase 3 multicentre, randomised, double-blind, placebo-controlled trial that evaluated SC lanadelumab for long-term prophylactic (LTP) treatment of acute attacks in 125 patients with Type I or II HAE. Participants were randomised to receive placebo (n=41) or one of three lanadelumab groups: 150mg every four weeks (n=28), 300mg every four weeks (n=29) and 300mg every two weeks (n=27). Because the current licence for lanadelumab is for the 300mg dose, the company did not present data for the 150mg dose in the CS. The primary efficacy endpoint of HELP-03 was the number of investigator-confirmed HAE attacks during the 26-week treatment period.

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See erratum

Participants who completed HELP-03 were given the option to enter the ongoing open-label extension study, HELP-04, and those participants who consented to join HELP-04 were termed rollover patients (n=109). Rollover patients (n=109) received their first 300mg SC lanadelumab dose on Day 0 and then did not receive another dose until their first HAE attack, at which point they received 300mg lanadelumab every two weeks thereafter. HELP-03 participants who chose not to participate in HELP-04 were followed-up for eight weeks. Patients who did not participate in HELP-03 were also invited to enrol in HELP-04. These non-rollover patients (n=103) included some people who were receiving another prophylactic therapy. Non-rollover participants received 300mg SC lanadelumab every two weeks regardless of their first HAE attack. Participants will receive their last dose on day 350 (maximum of 26 doses) and will then be followed-up for four weeks. The interim 6-month results are presented in section B.2.6, Document B of the CS. Data from HELP-04 were not used to populate the economic model.

A Phase Ib study, DX-2930-02 was presented as supporting evidence to inform the indirect treatment comparison (ITC). This was a multicentre, randomised, double-blind, multiple-ascending dose study that compared SC lanadelumab with placebo/on-demand standard care in 37 people. There were four lanadelumab groups: Lanadelumab 30mg q2w (n=4), Lanadelumab 100mg q2w (n=4), Lanadelumab 300mg q2w (n=5), Lanadelumab 400mg q2w (n=11). These data were not included in the economic model because, according to the company, they are superseded by the HELP-03 trial and few participants received the relevant lanadelumab dose.

The key results of the clinical effectiveness evidence indicate that in HELP-03 both lanadelumab 300mg treatment groups met the primary endpoint and showed statistically significant and clinically meaningful reductions (>50% HAE attacks) in the number of attacks during the treatment period compared with placebo. Compared with placebo, lanadelumab 300mg q2w and 300mg q4w reduced investigator confirmed attacks by 80.9% and 73.1%, respectively (p<0.001 for both). All rollover patients in HELP-04 continued to experience a reduction in mean attack rate from baseline over 182 days. Lanadelumab rollover patients experienced an [redacted] total reduction in attacks per month from baseline, while placebo rollover patients experienced a reduction of [redacted] in mean attack rate from baseline. Non-rollover patients who received lanadelumab 300mg q2w in HELP-04 also showed reductions in the number of HAE attacks per month over 6 months (182 days), irrespective of previous LTP. The baseline mean of [redacted] attacks per months decreased to [redacted] attacks per month, corresponding to a reduction in attack rate of [redacted]

SUPERSEDED

See erratum

Lanadelumab was favoured compared with placebo for all secondary endpoints in HELP-03. No significant differences were observed between landelumab and placebo for EQ-5D-5L scores over the HELP-03 treatment period , although significant improvements in AE-QoL scores were observed for lanadelumab from Day 0 to Day 182 (total AE-QoL score least square mean change placebo [redacted] lanadelumab [redacted].

Generally, lanadelumab was well-tolerated in HELP-03 in terms of adverse events and in keeping with the known safety profile. A total of 4 patients across the lanadelumab groups experienced four serious TEAEs compared with none in the

placebo group. According to the company, none of these events was considered related to the lanadelumab treatment. One patient in the lanadelumab 300mg q2w arm and three patients in the lanadelumab 300mg q4w treatment arm were hospitalised due to AEs. The company did not consider these events treatment-related. No placebo participants experienced an adverse event of special interest (AESI), pre-defined as hypersensitivity reactions and disordered coagulation, and only 5 lanadelumab participants experienced eight AESIs.

The most frequently reported TEAEs were [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients), [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients), [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients), [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients) and [redacted] of lanadelumab-treated patients compared with [redacted] in the placebo-treated arm). Similarly, the most commonly reported treatment related TEAEs in the 300 mg lanadelumab arms were [redacted] Overall, [redacted] patients in lanadelumab treatment arms and [redacted] patients in the placebo arm had related TEAEs. Ten (11.8%) lanadelumab-treated and two (4.9%) placebo-treated patients had at least one treatment-emergent antidrug antibody (ADA)-positive sample during the treatment period; all antibody titres were low (range: 20–1,280). One patient in the placebo arm and one patient in the lanadelumab 300mg q4w arm discontinued treatment due to a TEAE. No deaths were reported in the study. Adverse events were not used by the company to inform the economic model.

SUPERSEDED
See erratum

The only study eligible for comparison with HELP-03 was CHANGE, which tested C1-INH IV against placebo using a cross-over design. The ERG agrees with the company that currently this is the only available source of evidence. A Bayesian NMA of fixed effect models was performed using data from the HELP-03 study and the CHANGE cross-over study. The outcomes assessed in the NMA were attack rate and time to first attack after Day 0 and Day 70. The treatment comparisons showed that patients treated with lanadelumab (300mg q2w and 300mg q4w) had lower attack rates than patients receiving placebo and an improvement in the relative risk of

attack compared with those treated with C1-INH IV. In particular, for patients treated with lanadelumab 300mg q2w compared with those receiving placebo, the attack rate ratio [redacted], which indicates [redacted] attack rate reduction. For patients treated with lanadelumab 300mg q4w compared with those receiving placebo, the rate ratio was [redacted] which indicates a [redacted] attack rate reduction. Similarly, the rate ratio for lanadelumab 300mg q2w compared with C1-INH IV is [redacted] which indicates that patients treated with lanadelumab had a [redacted] reduction in attack rate compared with patients treated with C1-INH IV. The rate ratio for lanadelumab 300mg q4w compared with C1-INH IV was [redacted] which corresponds to a [redacted] reduction in attack rate compared with patients receiving C1-INH IV. For patients treated with C1-INH IV compared with those receiving placebo the rate ratio was [redacted]

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

SUPERSEDED

From the evidence provided by the HELP-03 study, lanadelumab has been shown to benefit patients with HAE during the 26-week treatment period when compared with placebo. This is especially true for participants treated with the 300mg q2w dose. There is also some evidence that lanadelumab is also more effective than the only other comparison treatment C1-INH IV from the CHANGE study. The ERG is satisfied that the methods used to assess both the HELP-03 trial itself and the indirect comparison with CHANGE using NMA are appropriate; however, whether this evidence could be considered sufficient still needs to be determined.

See erratum

1.4 Summary of cost effectiveness submitted evidence by the company

The company's economic case positioned the medicine within its marketing authorisation, in those who are not controlled with or are not suitable for oral prophylactic treatment. They further noted that they expect lanadelumab to be used in patients who would otherwise be considered for treatment with C1-INH prophylaxis. On this basis, the company made the case that oral prophylaxis was not a relevant comparator, and focused on comparison with intra-venous C1-INH prophylaxis. The C1-INH comparator was a weighted average of two branded medicines available on the NHS in England: Cinryse (IV) and Berinert (IV). The proportion on each medicine was based on recent prescribing data (although both medicines can also be used to treat attacks, so the volumes are not only for prophylaxis).

The company used a simple model to estimate lifetime NHS costs and QALYs. This had two states, alive and dead, with each cycle in the 'alive' state reflecting the proportion of time spent experiencing an attack. In the base-case all attacks were considered as one homogeneous experience, with an average EQ-5D utility for attack and attack free taken from a published Swedish study. The use of an external source of utility values was justified by the company on grounds that too few EQ-5D observations in HELP-03 coincided with attacks. The company also included a utility benefit in the model for subcutaneous administration versus IV infusion, which was derived from a literature review. Lanadelumab is self-administered by subcutaneous injection every 2 or 4 weeks at home, while C1-INH is self-administered by IV infusion at least twice per week.

To predict the pattern and number of attacks over time the company fitted Poisson regressions independently to each treatment arm of HELP-03, and included the baseline attack rate and attack rate in the last 28 day period as covariates. The company used this regression approach to estimate and extrapolate the attack rate per 28 day period in the relevant lanadelumab arms (300mg every two weeks, and 300mg every 4 weeks) and the placebo arm of HELP-03. The company then used the regression based predictions directly to model the attack rate per cycle for patients on lanadelumab, with an adjustment for the proportion of patients assumed to switch from the higher every two weeks dose (q2w) to the lower every 4 weeks (q4w) dose. To model the per cycle attack rate in the C1-INH arm, the company applied the rate ratio for C1-INH versus placebo, derived from an indirect treatment comparison, to the extrapolated placebo arm attack rate from HELP-03.

No impact on mortality was assumed and UK population values for age-sex specific mortality were applied. In line with the RCT patients were assumed to be 41 years old when starting prophylaxis.

In terms of costs, the company base case analysis included drug acquisition costs, adverse event costs, and costs related to the treatment and management of acute attacks. Costs of acute attacks included drug treatment costs, hospitalisation costs and accident and emergency costs. Fixed proportions of attacks were assumed to require

treatment and hospitalisation, but the drug treatment costs for acute attacks did vary by treatment arm [redacted] However, lanadelumab is not indicated for treating acute attacks so the company used data on the treatment of attacks in the HELP-03 RCT, excluding treatments that would not be used in the NHS.

In terms of lifetime costs of medicines, the modelling assumed that 44.4% and 76.9% of those in the lanadelumab arm would switch from the q2w dose to the lower q4w dose from month 6 and month 12 respectively. These are the proportions of patients who remained attack free on lanadelumab 300mg q2w over 6 months, and between day 70 and day 182 of the HELP-03 study, respectively. The assumption being that those who remain attack free on the higher dose will be switched in clinical practice to the lower dose. It was assumed that the proportion on the lower dose would remain stable beyond 12 months at 76.9%. It was also assumed that a small proportion of patients (8.8%) would discontinue treatment by month seven in both arms of the model, based on the observed proportion in HELP-03. However, the original model only used this discontinuation proportion to adjust the treatment costs, and not the attack rates applied in the model. Beyond cycle seven, it was assumed all patients would remain on their assigned prophylactic treatment for life. Longer term discontinuation due to loss of efficacy wasn't explored in the company's originally submitted economic model.

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In the company base case lanadelumab dominated C1-INH prophylaxis, with a substantial cost saving [redacted]) being the main driver of a high incremental net monetary benefit (£470k at a threshold of £30,000 per QALY). [redacted] of the difference in costs is explained by costs of treating attacks ([redacted] attributable to differences in treatments and [redacted] to differences in hospitalization costs). The difference in prophylaxis medicine costs accounts for 14%. The reported QALY gain for lanadelumab was modest in comparison ([redacted], with >70% being attributable to the utility increment for subcutaneous administration and the remainder due to less time spent with attacks.

The company model predicts that over a lifetime, patients on C1-INH will experience 526 attacks, of which 315 will be moderate or severe, and 62 will require

hospitalisation. With lanadelumab, the equivalent figures are 172, 103 and 20. This equates with a 67% reduction in the number of attacks experienced.

The company provided results of one-way sensitivity analysis which showed the NMB to be most sensitive to uncertainty surrounding the parameter estimates for the covariates included in the Poisson regressions for the placebo arm and the landelumab q4w arm of HELP-03. These inputs are key determinants of the predicted attack rate in the respective arms of the model. Scenario analyses provided by the company demonstrated a substantial increase in incremental NMB when the dosing frequency of C1-INH was [redacted] (assuming no change in efficacy), and a sizeable reduction in NMB when the attack rate in the lanadelumab arm was estimated by applying rate ratios from the indirect comparison to the predicted attack rate in the placebo arm of HELP-03. Further scenario analyses provided by the company in response to clarification questions further illustrated the sensitivity of the incremental NMB to the percentage of patients assumed to switch to the lower q4w lanadelumab dose, and the percentage of the C1-INH cohort assumed to be on Berinert.

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See erratum

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG identified several issues with the company's original model and base case analysis.

- The initial model structure provided by the company did not appear to account for expected changes in attack rates for those discontinuing treatment (on lanadelumab or C1-INH prophylaxis), did not allow for treatment switching (from lanadelumab to C1-INH), and did not explore the potential impact of longer-term loss of efficacy and discontinuation in the lanadelumab arm. The ERG therefore requested some structural changes to the model that would allow these issue to be explored.
- The arm of the economics model representing 'usual care' differs from the published NHS England Commissioning Policy for C1-INH in several ways. These include: criteria for starting prophylaxis with C1-INH; the definition of a clinically significant attack; the criteria for reducing frequency of use of C1-INH and criteria for stopping C1-INH prophylaxis. In the company's response

to the ERG's clarification questions, the company defended the base case because it said clinical practice did not fully align with the policy and clinicians anticipated that NHS policy was likely to be revised.

- The ERG also have some concern, given the NHS commissioning policy for C1-INH, that in certain circumstances 'usual care' may involve 'no prophylaxis' for a minority of patients. The company declined to provide an ICER against this alternative, saying it did not represent the proposed positioning of lanadelumab and was outside NICE scope. For illustrative purposes the ERG explored the impact of constructing a 'no prophylaxis' arm based on the placebo arm of the RCT, which suggests the cost per QALY for C1-INH and for lanadelumab versus 'no prophylaxis' is likely above usually accepted thresholds.

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- The company base case uses the Poisson regressions fitted independently to the lanadelumab arms of HELP-03 to extrapolate attack rates in the landelumab arm of the model, whilst estimating the attack rate in the C1-INH arm relative to the predicted attack rate based on the placebo arm of HELP-03. This approach leads to a 67% reduction in attacks for landelumab versus C1-INH in the model, when the rate ratios for lanadelumab versus C1-INH from the NMA are consistent with a [redacted] reduction in attacks (after accounting for the proportion of patients on each dose of lanadelumab).

See erratum

- The assumption that 76.9% of the patients in the lanadelumab arm will remain on the lower q4w dose from month 12 onwards appears speculative to the ERG, and was not thoroughly tested in the sensitivity analysis originally provided in the company submission.
- C1-INH is available as two branded medicines Cinryze and Berinert. In the base case these have [redacted] and [redacted] market share respectively, but this is uncertain and results are sensitive to changes in the distribution, particularly if applied in combination with other changes.
- Validation of the predictions of the model for C1-INH were confined to clinical specialist opinion in the context of an advisory board meeting. No validation was made against external data on the observed use of these medicines for reductions in attacks compared to baseline, changes in doses, quality of life impacts, etc.

- In the company model, the costs of treating attacks was estimated differently according to the prophylaxis received; this worked in favour of lanadelumab. The proportions of patients with attacks attending A&E and subsequently admitted are uncertain. The cost used for in-patient admissions seemed inappropriate and produced a cost that was very high for an assumed 1-day stay (excluding drug costs).
- The company chose not to use EQ-5D data from the HELP-03 RCT in the economics model because it does not capture the disutility of attacks. However, switching to an alternative source involved using lower 'without attack' values than the RCT data suggested. The alternative study used had some strengths, but the values came from a self-selected sample of Swedish patients recalling quality of life during attacks that are classified by severity scale with some differences to the RCT definitions (but applied as though they were the same). Disutility of attacks was assumed to only depend on severity, but the location on the body may also be important. In response to an ERG clarification question the company said patients and clinicians had told them this was less important and they could not include it in the model due to lack of data. Overall, the approach to estimating the disutility of attacks had very limited impact on the cost-effectiveness results.
- Disutility of iv administration was also included but rolled several possible sources of disutility into one. The ERG's preference would have been to model them separately: for example, one element was the problem of infusion site reactions, but data are available on how common this is, and duration of utility loss could have been estimated. Instead, the study used for base-case values had several issues, the main one being the poor match between the regimes valued in utility terms and the regimes for C1-INH and lanadelumab.

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1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The attack rates in the company's economic model are based on randomised data, synthesised within a network meta-analysis, which provides relatively robust data on comparative effectiveness of the alternative prophylactic treatments (at least in the short-term) when considering the rarity of the disease.

The model considers the appropriate costs and health benefits, in line with the NICE reference case.

1.6.2 Weaknesses and areas of uncertainty

The two main studies used in this submission (HELP-03 and CHANGE) are small. With regard to HELP-03, while benefits of the 300mg q2w dose over the placebo were observed, the sample size did not allow for sub-group analyses or adjustment for any of the usual patients' characteristics.
Likewise, the small sample size issue impacted on the NMAs. Only fixed effect models could be used to estimate the difference between lanadelumab and the best comparator treatment, C1-INH IV.

Furthermore, there is uncertainty with regard to the evidence provided by the two studies included in the NMA. The studies had very different designs (HELP-03 was a 4-arm parallel study, CHANGE was a crossover study), which would impact especially with respect to the structure of the SEs from the two designs.

While the ERG has been able to verify the results of the NMA for 'attack rate', only the Wood et al.'s adapted SEs for the log HRs for were provided for the 'time to first attack' at 0-182 days and 70-182 days. It has not been possible for the ERG to verify the original HRs based on any adjusted models for either of these outcomes.

As is often the case, the economic modelling relied on short term data to extrapolate expected differences in costs and health benefits over the life-time of treated patients. This inevitable requires a number of uncertain assumptions – as highlighted above.

Whilst the company provided a range of sensitivity analysis that helped identify which factors were the main 'drivers' of the economics results, the ERG believe further scenarios were required to fully explore uncertainty in the model results

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

In addition to the further analysis provided by the company. The ERG conducted some further analysis of its own using the revised model that the company provided in response to the clarification letter. The revised model provided the functionality to

assume that patients discontinuing landelumab would switch to a C1-INH or no prophylactic treatment, and that those discontinuing C1-INH would receive no prophylactic treatment. It also allowed for the attack rate and treatment costs for those discontinuing to be adjusted in line with the assumed next treatment, and removed the subcutaneous administration benefit for those discontinuing lanadelumab. Using this revised model, the ERG preferred an alternative base case which assumed the following changes to the company base case:

- No patients on C1-INH prophylaxis discontinue treatment, whilst the 8.8% observed to discontinue lanadelumab in HELP-03 would in practice switch to receiving a C1-INH.
- The proportion discontinuing lanadelumab incur the cost of C1-INH and the corresponding attack rate, and cease to receive the utility benefit of subcutaneous administration. In implementing the above, the ERG also corrected an apparent error in the company's revised model, relating to a formula used to adjust the acute attack treatment costs for the proportion switching from lanadelumab to C1-INH.
- Hospitalisation for acute attacks incurs a lower admission cost based on the reference cost for a non-elective short stay for the HRG WJ11, identified by mapping from the ICD10 code for HAE Types I and II.
- The attack rate for those on lanadelumab is estimated by applying the rate ratios versus placebo (from the NMA) to the predicated placebo attack rate in HELP-03. This is for consistency with the approach used to estimate the attack rate for C1-INH in the model, and consistency with the relative effects of lanadelumab versus C1-INH as estimated from the NMA.

Lanadelumab remained dominant in this alternative base case, but with reduced cost savings [redacted]), a reduced QALY gain ([redacted]), and a reduced incremental NMB (348,380). From this alternative base, the cost-effectiveness conclusions were also more sensitive to changes in the percentage of patients assumed to switch to the q4w dose in the lanadelumab arm, and the percentage of the C1-INH arm on Berinert. Under plausible combinations of these two important parameters, such as 60% switching to q4w and 60% on Berinert, lanadelumab ceased to be cost saving, with an ICER above accepted thresholds. The result of this model was also sensitive to the

assumption that no one discontinues to no prophylactic treatment in the C1-INH arm. This results in lower proportion of patients being on long-term prophylaxis in the C1-INH arm compared to the lanadelumab arm, and the economic case for lanadelumab is heavily dependent on comparison with this high cost comparator. Further exploratory scenarios comparing both C1-INH and lanadelumab to a no prophylactic treatment arm (based on the placebo arm of HELP-03), further illustrate the reliance of the economic case on comparison with C1-INH.

Given the uncertainties in the economic case, the ERG believe the following points require careful consideration by the committee:

1. Which approach to use for estimating attack rates in the lanadelumab arms of the model (q2w and q4w): direct regression estimates or rate ratios from the NMA applied to the placebo arm attack rate? The ERG prefers the latter because the model then generates a percentage reduction in attacks that is consistent with the effect for lanadelumab versus C1-INH derived from the NMA.

2. What to assume with respect to discontinuation rates in each arm, and what treatment follows discontinuation. The important issue is whether provision of lanadelumab results in more people being on long-term prophylaxis than would be otherwise be the case with C1-INH.

3. What treatment costs to apply for acute attacks, particularly hospitalisation costs.

4. The percentage switching to the less frequent q4w lanadelumab dose in the long-run. The ERG believe this is a highly uncertain and influential parameter, which can change the conclusion of the economic evaluation from positive to negative within a plausible range.

5. The percentage on the C1-INH Berinert as opposed to Cinryze, which is also important and becomes much more so when it interacts with changes in the proportion of lanadelumab patients switching to less frequent doses (see point above).

6. The potential relevance of a ‘no prophylaxis’ comparator for a small number of patients who are not suitable for or not adequately controlled on oral prohylaxis, but

who may otherwise manage with just on-demand treatment with C1-INH or icatibant treatment for acute attacks.

2 Background

2.1 Critique of company's description of underlying health problems

The company's description of hereditary angioedema (HAE) in terms of prevalence, symptoms and complications appears generally accurate and appropriate to the decision problem. HAE is a rare genetic disorder affecting between 1/50,000 and 1/100,000 people in the UK [1] and involves inherited or spontaneous mutations in the gene encoding C1-INH (SERPING1). [2-4] The C1-INH protein is a serine protease inhibitor (SERPIN) and is the major inhibitor of contact system proteases (plasma kalllikrein and coagulation factor XIIa). Mutations in the SERPING1 gene cause dysregulation in the kallikrein-kinin system, resulting in activity excess of kallikrein, and over-production of bradykinin, ultimately leading to increased vascular permeability and localised symptoms associated with angioedema.

There are three types of HAE. [2, 3] Types I and II are due to genetic mutation in SERPING1 and account for almost all HAE cases (Type I accounts for ~85% of all HAE cases and Type II accounts for ~15% of all HAE cases). Type III HAE is associated with normal C1-INH and is much rarer than Types I and II.[5] The company submission focuses on Types I and II only. The company report data from international Icatibant Outcomes Survey (IOS), where the average age of UK patients was 42.9 years and 39.7% were male. People first experience symptoms at a mean age of 11.3 years [6] but there can be a delay between initial symptom presentation and diagnosis. The mean age of people at diagnosis in the UK is 21.5 years.[6]

People with HAE experience angioedema attacks, involving unpredictable tissue swelling. The company report data from a study conducted in Hungary, which showed that while 30% of attacks have recognisable triggers, the majority occurred spontaneously and can affect any part of the body. The ERG believes these data are generalizable to the UK population. [7, 8] HAE attacks are broadly categorised as laryngeal, abdominal and peripheral, e.g. hands and feet. The company cite data from a UK audit of 376 patients reporting that the annual attack rate for laryngeal, abdominal and peripheral attacks as 4% (0.5 per patient), 38% (5 per patient) and 58% (8 per patient) respectively.[7] Laryngeal attacks can be life-threatening due to restricted

airway and asphyxiation.[9-11] In a German cohort of 728 patients, 70/214 deaths were due to asphyxiation associated with laryngeal attack, 90% of which were experienced in undiagnosed patients. [10] In an Italian survey of approximately 1000 patients, five deaths due to asphyxiation due to laryngeal attacks were reported in patients who received on-demand therapy.[12] Five deaths due to angioedema (hereditary and acquired) were reported in England and Wales by the Office of National Statistics for 2017. [13] Undiagnosed HAE patients experience poorer survival from laryngeal attacks compared with diagnosed HAE patients (mean age at death is 40.8 years compared with 72 years).[6, 10]

Acute HAE attacks have a substantial impact on quality of life and functioning, both in terms of symptoms and ongoing fear of attack. The company submission lists a range of symptoms that can accompany swelling depending on the bodily location of the attack in the CS on page 19, Document B:[8, 14]

Swelling and other symptoms can worsen over 12 to 36 hours and can spread to other sites. In the IOS study, the median duration of untreated attacks was 72 hours and, for UK patients, 65.5% of HAE were classed, in terms of their impact on daily activities, as either severe or very severe and. 26.1% were moderate prior to treatment. 8.5% were mild or have very mild interference with daily activities.[6]

The company note that patients may also experience detrimental impacts on their education and careers due to school/work absenteeism, with work/activity impairment worsening with increased frequency and/or painful attacks and severity of depression/anxiety. [6, 7, 15, 16] In a UK audit, 37% of 223 adult patients rated the impact of HAE on their quality of life as moderate or severe and, of the 29 parents who responded on behalf of their children, 14% reported that the impact was moderate, although none reported the impact as severe.[7] The company reports data from several international studies that have shown people with HAE experience poorer quality of life compared with the general population, and that quality of life for patients diminishes with increased frequency of attacks.[2, 15, 17-22] Given the unpredictable nature of HAE attacks, the fear of attack, along with symptoms and impact of attacks on daily activities during attacks, can cause persistent depression and anxiety. The company cite two surveys [15, 23] that have reported that 38% to 49.9% of HAE patients

have clinically meaningful anxiety and 14% to 24% of patients have clinically meaningful depression. Severity of anxiety and depression increased with increasing attack frequency.[15] Furthermore, the company notes that carers and family members can also be affected by the condition, in terms of missed work/leisure time to care for patients [16] and the emotional impact associated with the unpredictability of attacks.[24]

People with HAE also experience a quality of life burden associated with treatment(s), especially IV treatment administration. The company notes that C1-INH IV treatments can be required from a minimum of twice a week to a maximum of four times per week, with studies reporting that 62% of patients have difficulties finding a usable vein or getting the infusion to work properly and 50% prefer oral, SC or non-IV administration to more invasive IV treatments.[25, 26] Direct injection-related side effects (e.g. rash/erythema, infusion site pain) are more common with a higher frequency of treatment administration.[27]

2.2 Critique of company's overview of current service provision

The ERG considers the company's description of current service provision is accurate. There are three main treatment strategies for HAE: treatment of acute attacks, short-term prophylaxis (STP) of attacks before known triggers and long-term prophylaxis (LTP) to reduce the need for acute treatment. The company submission (CS) covers LTP for people with Type I and II HAE only. Under current UK guidance, [11] LTP treatment is considered for people who experience recurrent oral therapy-unresponsive attacks of angioedema.

The company outlines current LTP treatment options:

- Oral prophylaxis:
    - Attenuated androgens (e.g. danazol and oxandrolone). These treatments do not have marketing authorisations in the UK for HAE.
    - Anti-fibrinolytics (e.g. tranexamic acid)
- Plasma-derived IV C1 esterase inhibitors (C1-INHs):
    - Cinryze intravenous (IV)
    - Cinryze subcutaneous (SC). Not licensed or available in the UK

    - Berinert IV (licensed for acute treatment and short-term prophylaxis but not LTP)
- Recombinant C1-INH:
    - Ruconest is a non-plasma-based C1-INH produced by recombinant DNA technology in the milk of transgenic rabbits. It has a licence for acute use only.

NHS England guidance recommends oral prophylaxis as the first-line treatment option. C1-INH is only considered as a LTP option for patients who fail or are intolerant of oral prophylaxis, or who are contraindicated for oral prophylaxis. Patients must also be under the care of a specialist team and treatment eligibility should be discussed with at least three consultant immunologists.[11]

The company state that anti-fibrinolytics may be used in a minority of patients (including in children, for whom it is the recommended first choice [3, 11, 13] but are not recommended by the World Allergy Organization (WAO) or European Academy of Allergy and Clinical Immunology guidelines (EAACI). WAO and EAACI recommend C1-INH as first-line therapy and oral attenuated androgens as second-line therapy for LTP, which the company notes is opposite to UK guidance.[3] The company also note that Berinert 2000/3000 SC is licensed, but is not commercially available, in the UK. For this reason, it was not included in the company's decision problem. The ERG agrees with the company that Berinert SC is not an appropriate comparator for this submission.

The company presents the current clinical care pathway in Figure 1, Document B of the CS and this is reproduced by the ERG as Figure 1 in this report.

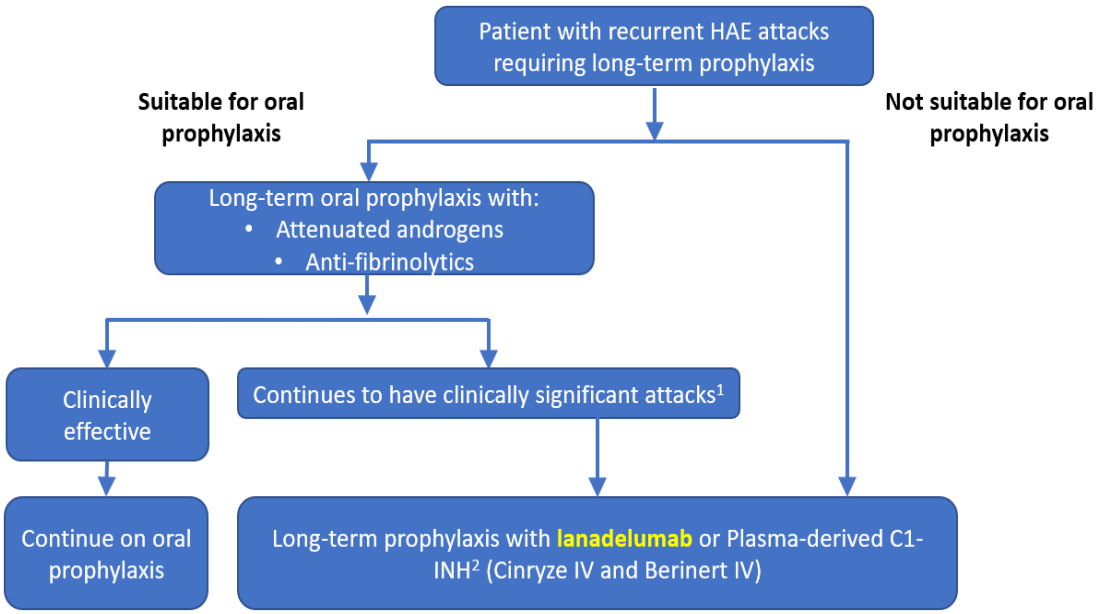

Figure 1 Current clinical pathway for long-term prophylactic management of HAE in the UK and proposed positioning of lanadelumab

3 Critique of company's definition of decision problem

3.1 Population

The NICE final scope for this appraisal specified the population as people aged 12 years and older with HAE. The CS addresses people aged 12 years and older with Type I or II HAE who have at least one angioedema attack every four weeks. The company state the rationale for the difference in scope is because the key evidence base for lanadelumab is the HELP-03 trial,[28] which was limited to the narrower patient population. The HELP-03 trial is the main evidence provided in the CS. The ERG agrees that the population addressed in the company's decision problem matches the HELP-03 trial population. The NICE final scope for perspectives for outcomes, presented in Table 2, Document A, of the CS refers to "all direct health effects, whether for patients or, when relevant, carers." While the company present information to highlight the detrimental impact HAE has on the quality of life for carers, the company stated in their response to the ERG's clarification queries that no utility data exist that quantify the impact of HAE on caregivers, or how lanadelumab might lead to improvements in quality of life for caregivers.

3.2 Intervention

The intervention in both the NICE final scope and the CS is lanadelumab. Lanadelumab (TAKHZYRO) is indicated for the routine prevention of HAE attacks in patients aged 12 years and older. It is available as a subcutaneously injectable solution and may be self-administered by patients or administered by caregivers at home following training in subcutaneous injection technique by a healthcare professional. One vial contains 300mg of lanadelumab in 2 mL solution. Each vial, which should be stored in a refrigerator (2°C to 8°C), is intended for single use only. The summary of product characteristics (SPC) [29] states that the recommended starting dose is 300mg every fortnight. A dose reduction of 300 mg lanadelumab every 4 weeks may be considered in patients who remain attack free following initial treatment. [29] Lanadelumab is not intended for the treatment of acute attacks. European Medicines Agency (EMA) marketing authorisation for lanadelumab was approved in November 2018. [29-31] The company provide further details of the technology in Table 2 of the

CS, Document B, pages 13-14, and this table is reproduced by the ERG as Table 1 below.

Table 1 Technology being appraised

UK approved name and brand name	Lanadelumab (brand name: Takhzyro; alternative identifier: DX-2930; ATC code: B06AC05)
Mechanism of action	Fully human monoclonal antibody (immunoglobulin G1/ κ-light chain) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. [29] Lanadelumab provides sustained inhibition of plasma kallikrein-induced proteolysis of high-molecular-weight kininogen (HMWK), which produces cleaved HMWK (cHMWK) and bradykinin, a potent vasodilator that increases vascular permeability resulting in HAE attacks and associated swelling and pain. Patients with HAE due to C1-INH deficiency or dysfunction have increased plasma kallikrein activity, both during and in between HAE attacks. In inhibiting active plasma kallikrein proteolytic activity and subsequently limiting bradykinin generation, lanadelumab directly addresses the mechanism of HAE attacks. [29] Furthermore, lanadelumab is highly selective and binds active kallikrein without binding similar proteins (e.g. other serine proteases the pre-kallikrein zymogen, factor X1a and tissue kallikrein 1 gene). [29]
Marketing authorisation/CE mark status	The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) granted a positive opinion on 18 October 2018 with marketing authorisation expected in December 2018. [29, 30, 32] Lanadelumab was designated as an orphan medicinal product on 9 October 2015 and reviewed under EMA's accelerated assessment programme. [33]
Indications and any restriction(s) as described in the summary of product characteristics (SPC)	The indication is: [29] Lanadelumab is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.

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Method of administration and dosage	Lanadelumab is administered by subcutaneous (SC) injection, by the patient themselves or by a caregiver, only after training on SC injection technique by a healthcare professional. [29] The injection should be restricted to the recommended injection sites: the abdomen, the thighs, and the upper outer arms; rotation of the injection site is recommended. [29] The recommended starting dose is 300mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction of 300mg lanadelumab every 4 weeks may be considered, especially in patients with low weight.
Additional tests or investigations	In case of a severe hypersensitivity reaction, discontinue lanadelumab and institute appropriate treatment. No other tests or investigations are required. [29]
List price and average cost of a course of treatment	A list price of £12,420 per 300 mg vial has been approved by the Department of Health and Social Care. Expected cost of treatment is [redacted] in the first year, followed by an annual cost of [redacted] thereafter, based on the PAS price.
Patient access scheme (if applicable)	A confidential PAS has been submitted and is expected to be approved prior to the first appraisal committee meeting. This arrangement provides lanadelumab to NHS patients at a [redacted] discount to list price.
Key: C1-INH, C1 esterase inhibitor; CHMP, Committee for Medicinal Products for Human Use; CHO, Chinese hamster ovary; EMA, European Medicines Agency; HAE, hereditary angioedema; PAS, patient access scheme; SC, subcutaneous.	

3.2.1 Safety

The SPC reports that the most common (52.4%) adverse reactions associated with lanadelumab use are injection site reactions such as injection site pain, erythema and bruising, of which 97% were of mild intensity, and 90% resolved within 1 day after onset with a median duration of 6 minutes.

Table 1 in the SPC lists the adverse reactions commonly associated with lanadelumab in 84 participants with HAE in the HELP-03 study [28] and this is reproduced by the ERG as Table 2 in this report. The frequencies of reactions are defined as very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 2 Adverse reactions reported with lanadelumab

System organ class	Adverse drug reaction	Frequency
Immune system disorders	Hypersensitivity[a]	Common
Nervous system disorders	Dizziness	Common
Skin and subcutaneous tissue disorders	Rash maculo-papular	Common
Musculoskeletal and connective tissue disorders	Myalgia	Common
General disorders and administration site conditions	Injection site reactions[b]	Very common
Investigations	Alanine aminotransferase increased	Common
	Aspartate aminotransferase increased	Common

a. Hypersensitivity includes: pruritus, discomfort and tingling of tongue.
b. Injection site reactions include: pain, erythema, bruising, discomfort, haematoma, haemorrhage, pruritus, swelling, induration, paraesthesia, reaction, warmth, oedema and rash.

Dedicated studies have not been conducted in special patient populations but hepatic and renal impairment in not expected to affect exposure to lanadelumab or the safety profile. Dose adjustment is not required in patients with hepatic or renal impairment or in patients aged older than 65 years.

3.3 Comparators

The NICE final scope specifies the comparators for lanadelumab as C1-INHs, attenuated androgens and anti-fibrinolytics. The comparator addressed in the CS is limited to plasma-derived C1-INHs (Cinryze IV and Berinert IV). The company state the rationale for the narrowed scope because "Oral prophylactic treatments (attenuated androgens and anti-fibrinolytics) are not considered comparators given that lanadelumab would be used for patients who are not controlled with or who are not suitable for oral prophylactic treatment." Other treatments such as non-plasma derived C1-INH (Ruconest) were deemed unsuitable for inclusion by the company due to feedback from clinical experts which indicated [redacted] in the UK at present. [redacted] The company state that Cinryze IV and Berinert IV are

appropriate comparators for this submission. Cinryze IV is licensed for prophylactic treatment of HAE and based on clinical feedback and hospital dispensing data, [redacted] Cinryze SC is not licensed or available in the UK. The ERG agrees with the company that oral treatments are not suitable comparators for lanadelumab in this patient population. The ERG also agrees that Cinryze IV and Berinert IV are appropriate comparators.

3.4 Outcomes

The outcomes stated in the NICE final scope are: frequency of angioedema attacks, severity of angioedema attacks, need for acute treatment, mortality, adverse effects of treatment and health-related quality of life (HRQOL). The company present several additional outcomes that were reported in the HELP-03 trial. These include time to first attack, high morbidity attacks in the treatment period (severe, hospitalised, haemodynamically significant or laryngeal), proportion of responders with a ≥50% reduction in attack rate, proportion of responders with a 100% reduction in attack rate and mean attack-free days.

3.5 Other relevant factors

The company notes that attenuated androgens can affect a woman's fertility due to the risk of virilisation to the female foetus, and women of childbearing age should be advised to use effective, non-hormonal methods of contraception. Lanadelumab does not impact on a woman's ability to have children. The company state that consideration should be given to the treatment options available to women who have completed their family to ensure any recommendations as a result of this appraisal do not directly or indirectly discriminate on the basis of sex.

The company state that the three C1-INHs included in the scope are derived from human plasma (Cinryze IV and Berinert IV) or rabbit DNA (Ruconest). Lanadelumab is not based on human or animal products. The company state that consideration should be given to people who are unwilling to receive human or animal products to ensure recommendations do not directly or indirectly discriminate on the basis of religion.

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

The CS provides details of the searches that were undertaken to identify the studies included in the clinical effectiveness review. The major relevant databases searched were: MEDLINE, EMBASE, Medline In-Process, The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Cochrane Central Register of Controlled Trials and the Health Technology Assessment Database. Searches were conducted in June 2017 and updated in July 2018. The initial searches were not limited by date of publication. In addition, the company searched health technology assessment and trial registry websites, as well as several conference proceedings from 2016 to 2019. The company also conducted bibliographic searches of key systematic reviews and meta-analyses.

The search strategies are documented in full in Appendix D of the CS and are reproducible. The search strategies are fit for purpose, including both relevant controlled vocabulary and text terms with appropriate use of Boolean operators.
In general, the ERG considers the literature searches conducted by the company were comprehensive and adequate.

4.1.2 Inclusion criteria

The company conducted a systematic review to assess the efficacy and safety of long-term prophylaxis therapies of Type I and II HAE. The company provides details of their inclusion criteria in Table 7, Appendix D of the CS (reproduced as Table 3 below). The company states that two reviewers assessed the eligibility of potentially relevant studies and that any uncertainty regarding study inclusion were resolved by a third independent reviewer. The company identified 60 articles from 10 randomised controlled trials (RCTs) and 39 articles from 28 non-RCTs. The company excluded [redacted] androgen studies (danazol and methyl testosterone) as they were not considered relevant comparators. [redacted] plasma-derived C1-INH SC studies (two Cinryze and two Haegarda) were excluded by the company as no plasma-derived C1-INH SC

treatments are approved in the UK for LTP treatment, and [redacted] non-plasma derived C1-INH (Ruconest) [redacted] was excluded as [redacted]. Furthermore, [redacted]. The main source of clinical evidence considered in the CS consists of two lanadelumab studies (DX-2930-02 and HELP-03) and [redacted] plasma-derived C1-INH [redacted], used to inform the indirect treatment comparison (ITC). In general, the ERG considers the methods used for identifying relevant evidence appropriate and agrees with the company's selection of relevant randomised evidence. Nevertheless, the ERG clinical advisor notes that there is a suggestion that the use of non-plasma derived C1-INH (Ruconest) is likely to increase in the near future due to the fact that it is now recommended by the Scottish Medicines Consortium (in August 2018) and the All Wales Medicines Strategy Group (in November 2018) for the treatment of acute angioedema. The ERG agrees with the company, however, that the exclusion of the Ruconest study is unlikely to impact the clinical effectiveness results presented in the CS due to the small number of participants and follow-up. A further unpublished, ongoing, open label long-term extension study (HELP-04) is presented by the company as evidence for the use of lanadelumab.

The other non-RCT studies identified by the systematic review were not used for comparative effectiveness. At clarification, the company explained that "*given we have higher quality RCT evidence for the only relevant comparator, C1-INH intravenous … that was used to inform the NMA [network meta-analysis]… the non-RCT evidence was considered not to be required*." Whilst the ERG agrees that, in principle, RCTs provide the most reliable evidence on the clinical effectiveness of an intervention, it is questionable whether they are the best study design to capture long-term or uncommon adverse events. [34] Therefore, for completeness of evidence, it would have been desirable if the company had presented any relevant non-RCT studies, especially as the open-label extension for the CHANGE trial, which was included in the network meta-analysis (NMA), is one of the non-RCT studies that the company chose not to present in the CS.

Table 3 Eligibility criteria applied to the clinical evidence literature search

	Inclusion criteria	Exclusion criteria
Population	Patient with Type I and Type II HAE Any race Age: ≥12 years	Healthy volunteers Paediatric population (<12 years) Type III HAE Disease other than HAE
Interventions	Studies assessing all prophylactic therapies, either short-term or long-term (as mono- and/or combination therapy) such as: • Berinert • Cinryze (formerly Cetor) • Lanadelumab (DX-2930) • Attenuated androgens: • Danazol • Stanozolol • Oxandrolone • Methyl testosterone • Testosterone • Ruconest • Haegarda	• Non-pharmacological treatments such as fresh frozen plasma, solvent detergent plasma, antifibrinolytic agents etc. • Acute treatments such as icatibant (Firazyr), ecallantide (Kalbitor) • Surgery • Studies assessing interventions – not in the list
Comparators	No restrictions	None
Outcomes	No restrictions	None
Study design	• RCTs irrespective of blinding status • Non-RCTs • Observational studies • Single-arm studies • Cohort studies (both prospective and retrospective) • Long-term follow-up studies • Systematic reviews and meta-analyses of RCTs[a]/non-RCTs[a]	• Case reports, case series • Pharmacokinetic and economic studies • Preclinical studies • Reviews, letters and comment articles

	Inclusion criteria	Exclusion criteria
Language	Not limited by language of publication[b]	None
Key: C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; RCT, randomised controlled trial. **Notes:** a , Systematic reviews and meta-analyses of RCTs and non-RCTs will be included and flagged. Bibliographies of these systematic reviews will be screened to check if literature searches have missed any potentially relevant studies; b , These will be explored if sufficient evidence from English language studies have not been identified.		

4.1.3 Critique of data extraction

The company states that one researcher conducted data extraction using a data extraction form in Microsoft Excel. All data were checked and verified against the original source by a second researcher. While double data extraction is the current recommended method, [35] the ERG considers the data extraction methods used by the company to be adequate.

4.1.4 Quality assessment

The company conducted quality assessment using the NICE criteria for the assessment of bias in RCTs for HELP-03 and the Downs and Black checklist for HELP-04. [36 37] The ERG broadly agrees with the company that HELP-03 is a well-conducted trial at low risk of bias. The ERG also agrees with the company's quality assessment of the HELP-04 extension study. The company did not provide a quality assessment of the DX-2930-02 study. Overall, the ERG considers DX-2930-02 at low risk of bias but notes that the number of patients was small in all treatment groups (i.e., lanadelumab 30mg n=4; lanadelumab 100mg n=4; lanadelumab 300mg n=5; lanadelumab 400mg n=11; placebo n=13).

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the CRD criteria. Results are presented in Table 4.

Table 4 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

4.1.5 Evidence synthesis

The main evidence presented by the company is the HELP-03 trial [28] and the ongoing HELP-04 open label extension study. [38] The company indicates that HELP-03 is the only clinical study of lanadelumab versus placebo. Therefore, a meta-analysis of available evidence was deemed unfeasible. The primary efficacy endpoint of HELP-03 was the number of investigator-confirmed HAE attacks during the treatment period. A Phase Ib study, DX-2930-02 [39] is presented as supporting evidence to inform the indirect treatment comparison (ITC). The company explains that data from HELP-04 were not used to populate the economic model as the study is currently ongoing. However, interim 6-month results of HELP-04 are presented in section B.2.6 of Document B. The results from DX-29320-02 were also not included in the economic model because, according to the company, they are superseded by the HELP-03 trial. At clarification, the company stated that "*the DX-2930-02 study was a Phase Ib, 120-day dose finding study, which included just five patients on the approved 300mg dose of lanadelumab every two weeks and no patients treated every four weeks. All other patients (n=19) receving lanadelumab in study DX-2930-02 received non-approved doses of lanadelumab and were therefore, not relevant to the decision problem*." The ERG is of the opinion that it would have been useful to present data for the patients on the relevant lanadelumab dose, particularly for adverse events, but accepts that, due to the small number of participants, these data were unlikely to have altered the clinical effectiveness results presented in the CS.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

HELP-03 was an international phase 3 multicentre, randomised, double-blind, placebo-controlled trial that evaluated SC lanadelumab for LTP treatment of acute attacks in 125 patients with Type I or II HAE. Participants were randomised to receive placebo (n=41) or one of three lanadelumab groups: 150mg every four weeks (n=28), 300mg every four weeks (n=29) and 300mg every two weeks (n=27). The company clarifies that, because the current licence for lanadelumab is at the 300mg dose, the data for the 150mg dose are not presented in the CS. The ERG agrees that it is appropriate to only present data for the 300mg dose in this submission. Participants who completed HELP-03 were given the option to enter HELP-04 and those that consented were termed rollover patients. Rollover patients (n=109) received their first 300mg SC lanadelumab dose on Day 0 and then did not receive another dose until their first HAE attack, at which point they received 300mg lanadelumab every two weeks thereafter. HELP-03 participants who chose not to participate in HELP-04 were followed-up for eight weeks. Patients who did not participate in HELP-03 were also invited to enrol in HELP-04. These non-rollover patients (n=103) included some people who were receiving another prophylactic therapy. Non-rollover participants received 300mg SC lanadelumab every two weeks regardless of their first HAE attack. Participants will receive their last dose on day 350 (maximum of 26 doses) and will then be followed-up for four weeks.

DX-2930-02 was a phase Ib, multicentre, randomised, double-blind, multiple-ascending dose study that compared SC lanadelumab with placebo in 37 people with HAE. There were four active treatment groups: lanadelumab 30mg, 10mg, 300mg and 400mg. Lanadelumab was administered in a staggered dose-escalating fashion. Patients who experienced HAE attacks in the placebo group received standard care, on-demand treatment.

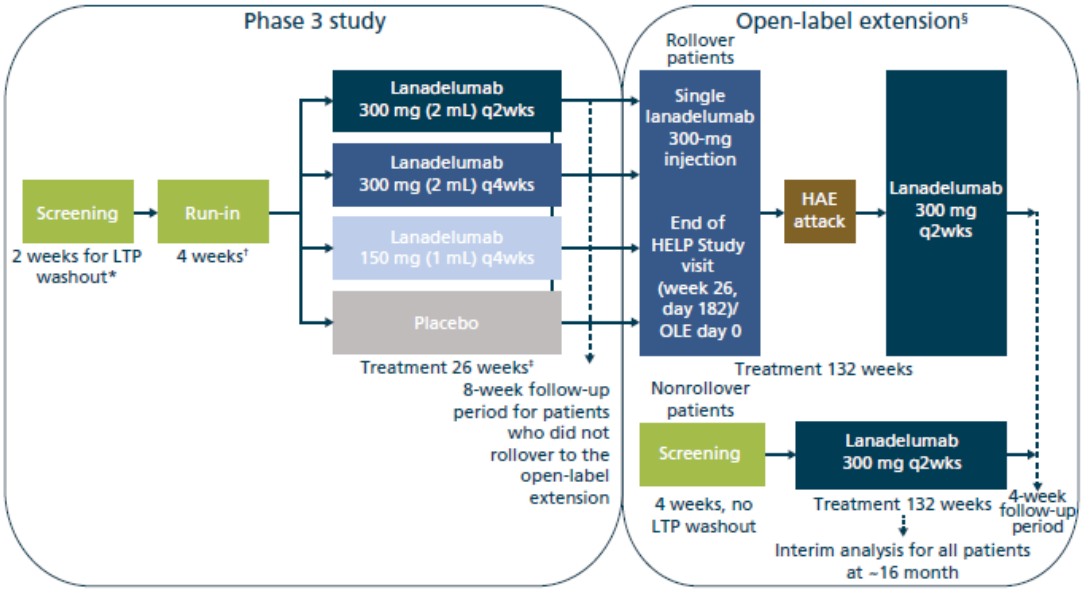
The company presents summaries of the HELP-03 and HELP-04 study design in Tables 4 and 5 and Figure 3 in Document B of the CS and these are reproduced by the ERG as Table 5 and Figure 2 in this report. The company also presents a summary of the DX-2930-02 study design in Table 6, Document B, of the CS and this is reproduced by the ERG as Table 6 below.

Table 5 Clinical effective evidence – HELP-03 and HELP-04

Study	**HELP-03: NCT02586805**		**HELP-04: NCT0274159661,**	
Study design	HELP-03 was a Phase III, multicentre, randomised, double-blind, placebo-controlled trial.		HELP-04 is an ongoing Phase III, multicentre, open-label, long-term safety and efficacy study.	
Population	People aged 12 years and older with hereditary angioedema Types I or II who have at least one angioedema attack in 4 weeks in the run-in period		HELP-03 rollover patients: Patients who completed the 26-week treatment period in HELP-03 and enrolled in the open-label extension study HELP-04 Non-rollover patients: Patients aged 12 years and older with HAE Types I or II who had a historical baseline attack rate of at least one attack per 12 weeks	
Intervention(s)	Lanadelumab 300mg q4w (n=29) Lanadelumab 300mg q2w (n=27) Lanadelumab 150mg q4w (n=28)		HELP-03 rollover patients (n=109): 300mg dose at Day 0 followed by 300mg q2w following first HAE attack. Non-rollover patients (n=103): 300mg dose at day 0 then 300mg q2w for the entire study.	
Comparator(s)	Placebo (n=41)		N/A	
Indicate if trial supports application for marketing authorisation	Yes	✓	Yes	
	No		No	✓
Indicate if trial used in the economic model	Yes	✓	Yes	
	No		No	✓
Rationale for use/non-use in the model	HELP-03 presents the pivotal, regulatory and clinical evidence in support of lanadelumab in the population directly relevant to the decision problem.		As HELP-04 is currently an ongoing study, it was therefore not used in the model.	
Reported outcomes specified in the decision problem	• **Frequency of angioedema attacks (attack rate during treatment period [Day 0 to**		N/A	

	Day 182]; between Day 14 and Day 182; and between Day 70 and Day 182) • Severity of angioedema attacks (number of patients with moderate or severe attacks during treatment period) • Need for acute treatment • Mortality • Adverse effects of treatment • Health-related quality of life	
All other reported outcomes	• Time to first attack after Day 0 and Day 70 • High morbidity attacks in treatment period (severe, hospitalised, hemodynamically significant or laryngeal) • Proportion of responders with a ≥50% reduction in attack rate • Proportion of responders with a 100% reduction in attack rate • **Mean attack-free days** (**Day 0 to Day 182**; Day 0 to Day 28; Day 0 to Day 84; **Day 70 to Day 182**)	• Long-term safety of lanadelumab • Long-term efficacy of in preventing HAE attacks over 132 weeks

Key: HAE, hereditary angioedema; N/A, not applicable; q2w, every 2 weeks; q4w, every 4 weeks.
Source: HELP-03 CSR (Shire. HELP Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]); Banerji et al., 2018 [28] NCT02741596 [40]; Riedl et al. 2017 [38]; Riedl et al., 2018 (Riedl MA BJ, Yang WH, Longhurst HJ, Magerl M, Hébert J, Martinez-Saguer I, on behalf of the HELP OLE Study investigators. Lanadelumab Reduces Hereditary Angioedema Attack Rate: Interim Findings From the HELP Open-label Extension Study. American College of Allergy, Asthma & Immunology Annual Scientific Meeting. Seattle, WA: USA, 2018 [Unpublished data])



Key: HAE, hereditary angioedema; LTP, long-term prophylaxis; q2wks, every 2 weeks; q4wks, every 4 weeks.
Notes: *, LTP washout only for patients ≥18 years of age; †, Run-in period could be shortened if the patient experienced ≥3 attacks before completion of 4 weeks; run-in period could be extended to 8 weeks if the patient did not experience any attacks during 4 weeks; ‡, Treatments administered as 2 separate 1-mL injections in the upper arm q2wks to maintain the blind; §, NCT02741596.
Source: Riedl et al. 2018 (Riedl MA BJ, Yang WH, Longhurst HJ, Magerl M, Hébert J, Martinez-Saguer I, on behalf of the HELP OLE Study investigators. Lanadelumab Reduces Hereditary Angioedema Attack Rate: Interim Findings From the HELP Open-label Extension Study. American College of Allergy, Asthma & Immunology Annual Scientific Meeting. Seattle, WA: USA, 2018 [Unpublished data])

Figure 2 HELP-03 and the open-label extension study HELP-04 study design

Table 6 Clinical effectiveness evidence – DX-2930-02

Study	DX-2930-02: NCT02093923				
Study design	DX-2930-02 was a Phase Ib, multicentre, randomised, double-blind, placebo-controlled, multiple-ascending-dose study.				
Population	People aged 12 years and older with hereditary angioedema Types I or II who had two or more attacks of angioedema per year, with at least one attack in the previous 6 months				
Intervention(s)	Lanadelumab 30mg q2w (n=4) Lanadelumab 100mg q2w (n=4) Lanadelumab 300mg q2w (n=5) Lanadelumab 400mg q2w (n=11)				
Comparator(s)	Placebo (n=13)				
Indicate if trial supports application for marketing authorisation	Yes		**Indicate if trial used in the economic model**	Yes	
	No	✓		No	✓
Rationale for use/non-use in the model	DX-2930-02, a Phase Ib study, was not used in the model as results from the Phase III HELP-03 study superseded it.				
Reported outcomes specified in the decision problem	N/A				
All other reported outcomes	• HAE attack rate per week • Safety				
Key: q2w, every 2 weeks **Source:** Banerji et al. 2017[41]					

The company states that the HELP-03 population are generally representative of the overall HAE population in terms of demographic and baseline disease characteristics. The company presents the baseline characteristics of the HELP-03 intention-to-treat (ITT) population in Table 8, Document B, of the CS and this is reproduced by the ERG as Table 7 in this report. The ERG agrees with the company that the treatment groups are balanced at baseline and the HELP-03 participants are representative of the overall UK HAE population. Two analysis populations are presented for HELP-03. All efficacy analysis were carried out on the ITT population, and were analysed according to the randomised treatment assignment. Safety, pharmacokinetic (PK), pharmacodynamic (PD) and QoL analyses were performed using the safety

population, defined by the company as all participants who received any dose of study treatment and were analysed according to treatment received.

Table 7 Baseline demographic and disease characteristics HELP-03: ITT population

Characteristics	Placebo	Lanadelumab				Placebo and Lanadelumab
	Placebo (n=41)	300mg q2w (n=27)	300mg q4w (n=29)	150mg q4w (n=28)	Total (all lanadelumab arms) (n=84)	Total (placebo and lanadelumab) (n=125)
Age (years)[a]						
Mean (SD)	40.1 (16.75)	40.3 (13.35)	39.5 (12.85)	43.4 (14.91)	41.0 (13.66)	40.7 (14.69)
Median (range)	42.4 (12, 70)	38.4 (15, 62)	40.7 (12, 59)	45.3 (16, 73)	42.7 (12, 73)	42.4 (12, 73)
Age categories (years)[a], n (%)						
<18	4 (9.8)	2 (7.4)	3 (10.3)	1 (3.6)	6 (7.1)	10 (8.0)
≥18 to <40	14 (34.1)	12 (44.4)	10 (34.5)	9 (32.1)	31 (36.9)	45 (36.0)
≥40 to <65	21 (51.2)	13 (48.1)	16 (55.2)	15 (53.6)	44 (52.4)	65 (52.0)
≥65	2 (4.9)	0	0	3 (10.7)	3 (3.6)	5 (4.0)
Sex, n (%)						
Male	7 (17.1)	12 (44.4)	10 (34.5)	8 (28.6)	30 (35.7)	37 (29.6)
Female	34 (82.9)	15 (55.6)	19 (65.5)	20 (71.4)	54 (64.3)	88 (70.4)
Race, n (%)						
White	39 (95.1)	26 (96.3)	23 (79.3)	25 (89.3)	74 (88.1)	113 (90.4)
Black or African American	2 (4.9)	1 (3.7)	6 (20.7)	1 (3.6)	8 (9.5)	10 (8.0)
Asian	0	0	0	2 (7.1)	2 (2.4)	2 (1.6)
BMI, kg/m^2						
Mean (SD)	27.5 (7.7)	26.9 (4.7)	28.1 (5.2)	31.0 (7.8)	28.7 (6.2)	28.3 (6.7)
Age at onset of angioedema, mean (years)						
Mean (SD)	11.2 (8.21)	15.0 (8.67)	14.6 (11.16)	12.0 (8.76)	13.8 (9.61)	13.0 (9.22)
Median (range)	8.0 (2, 41)	14.0 (2, 43)	12.0 (1, 49)	10.5 (1, 40)	12.5 (1, 49)	12.0 (1, 49)
HAE type, n (%)						

Characteristics	Placebo	Lanadelumab				Placebo and Lanadelumab
	Placebo (n=41)	**300mg q2w (n=27)**	**300mg q4w (n=29)**	**150mg q4w (n=28)**	**Total (all lanadelumab arms) (n=84)**	**Total (placebo and lanadelumab) (n=125)**
Type I	38 (92.7)	23 (85.2)	27 (93.1)	25 (89.3)	75 (89.3)	113 (90.4)
Type II	3 (7.3)	4 (14.8)	2 (6.9)	3 (10.7)	9 (10.7)	12 (9.6)
History of laryngeal attacks, n (%)						
Yes	27 (65.9)	20 (74.1)	17 (58.6)	17 (60.7)	54 (64.3)	81 (64.8)
No	14 (34.1)	7 (25.9)	12 (41.4)	11 (39.3)	30 (35.7)	44 (35.2)
Primary attack locations (combined)[b], n (%)						
Laryngeal	10 (24.4)	5 (18.5)	6 (20.7)	3 (10.7)	14 (16.7)	24 (19.2)
Abdominal	35 (85.4)	21 (77.8)	27 (93.1)	20 (71.4)	68 (81.0)	103 (82.4)
Peripheral	30 (73.2)	23 (85.2)	22 (75.9)	25 (89.3)	70 (83.3)	100 (80.0)
Primary attack locations, n (%)						
Laryngeal	0	0	0	0	0	0
Laryngeal/abdominal	0	1 (3.7)	0	0	1 (1.2)	1 (0.8)
Laryngeal/peripheral	1 (2.4)	1 (3.7)	0	0	1 (1.2)	2 (1.6)
Laryngeal/abdominal/peripheral	9 (22.0)	3 (11.1)	6 (20.7)	3 (10.7)	12 (14.3)	21 (16.8)
Abdominal	11(26.8)	3 (11.1)	7 (24.1)	3 (10.7)	13 (15.5)	24 (19.2)
Abdominal/peripheral	15 (36.6)	14 (51.9)	14 (48.3)	14 (50.0)	42 (50.0)	57 (45.6)
Peripheral	5 (12.2)	5 (18.5)	2 (6.9)	8 (28.6)	15 (17.9)	20 (16.0)
Number of attacks in the last month						
Mean (SD)	4.15 (3.978)	2.96 (2.794)	3.76 (3.512)	4.61 (5.953)	3.79 (4.310)	3.90 (4.192)
Median (range)	3.00 (0.0, 15.0)	2.00 (0.0, 12.0)	2.00 (0.0, 14.0)	3.00 (0.0, 30.0)	3.00 (0.0, 30.0)	3.00 (0.0, 30.0)
Number of attacks in the last 3 months						
Mean (SD)	11.46 (10.824)	7.67 (7.504)	9.93 (10.074)	12.61 (17.223)	10.10 (12.346)	10.54 (11.842)

Characteristics	Placebo	Lanadelumab				Placebo and Lanadelumab
	Placebo (n=41)	**300mg q2w (n=27)**	**300mg q4w (n=29)**	**150mg q4w (n=28)**	**Total (all lanadelumab arms) (n=84)**	**Total (placebo and lanadelumab) (n=125)**
Median (range)	8.00 (0.0, 44.0)	6.00 (0.0, 28.0)	5.00 (1.0, 42.0)	9.00 (0.0, 90.0)	6.50 (0.0, 90.0)	7.00 (0.0, 90.0)
Number of attacks in the last 12 months						
Mean (SD)	45.46 (43.441)	22.15 (18.172)	37.07 (35.516)	47.07 (68.607)	35.61 (46.520)	38.84 (45.595)
Median (range)	30.00 (0.0, 185.0)	20.00 (0.0, 72.0)	24.00 (1.0, 140.0)	34.00 (2.0, 365.0)	24.00 (0.0, 365.0)	24.00 (0.0, 365.0)
Run-in HAE attack rate (attacks/month)[c]						
Mean (SD)	4.02 (3.265)	3.52 (2.327)	3.71 (2.507)	3.22 (1.830)	3.48 (2.225)	3.66 (2.611)
Median (range)	3.00 (1.0, 14.7)	3.11 (1.0, 9.0)	3.00 (1.0, 10.5)	3.18 (1.0, 6.7)	3.00 (1.0, 10.5)	3.00 (1.0, 14.7)
Run-in HAE attack rate category (attacks/month)[c], n (%)						
1 to <2	12 (29.3)	7 (25.9)	9 (31.0)	10 (35.7)	26 (31.0)	38 (30.4)
2 to <3	8 (19.5)	6 (22.2)	5 (17.2)	3 (10.7)	14 (16.7)	22 (17.6)
≥3	21 (51.2)	14 (51.9)	15 (51.7)	15 (53.6)	44 (52.4)	65 (52.0)
Prior long-term prophylactic treatment category, n (%)						
C1-INH only	22 (53.7)	9 (32.1)	18 (62.1)	11 (40.7)	38 (45.2)	60 (48.0)
Oral therapy[d]	1 (2.4)	0	1 (3.4)	2 (7.1)	3 (3.6)	4 (3.2)
C1-INH and oral therapy[d]	1 (2.4)	3 (11.1)	1 (3.4)	1 (3.6)	5 (6.0)	6 (4.8)
No LTP use	17 (41.5)	16 (57.1)	9 (31.0)	13 (48.1)	38 (45.2)	55 (44.0)
Prior long-term prophylactic treatment, n (%)						
Androgens	1 (2.4)	0	0	2 (7.1)	2 (2.4)	3 (2.4)
Androgens, antifibrinolytics, C1-INH	0	1 (3.7)	0	0	1 (1.2)	1 (0.8)
Androgens, C1-INH	1 (2.4)	2 (7.4)	1 (3.4)	1 (3.6)	4 (4.8)	5 (4.0)

Characteristics	Placebo	Lanadelumab				Placebo and Lanadelumab
	Placebo (n=41)	**300mg q2w (n=27)**	**300mg q4w (n=29)**	**150mg q4w (n=28)**	**Total (all lanadelumab arms) (n=84)**	**Total (placebo and lanadelumab) (n=125)**
Anti-fibrinolytics	0	0	1 (3.4)	0	1 (1.2)	1 (0.8)
C1-INH only	22 (53.7)	9 (32.1)	18 (62.1)	11 (40.7)	38 (45.2)	60 (48.0)
No LTP use	17 (41.5)	16 (57.1)	9 (31.0)	13 (48.1)	38 (45.2)	55 (44.0)

Key: BMI, body mass index; C1-INH, C1 esterase inhibitor; CSR, clinical study report; HAE, hereditary angioedema; ITT, intent-to-treat; LTP, long-term prophylaxis; q2w, every 2 weeks; q4w, every 4 weeks; SD, standard deviation.
Notes: [a], Age is calculated as the difference between date of birth and date of informed consent, truncated to years; [b], Patients may be counted in more than one category; [c], Run-in HAE attack rate is calculated as the number of HAE attacks occurring during the run-in period divided by the number of days the patient contributed to the run-in period multiplied by 28 days. A month is defined as 28 days; [d], Oral therapy includes androgens and antifibrinolytics.
Source: HELP-03 CSR; (Shire. HELP Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]) Banerji et al., 2018. [28]

The company presents the baseline characteristics for the HELP-04 study in Table 9, Document B, of the CS and this is reproduced by the ERG as Table 8 below.

Following clarification from the ERG, the company confirmed a typographical error for the percentage of HELP-04 participants who were male in the non-rollover group. The ERG has inserted the correct value in Table 8 in this report. The company states that 92.9% of the HELP-04 participants were ongoing in the study at the time of the interim data analysis (data from 26th May 2016 to 1st September 2017). The ERG agrees with the company that the rollover and non-rollover groups are mainly similar in terms of their baseline characteristics. The ERG notes that there are fewer people aged 18 years or younger enrolled in the rollover group (7.3%) than in the non-rollover group (12.6%). In their clarification response, the company states that this difference is unlikely to cause any meaningful variation in the results. The company also explains that, due to the small numbers of people in this age category in both studies (HELP-03 and HELP-04), it was not feasible to perform a robust sub-group analysis from the Poisson regression for this age group. The company further notes that HELP-03 sub-group analyses did not identify age as being a key driver for treatment effect, indicating that any differences in efficacy for younger people would be minimal. The ERG notes that the baseline attack rate for HELP-04 is higher than the rate for HELP-03 patients. The HELP-04 safety population includes all patients who received any study drug after study entry.

Table 8 Baseline demographic and disease characteristics for open-label extension study HELP-04

Characteristic	Rollover Patients (n=109)	Non-rollover Patients (n=103)	Total (n=212)
Age, mean (SD) [years]	41.9 (14.7)	39.5 (16.7)	40.7 (15.7)
Age categories (years), n (%)			
<18	8 (7.3)	13 (12.6)	21 (9.9)
≥18 to <40	38 (34.9)	39 (37.9)	77 (36.3)
≥40 to <65	57 (52.3)	46 (44.7)	103 (48.6)
≥65	6 (5.5)	5 (4.9)	11 (5.2)
Sex, n (%)			
Male	34 (32.2)	35 (34.0)	69 (32.5)
Female	75 (68.8)	68 (66.0)	143 (67.5)
Race, n (%)			
White	99 (90.8)	99 (96.1)	198 (93.4)
Black or African American	8 (7.3)	2 (1.9)	10 (4.7)
Asian	1 (0.9)	0	1 (0.5)
Other	1 (0.9)	2 (1.9)	3 (1.4)
BMI, mean (SD) [kg/m^2]	28.3 (6.8)	28.4 (7.5)	28.4 (7.2)
Age at onset of angioedema, mean (SD) [years]	13.5 (9.5)	11.6 (7.3)	12.6 (8.6)
HAE type, n (%)			
Type I	100 (91.7)	89 (86.4)	189 (89.2)
Type II	9 (8.3)	12 (11.7)	21 (9.9)
Unspecified	0	2 (1.9)	2 (0.9)
History of laryngeal attacks, n (%)	67 (61.5)	63 (61.2)	130 (61.3)
Number of attacks in the last month, mean (SD)	3.8 (4.2)	2.9 (2.9)	3.4 (3.6)
Number of attacks in the last 12 months, mean (SD)	37.7 (46.0)	30.4 (34.2)	34.2 (40.7)

Characteristic	Rollover Patients (n=109)	Non-rollover Patients (n=103)	Total (n=212)
Run-in HAE attack rate (attacks/month)[a]			
Mean (SD)	3.52 (2.46)	2.55 (2.75)	3.05 (2.66)
Median (range)	3.00 (1.0, 14.0)	1.84 (0.0, 15.4)	2.00 (0.0, 15.4)
Baseline HAE attack rate category (attacks/month)[a], n (%)			
<1	0	25 (24.3)	25 (11.8)
1 to <2	35 (32.1)	39 (37.9)	74 (34.9)
2 to <3	19 (17.4)	11 (10.7)	30 (14.2)
≥3	55 (50.5)	28 (27.2)	83 (39.2)
Prior long-term prophylactic treatment category, n (%)			
C1-INH only	53 (48.6)	53 (51.5)	106 (50.0)
Oral therapy[b]	4 (3.7)	8 (7.8)	12 (5.7)
C1-INH and oral therapy[b]	5 (4.6)	2 (1.9)	7 (3.3)
No LTP use	47 (43.1)	40 (38.8)	87 (41.0)

Key: BMI, body mass index; C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; LTP, long-term prophylaxis; q2w, every 2 weeks; q4w, every 4 weeks; SD, standard deviation.
Notes: [a], Run-in HAE attack rate is calculated as the number of HAE attacks occurring during the run-in period divided by the number of days the patient contributed to the run-in period multiplied by 28 days. A month is defined as 28 days; [b], oral therapy includes androgens and antifibrinolytics.
Source: Lanadelumab AMPC Dossier (Shire. Lanadelumab AMPC dossier: Submission of Clinical and Economic Data Supporting Formulary Consideration of: TAKHZYROTM (lanadelumab-flyo). 2018 [Unpublished data]); Riedl et al. 2018 (Riedl MA BJ, Yang WH, Longhurst HJ, Magerl M, Hébert J, Martinez-Saguer I, on behalf of the HELP OLE Study investigators. Lanadelumab Reduces Hereditary Angioedema Attack Rate: Interim Findings From the HELP Open-label Extension Study. American College of Allergy, Asthma & Immunology Annual Scientific Meeting. Seattle, WA: USA, 2018. [Unpublished data])

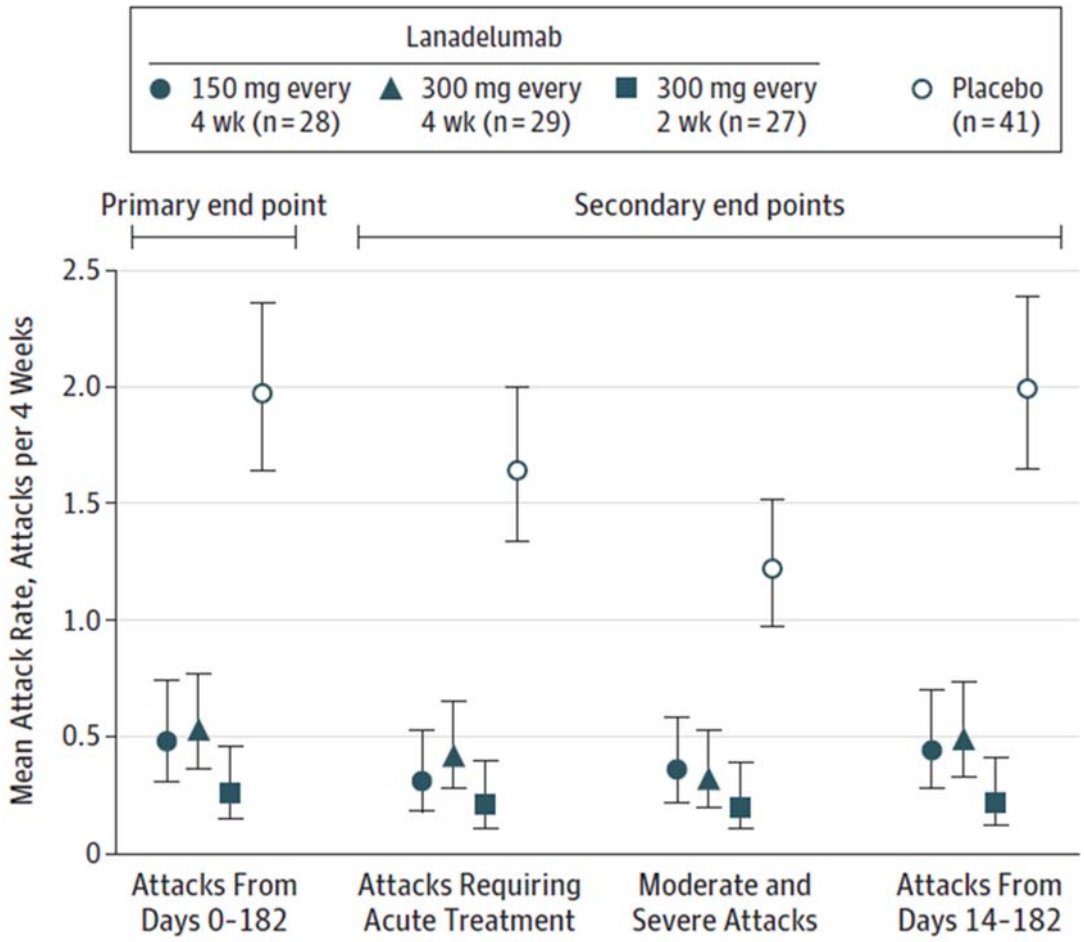
4.2.1 Primary endpoint – investigator-confirmed HAE attacks

Both lanadelumab 300mg treatment arms met the primary endpoint and showed statistically significant and clinically meaningful (reduction of >50% HAE attacks) reductions in the number of attacks during the treatment period compared with placebo. Compared with placebo, lanadelumab 300mg q2w and 300mg q4w reduced investigator-confirmed attacks by 86.9% and 73.3%, respectively ($p<0.001$ for both). Data for the primary endpoint analysis are presented in Table 12 and Figure 4, Document A of the CS, which are reproduced by the ERG as Table 9 and Figure 3 below. Sensitivity analyses are presented by the company in Appendix M of the CS and these show similar results to the primary analysis.

Table 9 Primary efficacy endpoint (investigator-confirmed HAE attacks) – ITT population

	Placebo (n=41)	Lanadelumab	
		300mg q2w (n=28)	300mg q4w (n=28)
Primary endpoint: number of investigator-confirmed HAE attacks from Day 0 to 182			
Run-in period HAE attack rate (attacks/4 weeks)			
Mean (SD)	4.022 (3.265)	3.519 (2.327)	3.711 (2.507)
Median (range)	3.00 (1.0, 14.7)	3.11 (1.0, 9.0)	3.00 (1.0, 10.5)
Treatment period HAE attack rate (attacks/4 weeks)			
Mean (SD)	2.455 (2.079)	0.309 (0.505)	0.604 (0.801)
Median (range)	1.69 (0.0, 8.3)	0.15 (0.0, 1.8)	0.45 (0.0, 2.9)
Model-based treatment period HAE attack rate (attacks/4 weeks)[a]			
LS mean (95% CI)	1.97 (1.640, 2.358)	0.257 (0.145, 0.458)	0.526 (0.358, 0.771)
% Change in mean attack rate versus placebo[b] (95% CI) Adjusted p-values[c]	N/A	-86.921 (-92.828, -76.150) <0.001	-73.271 (-82.379, -59.456) <0.001

Key: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; LS, least squares; q2w, every 2 weeks; q4w, every 4 weeks; SD, standard deviation.
Notes: [a], Results are from a Poisson regression model with fixed effects for treatment group (categorical) and normalised baseline attack rate (continuous), and the logarithm of time in days each patient was observed during the treatment period as an offset variable in the model. Pearson chi-squared scaling of standards errors was employed to account for potential over dispersion;
[b], % change in mean rate corresponds to 100% * (rate ratio - 1);
[c], Adjusted p-values are adjusted for multiple testing.
Source: HELP-03 clinical study report (Shire. HELP Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]); Banerji et al. 2017 (Banerji A, Riedl M, Bernstein J, et al. Lanadelumab for prevention of attacks in hereditary angioedema: results from the phase 3 HELP study. 2017 Annual Scientific Meeting of the American College of Allergy, Asthma and Immunology. Boston USA, 2017 [Unpublished data]); Banerji et al., 2018 [28]



Key: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; wk, week.
Note: Attack rates are model-based mean attacks per month, with a month defined as 4 weeks. The mean attack rate for each group is presented with error bars representing 95% CI.
Source: Banerji et al. 2018[28]

Figure 3 Primary and secondary endpoints by treatment group – ITT population

HAE attack rates in the long-term extension study HELP-04: Interim results

The company reports that rollover patients who received lanadelumab, and those that experience placebo in HELP-03 continued to experience a reduction in mean attack rate from baseline over 6 months (182 days). Lanadelumab patients experienced an [redacted] total reduction in attacks per month from baseline, while placebo patients experienced a reduction of [redacted] in mean attack rate from baseline. The company presents these data in Figure 10 and Table 20, Document B of the CS, which are reproduced as Table 10 below and Figure 11 in Appendix 1 of this report.

Table 10 Mean HAE attack rates reduction in rollover patients

	Rollover patients Study 03 treatment to Study 04 treatment				
	Placebo → 300mg q2w (n=33)	**300mg q2w → 300mg q2w (n=25)**	**300mg q4w → 300mg q2w (n=25)**	**150mg q4w → 300mg q2w (n=26)**	**All rollover patients (n=109)**
Mean HAE attack rate in attacks per month (SD)					
Baseline	3.81 (2.997)	3.47 (2.392)	3.54 (2.580)	3.18 (1.739)	3.52 (2.48)
HELP-03	2.39 (1.935)	0.26 (0.451)	0.54 (0.785)	0.44 (0.569)	1.01 (1.49)
HELP-04	0.39 (0.897)	0.19 (0.303)	0.47 (0.648)	0.19 (0.292)	0.31 (0.62)

Key: q2w, every 2 weeks; q4w, every 2 weeks; SD, standard deviation.
Source: Lanadelumab AMPC dossier (Shire. Lanadelumab AMPC dossier: Submission of Clinical and Economic Data Supporting Formulary Consideration of: TAKHZYROTM (lanadelumab-flyo). 2018 [Unpublished data])**;** Riedl et al. 2018 (Riedl MA BJ, Yang WH, Longhurst HJ, Magerl M, Hébert J, Martinez-Saguer I, on behalf of the HELP OLE Study investigators. Lanadelumab Reduces Hereditary Angioedema Attack Rate: Interim Findings From the HELP Open-label Extension Study. American College of Allergy, Asthma & Immunology Annual Scientific Meeting. Seattle, WA: USA, 2018 [Unpublished data])

The company reports that non-rollover patients who received landelumab 300mg q2w in HELP-04 also showed reductions in the number of HAE attacks per month over 6 months (182 days), irrespective of previous LTP. The baseline mean of [redacted] attacks per months decreased to [redacted] attacks per month, corresponding to a reduction in attack rate of [redacted] The company presents these data in Figure 11 and Table 21, Document B of the CS, which are reproduced and these are reproduced as Figure 12 and Table 49 in Appendix 1 of this report.

4.2.2 Secondary endpoints

The company presents secondary endpoint data for HELP-03 in Table 5, Document A, of the CS and this is reproduced by the ERG as Table 11 below. For all secondary endpoints, data favoured both lanadelumab groups compared with placebo and were statistically significant. The company maintains that results were also clinically meaningful. Moderate/severe investigator confirmed HAE attacks were also reduced for both rollover and non-rollover patients in the HELP-04 extension study and these

data are presented as Figure 12, Document B in the CS, and are reproduced by the ERG as Figure 4 in this report.

Table 11 Rank-ordered secondary efficacy endpoints – HELP ITT population

	Placebo (n=41)	Lanadelumab	
		300mg q2w (n=28)	300mg q4w (n=28)
1st rank secondary endpoint: number of investigator-confirmed HAE attacks requiring acute treatment from Day 0–182			
Run-in period HAE attack rate requiring acute treatment (attacks/4 weeks)			
Mean (SD)	3.596 (3.485)	3.110 (2.589)	3.460 (2.740)
Median (range)	[redacted]	[redacted]	[redacted]
Treatment period HAE attack rate requiring acute treatment (attacks/4 weeks)			
Mean (SD)	2.212 (2.156)	0.263 (0.505)	0.508 (0.793)
Median (range)	1.46 (0.0, 8.3)	0.00 0.0, 1.8)	0.15 (0.0 2.9)
Model based treatment period HAE attack rate requiring acute treatment (attacks/4 weeks)[a]			
LS mean (95% CI)	1.637 (1.337, 2.005)	0.208 (0.109, 0.396)	0.423 (0.276, 0.648)
% Change mean attack rate versus placebo[b] (95% CI) Adjusted p-values[c]		-87.299 (-93.494, -75.204) <0.001	-74.169 (-83.733, -58.983) <0.001
2nd rank secondary endpoint: number of moderate or severe investigator-confirmed HAE attacks from Day 0–182			
Run-in period HAE moderate or severe attack rate (attacks/4 weeks)			
Mean (SD)	2.341 (2.147)	2.169 (2.228)	2.576 (2.396)
Median (range)	1.93 (0.0, 9.3)	1.75 (0.0, 8.6)	1.93 (0.0, 7.6)
Treatment period HAE moderate or severe attack rate (attacks/4 weeks)			
Mean (SD)	1.418 (1.252)	0.246 (0.482)	0.374 (0.551)
Median (range)	1.22 (0.0, 6.5)	0.0 (0.0, 1.7)	0.0 (0.0, 2.3)
Model based treatment period moderate or severe HAE attack rate (attacks/4 weeks)[a]			
LS mean (95% CI)	1.216 (0.971, 1.522)	0.202 (0.106, 0.386)	0.325 (0.199, 0.529)
% Change mean attack rate versus placebo[b] (95% CI) Adjusted p-values[c]		-83.394 (-91.618, -67.099) <0.001	-73.285 (-84.316, -54.496) <0.001
3rd rank secondary endpoint: number of investigator-confirmed HAE attacks from Day 14–182			

	Placebo (n=41)	Lanadelumab	
		300mg q2w (n=28)	300mg q4w (n=28)
Day 14–182 HAE attack rate (attacks/4 weeks)			
Mean (SD)	2.342 (2.011)	0.307 (0.604)	0.558 (0.770)
Median (range)	1.66 (0.0, 8.2)	0.0 (0.0, 2.7)	0.33 (0.0, 3.0)
Model based HAE attack rate from day 14–182 (attacks/4 weeks)[a]			
LS mean (95% CI)	1.988 (1.652, 2.391)	0.218 (0.115, 0.414)	0.489 (0.326, 0.734)
% Change mean attack rate versus placebo[b] (95% CI) Adjusted p-values[c]		-89.008 (-94.325, -78.707) <0.001	-75.377 (-84.115, -61.833) <0.001

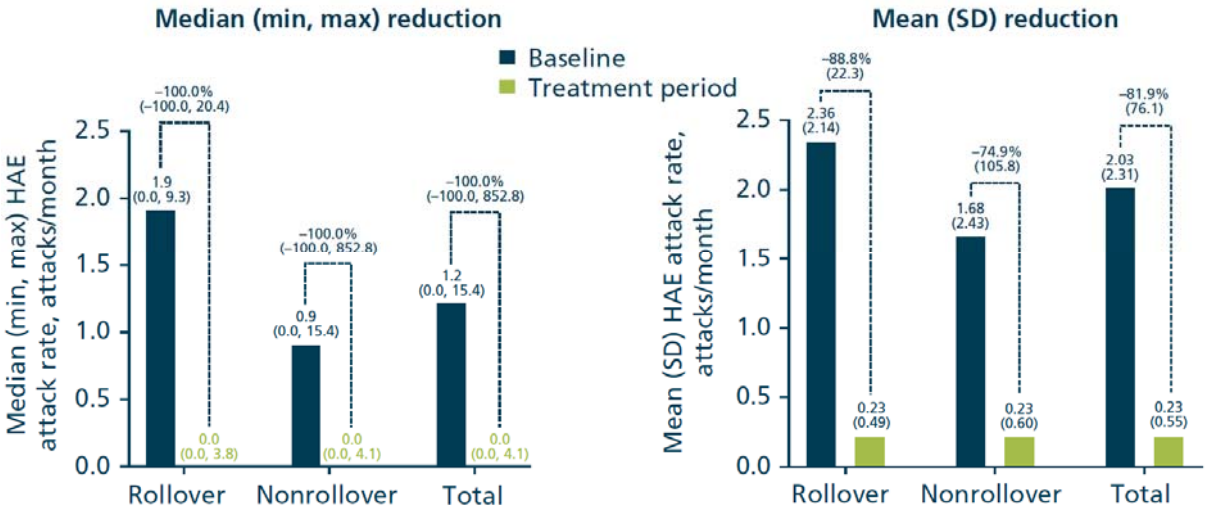
Key: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; LS, least squares; q2w, every 2 weeks; q4w, every 4 weeks; SD, standard deviation.

Notes: [a], Results are from a Poisson regression model with fixed effects for treatment group (categorical) and normalised baseline attack rate (continuous), and the logarithm of time in days each patient was observed during the treatment period as an offset variable in the model. Pearson chi-squared scaling of standards errors was employed to account for potential over dispersion;

[b], % change in mean rate corresponds to 100% * (rate ratio - 1);

[c], Adjusted p-values are adjusted for multiple testing.

Source: HELP-03 clinical study report (Shire. HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]); Banerji et al. 2017 (Banerji A, Riedl M, Bernstein J, et al. Lanadelumab for prevention of attacks in hereditary angioedema: results from the phase 3 HELP study. 2017 Annual Scientific Meeting of the American College of Allergy, Asthma and Immunology. Boston USA, 2017 [Unpublished data]); Banerji et al., 2018 [28]



Key: HAE, hereditary angioedema, SD, standard deviation.
Notes: *Baseline for the rollover population was defined as the number of investigator-confirmed HAE attacks occurring during the run-in period of the phase 3 HELP Study divided by the total number of days in the run-in period multiplied by 28 days. Baseline for the non-rollover population was defined as the historical rate of HAE attacks in the previous 12 weeks before screening divided by the number of days the patient contributed to the historical reporting period multiplied by 28 days. †Regular dosing period for rollover patients.
Source: Riedl et al. 2018 (Riedl MA BJ, Yang WH, Longhurst HJ, Magerl M, Hébert J, Martinez-Saguer I, on behalf of the HELP OLE Study investigators. Lanadelumab Reduces Hereditary Angioedema Attack Rate: Interim Findings From the HELP Open-label Extension Study. American College of Allergy, Asthma & Immunology Annual Scientific Meeting. Seattle, WA: USA, 2018 [Unpublished data])

Figure 4 Rate of moderate/severe HAE attacks and reduction from baseline* during the treatment period†

4.2.3 Key Exploratory endpoints

Time to first investigator-confirmed attack Day 70 to Day 182 visit – HELP-03 ITT Population

The company conducted an *ad hoc* analysis of the time to first attack and present the KM data in Figure 6, Document B of the CS. These are reproduced by the ERG as Figure 13 in Appendix 1 of this report. The median (95% CI) number of days to first attack after Day 70 was [redacted] days in the 300mg q4w arm compared to [redacted] days in the placebo arm. (Shire. HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017. [Unpublished data]) Similar results were observed between [redacted] (reported in Document B of the CS) and after day 14 and day 28 (reported in Appendix N of the CS).

Attack-free days

The company defined an attack free day as "*a calendar day with no investigator-confirmed HAE attack*" for HELP-03 and "no HAE attack on a particular day" for HELP-04. In comparison with [redacted] of patients in the placebo arm, 44.4% of patients in the lanadelumab 300mg q2w arm and [redacted] of patients in the lanadelumab 300mg q4w arm were attack-free until the Day 182 visit in HELP-03. (Shire. HELP Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]) [28]The mean percentage of attack-free days was higher for both lanadelumab 300mg treatment arms ([redacted] in the q2w group; [redacted] in the q4w group) in comparison with placebo ([redacted]). (Shire. HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]) Similar trends were observed for attack-free days after Day 14.

SUPERSEDED

The company states that patients treated with lanadelumab in HELP-04 reported a median of 100% attack-free days (mean 97.4%) for a median of 10.5.0 days (mean 125.7 days). The number and percentage of attack free days per month was similar for rollover and non-rollover patients (106 and 103, mean 97.3% and 97.6%, respectively). The median duration of the attack-free period was shorter for rollover patients than non-rollover patients (88.3 versus 164.5 days). (Riedl MA BJ, Yang WH, Longhurst HJ, Magerl M, Hébert J, Martinez-Saguer I, on behalf of the HELP OLE Study investigators. Lanadelumab Reduces Hereditary Angioedema Attack Rate: Interim Findings From the HELP Open-label Extension Study. American College of Allergy, Asthma & Immunology Annual Scientific Meeting. Seattle, WA: USA, 2018 [Unpublished data])

See erratum

Number of high-morbidity investigator-confirmed HAE attacks

The company defined high-morbidity attacks as "*any attack that had at least one of the following characteristics: severe, resulted in hospitalisation (except hospitalisation for observation <24 hours), haemodynamically significant (systolic blood pressure <90, required IV hydration, or was associated with syncope or near-*

syncope) or laryngeal." The percentage reduction in the incidence of high-morbidity investigator-confirmed HAE attacks during the HELP-03 treatment period compared with placebo was statistically significant for both lanadelumab 300mg treatment arms: 84.7% (p=0.011) and 86.3% (p=0.007) in the 300mg q2w and 300mg q4w arms, respectively. (Shire. HELP Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]) [28]

In the HELP-04 extension study, the company explains that the mean rate of high morbidity attacks decreased in rollover patients, from 0.48 at baseline to 0.03 during the treatment period, giving a mean reduction of 97.1%. The company claims that the baseline rate could not be determined for non-rollover patients but the mean rate of high-morbidity attacks was 0.05 during the treatment period for these patients, which was similar to the rate for rollover patients.

Number of investigator-confirmed laryngeal HAE attacks during the treatment period (Day 0 to Day 182) and during steady state treatment period (Day 70 to Day 182)
During the treatment period (Day 0 to Day 182) in HELP-03, the percentage reduction in the investigator-confirmed laryngeal HAE attack rate ranged from [redacted] in the lanadelumab treatment arms compared with placebo and ranged from [redacted] compared with placebo during Day 70 to Day 182; however, the number of patients with confirmed attacks was too low in each treatment arm for a statistically significant comparison with placebo.

HRQOL endpoints
In HELP-03 no significant differences, in terms of EQ-5D-5L scores, were observed between lanadelumab and placebo over the treatment period. Compared with placebo, statistically significant improvements in AE-QoL scores were observed in both lanadelumab arms over the treatment period. The AE-QoL results are presented by the company in Tables 17 and 18 in Document B of the CS, and are reproduced by the ERG as Tables 12 and 13 below. It worth noting that some of the analyses presented in the submission included the lanadelumab dose of 150mg, which is not relevant to the scope of this appraisal.

Table 12 ANCOVA results for change in AE-QoL scores from Day 0 to Day 182 by treatment arm, adjusted for baseline scores – ITT population

Treatment arm	AE-QoL least square mean change (SD)				
	Total	Functioning	Fatigue/mood	Fear/ shame	Nutrition
Placebo (n=38)	-4.72 (18.75)	-5.42 (22.72)	-1.79 (23.25)	-9 (24.02)	0.51 (22.5)
Lanadelumab 300mg q2w	-21.29 (18.35)#	-35.97 (22.29)#	-15.78 (22.79)	-17.59 (23.29)	-18.03 (22.01)#
Change vs. placebo, mean (95% CI); p-value	−16.57 (−28.53 to −4.62); 0.003	NR			
Lanadelumab 300mg q4w	-17.38 (18.67)#	-24.29 (22.66)#	-13.86 (23.22)	-16.3 (23.71)	-13.34 (22.32)
Change vs. placebo, mean (95% CI); p-value	−12.66 (−24.51 to −0.80); p=0.03	NR			
Lanadelumab 150mg q4w (n=26)	-19.82 (19.07)#	-27.76 (23.12)#	-9.33 (23.62)	-22.53 (24.38)	-19.82 (22.76)#
Change vs. placebo, mean (95% CI); p-value	−15.11 (−27.12 to −3.09); p=0.008	NR			
F and p-value	6.97****	12.23***	2.95*	3.8**	3.86**
Lanadelumab total versus placebo: least square mean change (SD)					
Placebo	-4.71 (18.64)	-5.41 (22.92)	-1.79 (23.17)	-9.05 (23.92)	0.49 (22.43)
Lanadelumab total	-19.47 (18.59)	-29.28 (22.88)	-13 (23.12)	-18.75 (23.74)	-17.01 (22.33)
F value	20.67***	32.7***	7.82**	9.27***	10.68***

Key: AE-QoL, Angioedema Quality of Life Questionnaire; ANCOVA, analysis of covariance; CI, confidence interval; ITT, intent-to-treat; q2w, every 2 weeks; q4w, every 2 weeks; SD, standard deviation.

Notes: For ANCOVAs: p-value ****<0.001 ***<0.01, **0.01- <0.04, *0.04<0.05, - ≥0.05; For *post-hoc* comparisons: p-value *<0.05; #: Significant differences between treatment and placebo arms on *post-hoc* pairwise comparison tests (Tukey-Kramer; p<0.05).

Source: HELP-03 CSR (Shire. HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]); Banerji et al 2018 [28]

Table 13 Proportion of patients achieving a clinically meaningful improvement in AE-QoL total and domain scores from Day 0 to Day 182

Treatment Arms	% Responders†† (95% CI)				
	Total	**Functioning**	**Fatigue/Mood**	**Fear/Shame**	**Nutrition**
Placebo (N=38)	36.8 (22, 54)	53 (36, 69)	42 (26, 59)	45 (29, 62)	42 (26, 59)
Lanadelumab 300mg q2w (N=26)	80.8 (61, 93)	81 (61, 93)	54 (33, 73)	73 (52, 88)	65 (44, 83)
P-value vs. placebo	0.001	NR			
Lanadelumab 300mg q4w (N=27)	63.0 (42, 81)	78 (58, 91)	67 (46, 83)	67 (46, 83)	52 (32, 71)
P-value vs. placebo	0.07	NR			
Lanadelumab 150mg q4w (N=26)	65.4 (44, 83)	73 (52, 88)	46 (27, 67)	81 (61, 93)	58 (37, 77)
P-value vs. placebo	0.047	NR			
Lanadelumab total (N=79)	70 (58, 79)	77 (66, 86)	56 (44, 67)	73 (62, 83)	58 (47, 69)

Key: CI, confidence interval; q2w, every 2 weeks; q4w, every 2 weeks.

Notes: ††, Responders were defined as patients who observed at least 6-point reduction in the AE-QoL total score from Day 0 to Day 182. **Source:** QoL data summary; Banerji et al., 2018 [28]

PK/PD

The company presents the correlation between lanadelumab concentrations and HAE attack rate over time for HELP-03 in Figure 9, Document B of the CS (reproduced by the ERG as Figure 14 in Appendix 1 of this report). Higher concentration of lanadelumab corresponds to lower HAE attack rates. The company claims that these results support the primary efficacy analysis.

Subgroup analyses

The company reports that in HELP-03 pre-specified subgroup analyses were performed for the primary efficacy endpoint. The company clarifies that subgroup analyses were based on the following baseline demographic and disease characteristics:

- Age (<18, 18 to <40, 40 to <65, ≥65 years)
- Sex (male, female)
- Race (white, other)
- Weight group (<50, 50 to <75, 75 to <100, ≥100kg)
- Body mass index (BMI) group (<18.5, 18.5 to <25, 25 to <30, ≥30kg/m2)
- Baseline period HAE attack rate (1 to <2, 2 to <3, ≥3 attacks/month)
- HAE type (Type I, Type II)
- Geographic region (US, Canada, Jordan, Europe)
- Type of LTP prior to study randomisation (C1-INH and oral therapy, C1-INH only, no LTP use and oral therapy)
- History of laryngeal HAE attack (yes, no)

The company affirms that [redacted] was observed in subgroups with adequate numbers of patients. The results of these subgroup analyses are presented as Figure 40 in Appendix E of the CS.

Adverse reactions

In the company submission all adverse events (AEs) analyses were performed using the safety population (56 patients in the lanadelumab group and 41 patients in the placebo group). The company reports that 41 AEs occurred in 23 patients (24.3%) during the pre-treatment period. The majority of AEs during the treatment period were mild to moderate in severity (98.5% in HELP-03 and 98.2% in HELP-04) and were managed with supportive care. The ERG agrees with the company that in general lanadelumab was well tolerated and there was no evident dose response toxicity.

4.2.4 Adverse events - HELP-03

Safety analyses for AEs were performed using the HELP-03 safety population. The company defines treatment-emergent adverse events (TEAEs) as "*events with an onset date on or after the start of study treatment, or those that worsened after the start of study treatment.*" The company explains that, because HAE attack-reported AEs included investigator-confirmed HAE attacks, the safety data presented in the CS are for non-HAE-reported AEs only. Non-HAE-attack reported AEs were defined as "*the subset of AEs identified in electronic data capture (EDC) as not a reported HAE attack (all AEs excluding HAE-attack-reported events).*"

SUPERSEDED

See erratum

The company presents AEs data in Tables 24-30, Document B of the CS. At clarification, in response to a question from the ERG, the company provided an updated version of these tables, removing the lanadelumab 150mg q4w dose, which is not considered in the current licence for lanadelumab. A summary of TEAEs during the 26-week treatment period is presented in Table 24, Document B, of the CS and reproduced by the ERG as Table 14 below. A higher percentage of people in the lanadelumab arms reported TEAEs than in the placebo arm but the ERG agrees with the company that, overall, lanadelumab was well tolerated. The proportion of people with severe TEAEs was comparable across treatment groups. A total of four patients across the lanadelumab arms experienced four serious TEAEs compared with none in the placebo arm. According to the company, none of these events were considered related to the lanadelumab treatment. One patient in the lanadelumab 300mg q2w arm and three patients in the lanadelumab 300mg q4w treatment arm were hospitalised due to AEs. These events were not considered treatment related by the company. No placebo participants experienced an adverse event of special interest (AESI), pre-

defined as hypersensitivity reactions and disordered coagulation, and only five lanadelumab participants experienced eight AESIs. Ten (11.9%) lanadelumab-treated and two (4.9%) placebo-treated patients had at least one treatment-emergent antidrug antibody (ADA)-positive sample during the treatment period; all antibody titres were low (range: 20–1,280). One patient in the placebo arm and one patient in the lanadelumab 300mg q4w arm discontinued treatment due to a TEAE. No deaths were reported in the study.

SUPERSEDED

See erratum

Table 14 Summary of TEAEs during the treatment period by treatment group – HELP-03 safety population

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (N=56)
Any TEAE	31 (75.6) 231	26 (96.3) 235	25 (86.2) 182	51 (91.1) 417
Any treatment-related TEAE	14 (34.1) 85	19 (70.4) 131	14 (48.3) 121	33 (58.9) 252
Any serious TEAE	0 (0.0) 0	1 (3.7) 1	3 (10.3) 3	4 (7.1) 4
Any related serious TEAE	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Any severe TEAE	4 (9.8) 7	2 (7.4) 2	4 (13.8) 6	6 (10.7) 8
Any related severe TEAE	1 (2.4) 4	0 (0.0) 0	1 (3.4) 2	1 (1.8) 2
Any investigator-reported AESI	0 (0.0) 0	3 (11.1) 4	1 (3.4) 2	4 (7.1) 6
Deaths due to TEAE	0 (0.0) -	0 (0.0) -	0 (0.0) -	0 (0.0) -
Hospitalisation due to TEAE	0 (0.0) 0	1 (3.7) 1	3 (10.3) 3	4 (7.1) 4
Discontinuation due to TEAE	1 (2.4) -	0 (0.0) -	1 (3.4) -	1 (1.8) -

Key: AESI, adverse event of special interest; EDC, electronic data capture; HAE, hereditary angioedema; n, number of patients experiencing the event, NE, non-estimated; m, number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.

Notes: Percentages are based on all patients in the safety population. Patients were counted once per category per treatment. TEAEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. Related TEAEs are TEAEs classified as related to study drug by the investigator; severe TEAEs are TEAEs classified as severe (Grade 3) or life threatening (Grade 4) by the investigator; Non-HAE attack reported AEs include the subset of AEs identified in EDC as not a reported HAE attack. 95% CI for relative risk is calculated by exact method.

Source: HELP-03 CSR; (Shire. HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017[Unpublished data])

Aa summary of the most commonly experienced TEAEs during HELP-03 treatment period (occurred in ≥5% of participants in any treatment arm) is presented in Table 25, Document B, of the CS and reproduced, for completeness, as Table 50 in

Appendix 2 of this report. The most frequently reported TEAEs were [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients), [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients), [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients), [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients) and [redacted] of lanadelumab-treated patients compared with [redacted] in the placebo-treated arm). Similarly, the most commonly reported treatment related TEAEs in the 300 mg lanadelumab arms were [redacted] Overall, [redacted] patients in lanadelumab treatment arms and [redacted] patients in the placebo arm had related TEAEs (see Table 51 in Appendix 2 for more details).

SUPERSEDED

In Table 26, Document B, of the CS, the company presents a summary of Grade 3 or higher (severe) TEAEs, which occurred in >2% of participants during the treatment period. These data are reproduced by the ERG as Table 52 in Appendix 2. [redacted] patients had [redacted] severe TEAEs in the two 300mg lanadelumab arms and [redacted] patients had [redacted] severe TEAEs in the placebo arm. For Grade 3 or higher treatment-related TEAEs, [redacted] patient in the lanadelumab 300mg q4w arm had [redacted] events of severe related TEAEs (alanine transaminase [ALT] and aspartate transaminase [AST] increased), and [redacted] patient in the placebo arm had [redacted] of injection site reaction (see Table 53 in Appendix 2).

See erratum

Serious treatment emergent AEs during the treatment period are presented in Table 29, Document B of the CS and reproduced by the ERG as Table 54 in Appendix 2 of this report. Overall, [redacted] patients treated with 300mg lanadelumab [redacted] experienced [redacted] serious emergent AEs during the treatment period compared with none of those treated with placebo. According to the company, none of these events was considered related to the study treatment.

During the treatment period, eight patients treated with 300mg lanadelumab and two (4.9%) patients receiving placebo had at least one treatment-emergent antidrug

antibody (ADA)-positive samples. The company reports that antibody titres were low (range, 20-1,280) and the formation of ADAs did not impact on the safety and efficacy of the clinical response.

Adverse events observed in the HELP-04 extension study

The company states that, at the time of the HELP-04 interim analysis, rollover and non-rollover patients had received a median of 15 (range 1 to 26) doses of lanadelumab. Over half (56.4%) of the lanadelumab doses were self-administered by patients, 20.8% at home (655/3157 doses) 357% and in clinic (1127/3157 doses). TEAEs were reported by 85.8% of all patients. A higher proportion of patients in the non-rollover group had TEAEs considered related to lanadelumab by the investigator (51.5%) compared with rollover patients (33.0%). The majority (98.2%) of TEAEs were mild to moderate in severity. Five patients (2.4%; four non-rollover and one rollover) withdrew from the study due to TEAEs. Two non-rollover patients withdrew due to hypersensitivity AESIs (oedema, wheals and joint pain; and rash at site of injection and slight swelling under the eyes). The company explains that neither event was serious, but one event was classified as treatment-related and severe because it coincided with a HAE attack and ongoing disease. One non-rollover patient withdrew due to a treatment-related injection site reaction (papules), also classified as a hypersensitivity AESI. One non-rollover patient withdrew due to elevated ALT and AST. The company claims that this event was unrelated to the study drug. One rollover patient withdrew due to upper gastrointestinal bleeding and pneumonia following ingestion of a caustic substance. Eight (3.8%) patients had an investigator-reported AESI (four rollover [8 events] and four non-rollover [5 events], and six of these events were considered to be treatment related. The company presents a summary of TEAEs in the HELP-04 study, and these are reproduced by the ERG as Table 15 below.

SUPERSEDED

See erratum

Table 15 Summary of TEAEs in long term extension study HELP-04

Event, n (%) events	Rollover Patients	Non-rollover Patients	Total
	n=109	n=103	N=212
Any TEAE	95 (87.2) 760	87 (84.5) 771	182 (85.8) 1531
Any treatment-related TEAE	36 (33.0) 287	53 (51.5) 427	89 (42.0) 714
Any serious TEAE	5 (4.6) 6	3 (2.9) 5	8 (3.8) 11
Any treatment-related Serious TEAE	0	0	0
Any severe TEAE	10 (9.2) 12	11 (10.7) 16	21 (9.9) 28
Any treatment-related severe TEAE	0	3 (2.9) 5	3 (1.4) 5
Any Investigator-reported AESI	4 (3.7) 8	4 (3.9) 5	8 (3.8) 13
Deaths due to TEAE	0	0	0
Hospitalisation due to TEAE	5 (4.6) 6	3 (2.9) 5	8 (3.8) 11
Any discontinuation due to TEAE	1 (0.9)	4 (3.9)	5 (2.4)

Key: AESI, Adverse event of special interest; HAE, hereditary angioedema; TEAE, treatment-emergent adverse event.

Notes: Data are from an interim analysis. Excludes HAE attack-reported events

Source: Lanadelumab AMPC dossier (Shire. Lanadelumab AMPC dossier: Submission of Clinical and Economic Data Supporting Formulary Consideration of: TAKHZYROTM (lanadelumab-flyo). 2018.[Unpublished data])**;** Riedl et al. 2018 (Riedl MA BJ, Yang WH, Longhurst HJ, Magerl M, Hébert J, Martinez-Saguer I, on behalf of the HELP OLE Study investigators. Lanadelumab Reduces Hereditary Angioedema Attack Rate: Interim Findings From the HELP Open-label Extension Study. American College of Allergy, Asthma & Immunology Annual Scientific Meeting. Seattle, WA: USA, 2018 [Unpublished data])

The most common TEAEs were injection site pain (35.8% of patients), viral upper respiratory tract infection (20.8% of patients), and headache (15.6% of patients; Table 32, Document B, of the CS). The most common treatment-related TEAEs were injection site pain (31.6% of patients) and injection site erythema. The company presents these data in Table 32, Document B, of the CS. An updated version of this table, including the number of adverse events (m) was provided by the company in response to an ERG clarification question and this is reproduced by the ERG as Table 16 below.

Table 16 Common TEAEs (≥5% of patients) and related TEAEs in long term extension study HELP-04

Event, n (%), m	Rollover Patients	Non-rollover Patients	Total
	n=109	n=103	N=212
Common TEAEs			
Injection site pain	34 (31.2) 275	42 (40.8) 319	76 (35.8) 594
Viral upper respiratory tract infection	26 (23.9) 33	18 (17.5) 20	44 (20.8) 53
Headache	17 (15.6) 34	16 (15.5) 25	33 (15.6) 59
Injection site erythema	12 (11.0) 22	14 (13.6) 48	26 (12.3) 70
Upper respiratory tract infection	13 (11.9) 18	13 (12.6) 18	26 (12.3) 36
Injection site bruising	4 (3.7) 9	12 (11.7) 33	16 (7.5) 42
Arthralgia	4 (3.7) 9	8 (7.8) 8	12 (5.7) 17
Back pain	10 (9.2) 12	2 (1.9) 2	12 (5.7) 14
Urinary tract infection	5 (4.6) 5	6 (5.8) 8	11 (5.2) 13
Nausea	6 (5.5) 7	5 (4.9) 8	11 (5.2) 15
Injection site swelling	3 (2.8) 14	7 (6.8) 12	10 (4.7) 26
Abdominal pain	3 (2.8) 4	6 (5.8) 6	9 (4.2) 10
Pain in extremity	6 (5.5) 7	2 (1.9) 2	8 (3.8) 9
Common treatment-related TEAE			
Injection site pain	31 (28.4) 237	36 (35.0) 289	67 (31.6) 526
Injection site erythema	11 (10.1) 21	14 (13.6) 48	25 (11.8) 69
Injection site bruising	2 (1.8) 2	10 (9.7) 31	12 (5.7) 33

Key: HAE, hereditary angioedema; TEAE, treatment emergent adverse event.
Notes: Data are from an interim analysis. Excludes HAE attack-reported events
Source: Lanadelumab AMPC dossier**;** Riedl et al. 2018[38]

The company states that ADA positive samples occurred in [redacted] of lanadelumab-treated patients [redacted] rollover and [redacted] non-rollover). Of the [redacted] patients with detectable ADAs, [redacted] rollover patients had pre-existing low-titre ADAs that were present prior to lanadelumab treatment in HELP-03. [redacted] were negative for ADAs during HELP-04. (Shire. Lanadelumab AMPC dossier: Submission of Clinical and Economic Data Supporting Formulary Consideration of: TAKHZYROTM (lanadelumab-flyo). 2018.[Unpublished data]); (Riedl MA BJ, Yang WH, Longhurst HJ, Magerl M, Hébert J, Martinez-Saguer I, on behalf of the HELP OLE Study investigators.

Lanadelumab Reduces Hereditary Angioedema Attack Rate: Interim Findings From the HELP Open-label Extension Study. American College of Allergy, Asthma & Immunology Annual Scientific Meeting. Seattle, WA: USA, 2018 [Unpublished data]).

The company notices that [redacted] patients developed neutralising ADAs; therefore, the prevalence of ADAs was [redacted] (Shire. Lanadelumab AMPC dossier: Submission of Clinical and Economic Data Supporting Formulary Consideration of: TAKHZYROTM (lanadelumab-flyo). 2018.[Unpublished data]); (Riedl MA BJ, Yang WH, Longhurst HJ, Magerl M, Hébert J, Martinez-Saguer I, on behalf of the HELP OLE Study investigators. Lanadelumab Reduces Hereditary Angioedema Attack Rate: Interim Findings From the HELP Open-label Extension Study. American College of Allergy, Asthma & Immunology Annual Scientific Meeting. Seattle, WA: USA, 2018 [Unpublished data]). Neutralising ADAs [redacted] patients who had prior exposure to lanadelumab during the Phase Ib study (DX-2930-02) and later entered HELP-04 as a non-rollover patient. The company reports that all ADA titres were low (range, [redacted] and the formation of ADAs did not impact on efficacy or exposure. The company also reports that no episodes of hypersensitivity were associated with ADAs and no participants withdrew due to ADAs. (Shire. Lanadelumab AMPC dossier: Submission of Clinical and Economic Data Supporting Formulary Consideration of: TAKHZYROTM (lanadelumab-flyo). 2018.[Unpublished data]).

Results of the NMA

A Bayesian NMA of fixed effect models was performed using data from the HELP-03 and CHANGE cross-over studies (attack rate and time to first attack after Day 0 and Day 70).

The treatment comparisons showed that patients treated with lanadelumab (300mg q2w and 300mg q4w) had lower attack rates than patients receiving placebo and an improvement in the relative risk of attack compared with those treated with C1-INH IV. For patients treated with lanadelumab 300mg q2w compared with those receiving placebo, the attack rate ratio [redacted] which indicates a [redacted] attack rate reduction. For patients treated with lanadelumab 300mg q4w compared with those receiving placebo, the rate ratio was [redacted] which indicates

a [redacted] attack rate reduction. Similarly, the rate ratio for lanadelumab 300mg q2w compared with C1-INH IV is [redacted] which indicates that patients treated with lanadelumab had a [redacted] reduction in attack rate compared with patients treated with C1-INH IV. The rate ratio for lanadelumab 300mg q4w compared with C1-INH IV was [redacted] which corresponds to a [redacted] reduction in attack rate compared with patients receiving C1-INH IV. For patients treated with C1-INH IV compared with those receiving placebo the rate ratio was [redacted]

The results for time to first attack after Day 0 and after Day 70 presented in the CS are summarised in Table 17 below.

Table 17 NMA results of time to first attack after Day 0 and Day 70

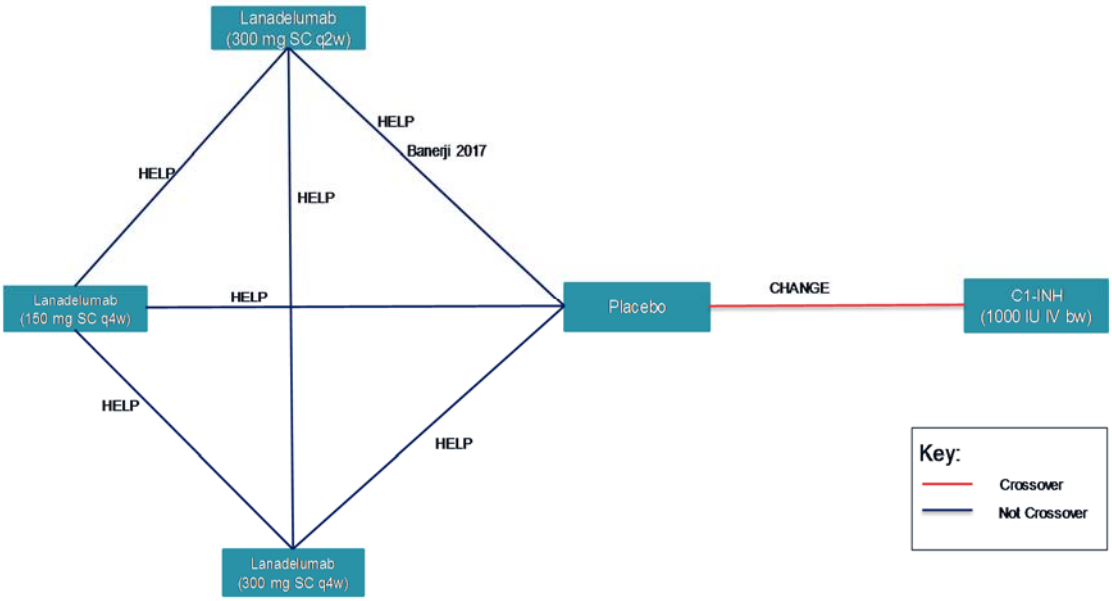
Source	Type of NMA	No of studies in the NMA	Treatment versus placebo	% of reduction
Time to first attack after Day 0				
HELP-03	Fixed effects	2	Lanadelumab 300mg q2w versus placebo [redacted]	[redacted]
HELP-03	Fixed effects	2	Lanadelumab 300mg q4w versus placebo [redacted]	[redacted]
CHANGE	Fixed effects	2	C1-INH IV versus placebo [redacted]	NR
Time to first attack after Day 70				
HELP-03	Fixed effects	2	Lanadelumab 300mg q2w versus placebo [redacted]	[redacted]
HELP-03	Fixed effects	2	Lanadelumab 300mg q4w versus placebo [redacted]	[redacted]
CHANGE	Fixed effects	2	C1-INH IV versus placebo [redacted]	NR

4.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison

The final evidence network included the HELP-03 trial and CHANGE,[42] a phase III crossover trial comparing placebo and C1-INH IV 1000IU twice weekly. The

The company presents the final network diagram for the ITC in Figure 13, Document B, of the CS. The network diagram is reproduced as Figure 5 below. The design and demographics of the two trials are presented by the company in Table 10, Appendix D, of the CS and reproduced by the ERG as Table 18 below. In both trials, the majority of participants were female (70% in HELP-03 and 91% in CHANGE). The

company judged both trials to be at low risk in terms of selection bias, performance bias and attrition bias. The ERG notes that the CHANGE trial has a small sample size (22 participants in total) but agrees with the company that both studies are similar in terms of their baseline demographic and disease characteristics.



Key: bw, twice weekly; C1-INH, C1 esterase inhibitor; IV, intravenous; q2w, every 2 weeks; q4w, every 4 weeks; SC, subcutaneous.

Figure 5 Final network diagram for ITC

Table 18 Trial design and demographics of the trials included in the indirect treatment comparison

Study	Trial type	Arms	Sample size	Treatment period (weeks)	Washout period (weeks)	Age, mean (SD)	Female N (%)	Mean (SD) weight (kg)	White ethnicity, n (%)	Prior use of prophylactic therapies, n (%)	Mean (SD) years since diagnosis
HELP-03[28]	Parallel	Lanadelumab (300mg SC q2w)	27	26	2	40.3 (13.35)	15 (55.6)	90.6 (25.2)	26 (96.3)	11 (40.7)	25.3 (N/A)[a]
		Lanadelumab (300mg SC q4w)	29	26	2	39.5 (12.85)	19 (65.5)	78.5 (16.6)	23 (79.3)	20 (70.0)	24.9 (N/A)[a]
		Lanadelumab (150mg SC q4w)	28	26	2	43.4 (14.91)	20 (71.4)	77.6 (15.6)	25 (89.3)	14 (50.0)	31.4 (N/A)[a]
		Placebo	41	26	2	40.1 (16.75)	34 (82.9)	76.3 (22.7)	39 (95.1)	24 (58.5)	28.9 (N/A)[a]
CHANGE[42]	Crossover	C1-INH (1000 IU IV)	11	12	12	41.7 (19.3)	9 (81.8)	70.5 (9.3)	10 (90.9)	2 (18.2)[b]	19.3 (14.4)
		Placebo (10ml of saline)	11	12	12	34.5 (14.8)	11 (100)	76.3 (25.7)	11 (100)	1 (9.1)[b]	16.8 (7.9)

Key: C1-INH, C1-esterase inhibitor; N/A, not available; q2w, every 2 weeks; q4w, every 4 weeks; SC, subcutaneous; SD, standard deviation

Note: [a] Years since diagnosis not available for HELP-03, so these values have been calculated using the mean age and the mean age at diagnosis; [b]Androgen therapy at baseline consisted of oxandrolone in different doses.

The ERG agrees with the company that the only study eligible for comparison with HELP-03 was CHANGE, which assessed C1-INH IV against placebo using a cross-over design. Still, the question remains about whether this is sufficient to disregard the differences between the two studies in terms of study design, especially with respect to the standard error structure between a parallel and a crossover design.

4.4 Critique of the indirect comparison and/ or multiple treatment comparison

The company present a Bayesian NMA, which includes two studies: HELP-03 and CHANGE, a phase III cross-over trial comparing C1-INH IV with placebo. The NMA relied upon Markov Chain Monte Carlo (MCMC) methods. The outcomes considered in the NMA were attack rate (i.e., number of attacks per 28-day cycle) estimated as rate ratios and the time to first attack after Day 0 and after Day 70 estimated as hazard ratios (HRs). To assess the relative treatment effects on time to first attack after Days 0 and 70, the company developed a Bayesian NMA using the methods described by Woods et al., 2010,[43] which allow the use of both HRs and count data in a single analysis.

All the indirect comparisons were only possible using a fixed effect model as the small sample size of studies in the data set would not support the additional parameter estimates required for a random effect model.

The NMA was limited by the fact that any assessment of inconsistency or adjustment for difference between studies' characteristics was not possible because the available evidence base consisting of only two studies of small sample sizes.

4.5 Additional work on clinical effectiveness undertaken by the ERG

4.5.1 Verification of the submitted NMA estimates

The company were requested to provide the associated SEs [and SEs of the log estimates) along with the original rate ratios estimates for 'attack rate' and HR estimates for the 'time to first event' (both for 0-182 days and 70-182 days)]. Failing this the full HELP-03 data and codes were requested, so that the ERG could replicate the models and directly obtain the estimates and their SEs. Either of these would have allowed the ERG to assess if the Woods et al., 2010 [43] equations had been correctly

applied. Basic data for the Kaplan Myer curves were provided by the company for the 'time to first event' variables.

Using the information provided by the company, the ERG has investigated the NMA results for attack rate. In particular, the ERG has looked at 1 comparison (300 q4w versus all other doses and placebo) for time to first attack for 0-182 days as well as for 70-182 days. The ERG has used WinBUGS 14 with the same criteria adopted by the company (i.e., 3 chains, 100,000 burn in and then a further 200,000 samples after convergence had been confirmed). Only the fixed effects models were replicated. The random effects models were not considered to be robust given the small sample sizes. Moreover, the random effects models were not used in the economic model.

4.6 Attack Rate (based on Table 11 Appendix D of the CS)

Only the original rate ratios submitted by the company were investigated since the ERG had no further data to replicate these analyses.

Table 19 'Attack Rate' estimates for use in the NMA

Study	Treatment group	Original Attack Rate Ratio	Log Rate Ratio	SE log rate ratio used in NMA (already adapted using Woods et al., 2010 equations)
HELP-03	Lanadelumab 300 q2w	[redacted]	[redacted]	[redacted]
HELP-03	Lanadelumab 300 q4w	[redacted]	[redacted]	[redacted]
HELP-03	Lanadelumab 150 q4w	[redacted]	[redacted]	[redacted]
HELP-03	Placebo	[redacted]	[redacted]	[redacted]
CHANGE	C1-INH IV	[redacted]	[redacted]	[redacted]

The ERG has verified the results given in Figure 3, Appendix D of the CS, using the fixed effects model and the submitted HRs and log SEs (already adapted using Woods et al., 2010[43] equations).

Table 20 'Attack Rate': NMA HRs derived by the ERG (in red using WinBUGS), compared with the results reported by the company

Treatment group	Ref	ERG median	ERG 2.5%	ERG 97.5%	Submitted results using R
Placebo	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300 q2w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300 q4w	300 4w	[redacted]	[redacted]	[redacted]	-
Lanadelumab 150 q4w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
C1-INH IV	300 4w	[redacted]	[redacted]	[redacted]	[redacted]

Table 20 above shows that the NMA attack rates and credible intervals calculated by the ERG are virtually identical to those obtained by the company.

4.7 Time to first attack for days 0-182 (based on Table 14, Appendix D of the CS)

SUPERSEDED

Tables 21 and 24 below are the original HR estimates submitted by the company for time to first attack for 0-182 days and for 70-182 days, respectively. In red are the estimates derived by the ERG using the basic Kaplan Myer (KM) data supplied by the company after clarification (i.e., allowing the ERG to produce the raw HRs).

See erratum

Table 21 'Time to first event (0-182 days)' estimates for use in the NMA

Treatment group	Original HRs	Ln HR(1)	ERG Raw HRs	ERG Ln HRs (2)	SE log HR used in NMA (already adapted using Woods equations) (3)
Lanadelumab 300mg q2w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 150mg q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo					[redacted]
C1-INH IV	Binary data from Table 12, Appendix D of the CS				

Using original submitted HRs (1) in Table 21 to verify the results given in Figure 15, Appendix D of the CS. As above only the fixed effects model are presented.

Table 22 'Time to first event (0-182 days)' NMA HRs derived by the ERG (in red using WinBUGS), compared with the company results. Based on the original submitted HRs [Table 21 (1)] and SE log HR [Table 21 (3)].

Treatment group	Ref	ERG median	ERG 2.5%	ERG 97.5%	Submitted results using R
Placebo	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg q2w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg q4w	300 4w	[redacted]	[redacted]	[redacted]	-
Lanadelumab 150mg q4w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
C1-INH IV	300 4w	[redacted]	[redacted]	[redacted]	[redacted]

Table 22 shows that the NMA HRs and credible intervals are virtually identical between the ERG's results and those obtained by the company.

SUPERSEDED

In Table 23 below the estimates were derived by the ERG using the KM data (i.e., the raw HRs). The original SE(Ln HR) estimates were used in Table 23.

Table 23 'Time to first event (0-182 days)' NMA HR's [Table 21 (2)] derived by the ERG (in red using WinBUGS), compared with the company results using the ERG derived Ln HR's and SE log HR [Table 21 (3)].

See erratum

Treatment group	Ref	ERG median	ERG 2.5%	ERG 97.5%	Submitted results as above	Comments
Placebo	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	
Lanadelumab 300mg q2w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	Slightly different
Lanadelumab 300mg q4w	300 4w	[redacted]	[redacted]	[redacted]	-	
Lanadelumab 150mg q4w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	Slightly different
C1-INH IV	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	

Although there are some differences, these do not alter the impact of HELP-03 with the second trial, CHANGE.

4.8 Time to first attack for days 70-182 (based on Table 15, Appendix D of the CS)

In Table 24, the ERG has used the original submitted HRs (1) in order to verify Figure 27, Appendix D of the CS. Table 25 shows that the ERG's results are slightly different, but largely comparable, with the company's results.

Table 24 'Time to first event (70-182 days)' estimates for the NMA

Treatment group	Original HR's	Ln HR(1)	ERG Raw HRs	ERG Ln HR's (2)	SE log HR used in NMA (already adapted using Woods et al's equations) (3)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg q2w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 150mg q4w					[redacted]
C1-INH IV	Binary data from Table 12 Appendix D of the CB				

SUPERSEDED

Table 25 'Time to first event (70-182 days)' NMA HR's HRs derived by the ERG (in red using WinBUGS), compared with the company results. Based on the original submitted HRs [Table 24 (1)] and SE log HR [Table 24 (3)].

See erratum

Treatment group	Ref	ERG median	ERG 2.5%	ERG 97.5%	Submitted results Figure 27
Placebo	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg q2w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg q4w	300 4w	[redacted]	[redacted]	[redacted]	
Lanadelumab 150mg q4w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
C1-INH IV	300 4w	[redacted]	[redacted]	[redacted]	[redacted]

As final check, using the KM data received from the company, the ERG derived raw HRs [Table 24 (2)] for the 'time to first attack 70-182 days', while using the same SE(Ln|HR) [Table 24 (3)]. These were used in the NMA and the resulting estimates presented in Table 26 and compared with the results in Figure 27, Appendix D of the CS.

Table 26 'Time to first event (70-182 days)' NMA HRs derived by the ERG (in red using WinBUGS) [Table 24 (2)], compared with the company results using the ERG derived LnHR's [Table 24 (3)],

Treatment group	Ref	ERG median	ERG 2.5%	ERG 97.5%	Submitted results as above	Comments
Placebo	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	Similar
Lanadelumab 300mg q2w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	Very different [a]
Lanadelumab 300mg q4w	300 4w	[redacted]	[redacted]	[redacted]		
Lanadelumab 150mg q4w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	Some difference
C1-INH IV	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	Similar

Using the raw HRs for the 'time to first attack 70-182 day' has the impact of changing the company significant result to now be non-significant (see [a] in Table 26 above).

4.9 Conclusions of the clinical effectiveness section

The evidence from HELP-03 shows that lanadelumab provides protection from attacks for patients with HAE during the 26-week treatment period. However, HELP-03 is a relative small study with only 27 participants in the arm of interest, 300mg q2w. While this is sufficient for detecting significant difference with respect to 'attack rate' and 'time to first event', the company states (and the ERG is in agreement with the company) that there was insufficient information for more detailed and/or more robust assessment. The company attempted several sub-group analyses all of which were non-significant. However, due to their sample sizes these subgroup analyses are at risk of Type II errors. The models for testing the outcome variables were simple, with the company stating in their clarification response that this was because of the small sample sizes (for example they did not include covariates that often are/should be considered, like age and gender).

The ERG has been able to verify the results of the NMA for the outcome Attack Rate if the RR and the SE's provided are accepted. Using additional information provided by the company the 'Time to First attack' for 0-182 and 70-182 days have also been checked. The additional information included the R code and the data used, which enabled the ERG to see that the SEs originally given were the Woods et al.-adapted SEs - not original SEs from the HR models which have not been provided in any form. The ERG derived raw HRs the 'Time to first event' variables based on the basic KM data provided at clarification and did them incorporate into NMA models just for investigation. However, the method section in the Shire Clinical Study report – DX-2930-03, states that HRs were derived from a GLM for count data, assuming a Poisson distribution with a log link function and Pearson chi-squared scaling of SEs to account for potential over-dispersion. The model included fixed effects for treatment group (categorical) and the normalised baseline attack rate (continuous). The logarithm of time in days each patient was observed during the treatment period was used as an offset variable in the model. The baseline attack rate and time offset variable were not provided to the ERG, and so could not be replicated. None-the-less this approach seems sensible. Indeed, Banerji et al., 2018[28] indicates that the HELP-03 participants receiving 300mg every 2 weeks had fewer attacks 12 months prior to screening suggesting some baseline adjustment to be valid. In addition, these results are linked to the CHANGE cross-over study, through the NMA. The impact of the cross-over would have automatically adjusted for all baseline variables, again suggesting that the adjustment for HELP-03 is a reasonable approach.

SUPERSEDED

See erratum

Providing the Committee is prepared to accept the company submission in terms of the HR estimates and their precision (already adapted using equations from Woods et al., 2010[43]), the ERG is happy to accept the company's NMA results. However, the Committee should be aware that the providence of the precision estimates for the rate ratios and HRs is not something the ERG has been able to validate.

While some attempt has been made to account for the differing study designs of Help-03 and CHANGE this remains a source of concern to the ERG.

5 Cost effectiveness

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 State objectives of cost effectiveness review. Provide description of company's search strategy and comment on whether the search strategy was appropriate. If the company did not perform a systematic review, was this appropriate?

The objective of the review of cost-effectiveness evidence was "to identify the cost-effectiveness studies available for acute and/or prophylactic treatment of patients with Type I and Type II HAE" (CS, Appendix G, page 79). It subsequently became clear that the company was primarily interested in studies of prophylaxis treatments, with studies of treatments for use during attacks being listed in the appendix but not presented in Document B (Table 33).

The search strategy:

- Was limited to material from the last 10 years (subsequently updated so effectively over 11 years)
- The appropriate databases were searched together with abstracts from HTA conferences as well as medical conferences relevant to HAE and HTA agency sites

The ERG's main criticism is of the HTA agency websites searched, essentially selecting the UK plus Canada. This ignored PBAC in Australia, TLV in Sweden and ruled out the inclusion of evaluations of any other country with a system that includes cost-effectiveness assessments in some cases such as the Netherlands, Norway, Brazil or some regions in Spain & Italy. The review did identify the 2018 publication by ICER, the American Institute for Clinical and Economic Review, finalised only very close to the deadline for the CS. This is regrettable as a more complete discussion of the methods and assumptions would have made an interesting comparison with the methods selected. These are included in some sections of the company's economics submission but a more complete comparison, including commenting on ICERs cost per QALY results, would have been desirable.

5.1.2 State the inclusion/ exclusion criteria used in the study selection and comment on whether they were appropriate

The company's approach:

- Restricted to evaluations of a range of medicines versus any comparator – this does not seem to have been strictly adhered to as a study of the cost-effectiveness of a national call centre was included
- Included publications in any language – the company does not seem to have gone beyond English, however.

A diagram is presented to show how the studies identified were reduced to the most relevant examples. It was not always clear what the text used means. For example, the biggest reason for exclusion was labelled 'Disease' – does this mean it was not HAE? If so, how was it included in the first place? Another label is 'study design' – how was this judged? Another label is 'prior 2017' which the ERG assumes to be 'prior to 2007', but no explanation is given.

Despite these criticisms about the transparency and presentation of what was done, the ERG is not aware of any relevant publication in a journal that was excluded.

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the <u>most important</u> cost effectiveness studies.

The studies identified by the company are listed in Tables 20 and 21 in Appendix G of the CS. The studies were assessed for the quality of the method in Table 22 in Appendix G of the CS. However, most studies related to the treatment of acute attacks with HAE, so in Document B of the CS only the two studies were mentioned. One was of long-term prophylaxis, but this evaluated a treatment that is not used in England. The other study is an evaluation of a national call centre for HAE patients in France; it was not clear why the company thought this was more relevant than studies of treating attacks. See Table 27 for the studies identified in the review.

Table 27 Results from the systematic review of economic evaluations

Study	Year	Summary of model	Health states	Patients/ setting	Intervention/ comparators	Relevance
Graham (2017) [44]	2017	Decision tree	Not reported	Patients with HAE in the US	Intervention: Haegarda Comparator: C1-estarase inhibitors (IV)	Setting of study not relevant
Javaud (2018) [45]	2018	Not Reported	Not Reported	Patients with HAE in France	Intervention: national call centre management facility (SOS-HAE) strategy Comparator: Usual practice	Relevant comparators not included
Key: HAE, hereditary angioedema.						

(CS, Document B, Table 33, page 128)

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details.

The CS review did not reach any stated conclusion in Document B other than the implicit one that there was no existing economic evaluation or model that could be used to address the NICE decision problem so a de novo approach was justified.

As stated, it was unfortunate the CS did not have the opportunity to present the ICER report in detail. ICER's findings were as follows: [when compared with treatment on demand for acute attacks], "Cinryze ($5,954,000 per QALY), Haegarda ($328,000 per QALY), and lanadelumab ($1,108,000 per QALY) all far exceeded cost-effectiveness thresholds of $100,000 to $150,000 per QALY". The ICER report noted discounts required to align with $100k to $150k thresholds, of 60%, 28% and 34% for Cinryze, Haegarda and Lanadelumab, respectively. [46]

Of course, the ERG does not support simplistic translation of conclusions from one jurisdiction to another and it is important to note ICER fully acknowledges the sensitivity of their results to changes in assumptions. However, an opportunity for the company to put forward its interpretation was lost.

5.2 Summary and critique of company's submitted economic evaluation by the ERG Suggested research priorities

5.2.1 NICE reference case checklist (Table only)

Table 28 presents the ERG's take on the company submission compared to the NICE reference case. The majority of issues are highlighted in this table, however, further issues concerning the company submission are discussed throughout the report.

Table 28 NICE reference

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Other established treatments available for preventing recurrent attacks of hereditary angioedema.	Yes, but the company proposed positioning for lanadelumab is in those who are not controlled with or are not suitable for oral prohphylactic treatment. They further note that it may be useful to specify that lanadelumab is expected to be used in patients who would otherwise be considered for treatment with C1-INH prophylaxis. Therefore, the comparator in the company model is a weighted average of two branded C1-INH medicines used in the NHS in England, Cinryze and Berinert. Given the lower administrative burden compared to C1-INH, the ERG does have some concern that lanadelumab may be used in a small number of patients who would otherwise manage without long-term prophylaxis.
Patient group	People with hereditary angioedema aged 12 and over	Yes but the population is a sub-set of the licensed indication. The license is for use in patients aged 12 and above with HAE types 1 and 2 as long-term prophylaxis. The company's proposed positioning is in patients who have tried oral prophylaxis (attenuated androgens and anti-fibrinolytics) with inadequate results and patients for whom oral prophylaxis is not clinically appropriate.

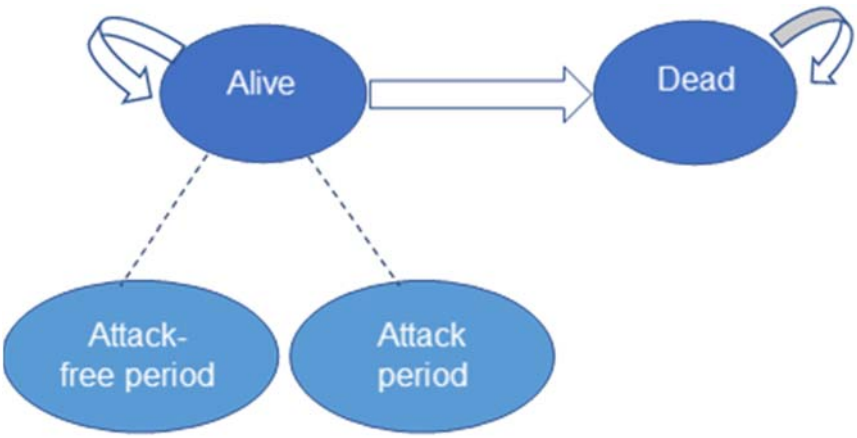
Perspective costs	NHS and Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Mostly covered. However, the company did not include an added mortality risk that could come from certain severe hereditary angioedema attacks such as laryngeal attacks.
Form of economic evaluation	Cost-effectiveness analysis	Yes, cost-utility analysis.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes, a lifetime horizon (60 years) was modelled, with a cohort starting age of 41. At the end of those 60 years when people were on average 101, 99% of the cohort had died.
Synthesis of evidence on outcomes	Systematic review	Yes, the systematic review identified 10 RCTs, and 4 of them were considered relevant according to the company, one of them being the HELP-04 extension study that, however, did not inform the modelling inputs.
Outcome measure	QALYs	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes, utility values were captured using the EQ-5D instrument. Due to limitations of the HELP-03 EQ-5D data, the company justified the use of published 'attack free' and 'with attack' utilities reported in a Swedish Nordenfelt (2014)[19] study. The ERG believe the company could have made better use of the baseline utility data from HELP-03, in combination with multipliers derived from the Swedish

		source, but subsequent analyses provided at the clarification stage showed this to have little impact on the estimates of net monetary benefit. The company also included a utility benefit for subcutaneous administration versus IV infusion derived from the literature.
Benefit valuation	Time-trade off or standard gamble	Yes, in the Swedish study informing utilities, EQ-5D-5L health state utility profiles were mapped to EQ-5D-3L values using the UK crosswalk algorithm from van Hout (2012)[47], that used TTO methodology.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes. A Swedish study [19]was applied in the base-case analysis, but using the UK crosswalk value set. In scenario analysis, the company utilised EQ-5D-5L response data from HELP-03, using the same UK cross walk algorithm.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes, both costs and QALYs were discounted at 3.5%.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes, a probabilistic sensitivity analysis was conducted, simultaneously varying

		most parameters to get the probabilistic base-case ICER.
Sensitivity analysis		Yes, however, these included mostly one-way sensitivity analyses and scenarios changing one assumption at a time. The ERG asked for further sensitivity analysis on the most uncertain parameters in the model. In addition, the ERG has conducted further analyses to further characterise the key uncertainties in the model results.

5.2.2 Model structure

The company structured the model (Document B, B3.2, page 130) using a patient-level cohort approach. Two states were defined, "Alive with HAE" and "Dead" with the state "Alive with HAE" divided into "Attack period" and "Attack-free period" (Figure 6).



(Source Figure 17, Company submission, Document B, page 131)

Figure 6 Model structure

The company explained their choice with reference to four factors:

- There are limits on data availability as HAE is an orphan disease (presumably in EMA regulatory terms, although this is not specified)
- The main treatment effect in the RCT programme is a reduced number of attacks
- "The evidence available from the trial data and the literature on the impact of HAE on health-related quality of life (HRQL) and resource use" – this seems to refer to the number of attacks being the main determinant of HRQL and NHS costs
- The need to capture attack severity and the subsequent impact on HRQL and resource use. This was not fully explained and, as the brief description of the model above shows, attack severity was not explicitly modelled.

SUPERSEDED

ERG commentary

The ERG was content with a cohort-level approach over a patient-level approach given the limited RCT data and the lack of a clear argument why the latter might give a different or more precise ICER to help the Appraisal Committee reach a recommendation.

See erratum

The ERG asked the company to explain the decision to only use attack frequency (ERG clarification questions B13). The company answered that the location of the attack does not have an important impact on the patient's quality of life, based on discussions with clinical experts and patient groups. A scenario analysis is not possible due to the lack of data on this issue.

Further issues that the ERG identified with the company's model included its failure to account for changes in attack rates for those discontinuing treatment (on lanadelumab or C1-INH prophylaxis), failure to allow for treatment switching (from lanadelumab to C1-INH), and failure to explore the impact of potential for longer-term loss of efficacy and discontinuation in the lanadelumab arm. The company assumed that an equal proportion (9%) of patients would discontinue treatment in both arms of the model by cycle 7 (based on HELP-03), and that thereafter all

patients would remain on their respective treatment for the entire duration of the model. However, the proportion discontinuing treatment were only accounted for in the estimation of treatment costs. Their attack rate was not adjusted upwards for lack of treatment or lower efficacy treatment, and a utility increment associated with lanadelumab's subcutaneous mode of administration over IV infusion continued to be applied for the full cohort. The ERGs clinical expert believed a C1-INH would be the most appropriate treatment option for those who discontinue treatment with lanadelumab, whilst those (rarely) discontinuing C1-INH would have an uncertain treatment pathway, perhaps with just on-demand treatment C1-INH or icatibant treatment for acute attacks. Therefore, the ERG requested some structural changes to the model at the clarification stage, which would allow these issues to be explored more fully. These were subsequently provided by the company.

5.2.3 Population

SUPERSEDED

The population considered in the company's model was a sub-set of the licensed indication. The license is for use in patients aged 12 and above with HAE types 1 and 2 as long-term prophylaxis.

See erratum

The HELP-03 study, which formed the basis of the label recruited patients who had at least one attack every four weeks during the run-in period. The company report that clinicians attending the NICE Scoping workshop had commented this was in line with their expectations of patients they would consider for prophylaxis
The company's proposed positioning is in patients who have tried oral prophylaxis (attenuated androgens and anti-fibrinolytics) with inadequate results and patients for whom oral prophylaxis is not clinically appropriate.

Only 8% of patients in HELP-03 match this proposed positioning (and 14% in the CHANGE RCT of C1-INH used in the indirect comparison). However, the company noted that within the RCT there were no significant differences in efficacy between sub-groups of patients based on previous treatment history. Therefore, they used the ITT population for HELP-03, irrespective of previous treatment history. The company report they were supported by their clinical specialist advisors who said there was no reason why lanadelumab would be more or less effective after oral prophylaxis.

ERG commentary

The ERG's clinical specialist advises the positioning of the medicine is plausible and is in line with perceived UK clinician expectations of the likely use of lanadelumab. However, comparison with the published commissioning policy of NHS England shows a difference: NHS England say patients should start on a C1-INH only when, whilst on oral prophylaxis, they continue to experience two or more clinically significant attacks per week over 56 days (8 weeks). The RCT required at least one attack of unspecified severity over 4 weeks.

This raises a question about the generalizability of the RCT evidence to the NHS in England, but it also raises concerns about whether the company's economic evaluation is targeted at the group who will use the medicine in England.

In their response to the clarification question from the ERG ((Company response to Clarification Questions, B1, pages 20-22) the company make the following points: Their economic model uses data from the whole RCT population, which aligns with the NICE scope.

Clinical experts do not agree with the NHS England policy and at the NICE Scoping workshop they discussed whether the policy would change.

They re-iterate they see lanadelumab being used as an alternative to C1-INH so if the NHS England policy changes then the company wish the use of lanadelumab to change with it.

They point out that very few patents in the RCT matched the NHS England criteria at baseline so an analysis based on their data alone is problematic.

With these caveats they then re-ran the Poisson model successively excluding patients with baseline attack below a threshold level of attacks that was steadily increased. They report the following results in Table 29:

Table 29 Results by baseline attack risk

Baseline attack risk (per 28 day cycle)	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB (£)
≥ 1 attack	[redacted]	[redacted]	Dominant	£408,206
≥ 2 attack	[redacted]	[redacted]	Dominant	£447,432
≥ 3 attack	[redacted]	[redacted]	Dominant	£489,232
≥ 4 attack	[redacted]	[redacted]	Dominant	£495,161
≥ 5 attack	[redacted]	[redacted]	Dominant	£543,225
≥ 6 attack	[redacted]	[redacted]	Dominant	£640,106
≥ 7 attack	[redacted]	[redacted]	Dominant	£766,649
≥ 8 attack	[redacted]	[redacted]	Dominant	£856,445

Key: ICER, incremental cost effectiveness ratio; NMB, net monetary benefit; QALYs, quality adjusted life years,

SUPERSEDED

Source: Company Response to Clarification Questions, page 21

This shows that for higher baseline levels of attacks, lanadelumab becomes more cost-effective compared to C1 INH.

See erratum

It was not clear what sample size each row of the table was based on or what was assumed about relative effectiveness when (as the company pointed out earlier) very few – if any – of the patients in either RCT in the indirect comparison would meet the NHS England criteria.

The analysis also appears to be based on all attacks, when the clarification question asked for the NHS England definition of clinically significant attacks to be applied. The 2016 NHS England Commissioning Policy defines an attack as being clinically significant if it is potentially life-threatening (on the head or neck) or if causes pain/disability such that usual activities cannot continue. In their response to a clarification question (Response to Clarification Questions B9, page 27), the company argue "the definition used in the Commissioning Policy would probably include the majority of attacks experienced by patients as, based on discussion with clinicians

and patient groups, most attacks impair usual activities" (page 27). Comparing this to the RCT definitions (Document B, page 69):

- *Mild: transient or mild discomfort; no medical intervention/therapy required*
- *Moderate: mild to moderate limitation in activity – some assistance needed; no or minimal medical intervention/therapy required*
- *Severe: marked limitation in activity, assistance required; medical intervention/therapy required, hospitalisations possible*

This suggests while severe and moderate attacks involve impairment, the NHS England definition requires the patient to be unable to continue with usual activities. The company were asked to re-run their model using the NHS England definition, but they stated this was not possible as data from the RCT did not allow it. It is notable that only 8% of attacks in HELP-03 were classified as severe (company economic model, sheet 'Utilities', cell C27).

5.2.4 Intervention and comparator

The intervention was lanadelumab, used in line with the license, and as described in the NICE Final Scope.

The comparators were the two branded C1-INH medicines used in the NHS in England, Cinryze and Berinert.

The NICE Final Scope refers to 'established clinical management' which includes these medicines but also attenuated androgens and anti-fibrinolytics. As noted in the previous section, attenuated androgens and anti-fibrinolytics are oral forms of prophylaxis and hence are not considered because the company's proposed positioning is after they have been considered and either ruled out or tried with inadequate results.

The CS notes that a non-plasma derived C1-INH, brand name Ruconest, is available but [redacted]

ERG commentary

The ERG's clinical specialist advises these are the relevant comparators for patients matching the company's proposed positioning.

An additional concern was that the availability of lanadelumab could expand use of prophylaxis in one of the following ways:

- *In patients who have had inadequate response to oral therapy but who do not want long-term iv prophylaxis*
- *In patients who have tried C1-INH but had inadequate response*
- *In patients who have tried C1-INH but who discontinued*

Responding to clarification questions from the ERG, the company said: "patients who receive C1-INH that experience inadequate control would receive a more frequent administration. As such, this is explored in a scenario analysis by increasing the frequency of the C1-INH dose, which shows increased cost-effectiveness of lanadelumab in this patient population." (Company response to Clarification Questions, B4, page 23)

The sensitivity analysis referred to only increases the cost of C1-INH, it does not increase the effectiveness. Therefore, the situation is not as clear as the response suggests.

Regarding the C1-INH intolerant group, the company emphasise the clinical advice they have received is that this is very rare. In their response to the clarification question, they said:
"We are aware that some patients cannot tolerate IV infusion; in these instances, off-label subcutaneous infusion with a higher dose of C1-INH may be considered, which would increase the costs under the comparator treatment, therefore not including this analysis is a conservative assumption." (Company response to Clarification Questions, B4, page 24)

The ERG asked for a cost-effectiveness estimate compared to 'placebo' as proxy for no prophylaxis. The company replied that they did not regard this as a relevant comparator (Company response to Clarification Questions, B2, page 22) and declined to provide a cost-effectiveness estimate.

5.2.5 Perspective, time horizon and discounting

The perspective covered costs to the NHS and QALY impacts on patients. This was in line with the NICE Reference Case.

The model was run for 60 years; given that patients were assumed to be 41 years of age at the start of treatment (in line with the HELP-03 RCT), this was assumed to be a lifetime horizon.

Sensitivity analyses were presented for time horizons of 40, 20 and 10 years. Shorter time horizons reduced the incremental net monetary benefit (NMB) favouring lanadelumab, but it remained positive.

The time preference discount rate was set to 3.5% for costs and QALYs; this was not stated in Document B but is evident from inspection of the cost-effectiveness model.

ERG commentary

All aspects were consistent with the NICE Reference case.

The only issue raised was the impact of starting treatment in patients who were younger or older than 41 when they commenced treatment. For older patients the company has provided a sensitivity analysis that reduced the time horizon and the NMB reduced. This is a partial proxy for older age at commencement, but other factors could also be different e.g. non-age baseline characteristics, age-adjustment for utilities, age-specific general mortality.

5.2.6 Treatment effectiveness and extrapolation

The company based their predictions of lifetime clinical effectiveness on the RCTs supplemented by the long-term follow-up study, together with the results from the indirect comparison to allow for comparisons with other therapies (namely, C1-INH).

<u>Extrapolating using Poisson distribution</u>

A Poisson regression was applied to the RCT data (described in Document B, Section 3.2 pages 13-132 and Section 3.3, page 135 onwards). The company explain the problem is to model the number of attacks in a period of time (in this case, one cycle of the model) and the Poisson distribution expresses the probability of a given number

of events occurring in a fixed period. Other distributions could have performed the same role (the negative binomial is cited) but the Poisson was a good fit to the observed data, so it was selected. No evidence on the comparative goodness-of-fit were presented, but Figure 19 of the company submission (Document B) demonstrates a satisfactory fit to the observed rates in HELP-03 over the first six cycles of the model. The company's approach captures the falling rate in the first 2-3 28-day cycles in the lanadelumab arms, followed by stabilisation during the following three cycles. However, the decision problem required a lifetime horizon, and so the Poisson regression was used for extrapolation forward in the model.

The method used was as follows:

1. Data on the number of attacks per month for months 1, 2, 3, 4, 5 and 6 in the RCT were extracted, as well as data for the baseline period (28 days) – see Table 35 (Document B, page 136)
2. Two potential co-variates were considered as predictors of the number of attacks in a cycle: the number of attacks in the previous cycle and the number of attacks at baseline. These were identified first in univariate analysis as being significant predictors of the number of attacks experienced in a given 28-day cycle. The company explained that no further covariates were included in the regression models since: (1) results from HELP-03 by sub-group did not indicate other factors were key drivers of the treatment effect, and (2) the small sample size in the RCTs meant a simple model avoided 'overfitting' the regression equation.
3. The full regression including both covariates was then applied independently to the data for each treatment arm of HELP-03, and the treatment specific coefficient estimates for baseline attack risk and attack rate in the previous 28 day cycle were used to estimate the number of attacks for patients on each treatment in each cycle of the model. The application of independent regressions for each arm of HELP-03 is explained as being in line with NICE DSU guidance for independent models to be applied when patient level data are available. The regression results are presented in Table 37 on page 138 of the company submission for the coefficients, and Figure 19, page 135 for the visual goodness-of-fit. Statistics on goodness-of-fit were not presented. It should be noted that the number of attacks in the previous cycle enters the

regression model as a patient level rate, with time contributed adjusted for withdrawal. Thus, it is the ERGs understanding that the predicted attack rates are adjusted for treatment discontinuation; i.e. they reflect rates whilst on treatment.

4. For application in the model, data from HELP-03 were extracted on the observed baseline attack rate and attack rate in each 28-day period, and these observed data were combined with the regression coefficients to estimate patient level attack rates for each cycle out to cycle 7. These were then averaged by treatment arm to give the average rate per cycle for each treatment arm.
5. Since no data were observed in HELP-03 beyond cycle 7, a simulation approach was used to estimate the attack rate in the previous 28 days for individual patients from cycle 8 onwards. This was done by fitting a Poisson distribution to the mean predicted attack rate in Cycle 7, and then randomly sampling from this to generate a predicted value for each individual. These simulated values were then combined with the regression coefficients to predict individual attack rates in cycle 8, which were then averaged for application in cycle 8 of the model.
6. This process was then repeated over the extrapolated time horizon of the model, so the Poisson regression for each treatment arm of HELP-03 could then be applied to all future cycles (770 in total)
7. Since the values for number of attacks in the previous cycle were simulated from a distribution, these were varied over 1000 iterations and the average was taken from across these iterations.

The predicted results over the first year are shown in Figure 20 (Document B, page 141). The company state this is a good fit to the observed HELP-03 data supplemented by HELP-04 beyond the end of the randomised phase. It can be noted that since the predicted average attack rate has stabilised within the 6-month observed period, the simulation approach essentially carries forward this stable attack rate indefinitely, with some random fluctuation due to the sampling approach.

ERG commentary

The Tornado diagram presented in the CS (Document B, Figure 24, page 173) shows the most important factors from the range considered by the company were the parameters of the Poisson regression.

Whilst the ERG had some concerns surrounding the apparent complexity of the approach used to extrapolate the attack rates for lanadelumab, it is relatively clear it is essentially carrying forward the stabilised attack rate observed within the 6 months of trial follow-up. The ERG does have further concerns that these attack rates have been adjusted for discontinuation, yet in the original company model they were applied to the whole surviving cohort, including those assumed to discontinue treatment. The ERG therefore requested further sensitivity analysis at the clarification stage, to allow the attack rate for the proportion who discontinue treatment to increase in line with the next treatment received (either C1-INH prophylaxis or no prophylaxis). This was subsequently provided, and the results are discussed further section 5.3 below.

The ERG also questioned the chosen covariates in the Poisson regression at the clarification stage, and asked (in question B7 of the clarification letter) whether there are other relevant covariates that were considered in the calculation. The company responded by providing a table showing the AIC values for each model and that way justified their chosen model. The company however, did not include any justification for how other potential covariates (other than the baseline attack rate and the attack rate at previous cycle) were excluded or justification for why no other terms were included in the analysis.

The Poisson regression was further questioned by the ERG because of the assumption that the baseline attack rate was assumed to be having an equal say in the very first cycle as in the last cycle in the model, 60 years later. Therefore, the ERG asked the company in the clarification letter (question B8) to clarify this assumption. The company responded by justifying the inclusion of both covariates based on that model having the lowest AIC value.

Combining results for lanadelumab q2w and q4w

Having derived predicted numbers of attacks for each treatment arm of the RCT, two adaptations had to be made: to combine the two lanadelumab doses into one realistic treatment path reflecting what the company believe to be the likely use of the medicine were it to be accepted for use in the NHS, and the incorporation of C1-INH as a comparator via indirect comparison.

For the lanadelumab arm it was assumed all patients commenced on q2w for 6 months and would then be assessed. Those who were attack-free were assumed to have the frequency reduced to q4w. On this basis it was assumed 44.4% of patients would switch after 6 months and cumulatively this would rise to 76.9% after 12 months. The former figure is based on the q2w arm results in the RCT; the latter is the proportion attack free in the RCT between days 70 and 182. The company note that the proportion remaining attack free beyond day 70 is a result of the steady state concentrations being achieved by this time point.

When a patient switched in the model, the equation for the q4w arm of the RCT was used.

The company acknowledged that in practice more patients might be switched to q4W over time, while others would switch back to q2w if attacks occurred again. The company argue that this is likely to balance out (Document B, page 142) and that the HELP-04 extension study suggests attack rates are stable over time.

ERG commentary

The ERG questioned the justification for the assumption that 76.9% of the lanadelumab treated cohort would be managed on the lower dose from 12 months onward in the model, particularly since this percentage was offered by the company as the percentage attack free in the context of [redacted] *In fact, the 76.9% relates to the proportion of the q2w arm of HELP-03 that remained attack free between day 70 and day 182 (a period just under 4 months); the observed period in HELP-03 when steady state concentrations of lanadelumab have been reached. Therefore, the ERG asked the company to explore the impact of extrapolating the percentage of patients on qw2 (during the steady state period) who would be free from attack over a* [redacted] *In their response to the*

clarification request, the company therefore fitted several standard parametric survival curves to the available time to event data, but ultimately selected a spline model with one internal knot as providing the best statistical and visual fit to the data (see Figures 8 and 9 in Section 5.2.8). They then used this to estimate the proportion expected to be attack free in steady lanadelumab concentration over a [redacted] *period* [redacted] *and used this to represent the percentage assumed to be on the lower lanadelumab dose in a scenario analysis. They also provided scenarios where they applied the percentage attack free from all other fitted curves they assessed (presented and discussed further under section 5.2.8 on resource use and costs).*

The ERG is satisfied that the selected spline model does provide a good statistical and visual fit to the observed time to attack data. However, the ERG has remaining concerns with respect to the rationale for assuming this extrapolated six month attack free percentage (on q2w) equates with the percentage of patients expected to accept and be on the lower dose (q4w) over the remining time horizon of the model. The assumption appears speculative to the ERG, without firm evidence to support it. It is of note that no patients in the open label extension (HELP-04) were put on q4w. Rather, all patients who were originally on q4w moved on to q2w. If patients and/or clinicians are motivated to minimise the attack rate, then it remains to be seen how acceptable and feasible it will be to move this percentage of patients to the lower dose which incurs a higher average attack rate.

SUPERSEDED
See erratum

An alternative way of looking at this could be to assume that the percentage who remain attack free over a period of [redacted] *to be the proportion more likely to accept this dose in the longer term. This might then put the percentage on q4w at around* [redacted] *in the long-run (approximated from the survival curves in Figure 6 of the CS). This remains uncertain and so the ERG present further scenario analysis where the assumed percentage on the low dose in the model moved through a range of possible values.*

Indirect comparison

The next step was to carry out an indirect comparison against C1-INH. This produced consistent estimates of the relative rates of attacks for C1-INH, lanadelumab q4w and lanadelumab q2w versus placebo, and versus each other. The rate ratio compared to

placebo was [redacted] for lanadelumab q2w [redacted] for q4w [redacted] and [redacted] for the C1-INH [redacted] The rate ratios for lanadelumab versus C1-INH were [redacted] and [redacted] for the q2w and q4w arms respectively. To estimate the attack rate in the C1-INH arm of the model, the rate ratio of [redacted] from the indirect comparison is applied to the predicted placebo arm attack rate from the company's Poisson regression. However, the treatment arm specific Poisson regression estimates are applied directly for the lanadelumab arms in the company base case. An option does also exist to use the rate ratios derived from the indirect comparison for lanadelumab versus placebo, in a manner consistent with the approach used in the C1-INH arm, and the company presented this as a scenario analysis. The estimated attack rates applied in the first 12 months of the company base case model are present in Figure 21 of the company submission (Document B, page 143).

ERG commentary

The ERG have concerns regarding the company's approach of applying the rate ratio for C1-INH versus placebo (from the indirect comparison) to estimate the C1-INH attack rate in the model, whilst using the treatment specific regression based attack rates from HELP-03 in the lanadelumab arm. This creates an inconsistency between the model based estimate of the percentage reduction in attacks for lanadelumab versus C1-INH, and the rate ratios for lanadelumab versus C1-INH from the indirect treatment comparison; i.e. the company base case predicts a [redacted] reduction in the attack rate, while the indirect comparison generates rate ratios consistent with a [redacted] reduction in attacks (after accounting for the proportion assumed to be on each dose of lanadleumab). The company present the latter as a scenario analysis, in which the incremental NMB is reduced but remains positive. For reasons of consistency highlighted above, the ERG tends to prefer this latter approach. Alternatively, consistency with the indirect comparison could be retained in the model by applying rate ratios (from the indirect comparison) to the estimated attack rate in one of the landelumab treatment arms.

<u>Taking account of attack severity and duration</u>

In HELP-03 attacks were defined as being mild, moderate or severe, as follows:

Mild – transient or mild discomfort

Moderate - mild to moderate limitation in activity, some assistance needed

Severe – marked limitation in activity, assistance required

Data for all treatment arms were pooled and the proportion of each level of severity was calculated. See Table 39 (Document B, page 144) for the results: 40% were mild, 52% were moderate and 8% were severe.

These proportions were then applied to each attack, irrespective of what prophylactic treatment regimen was being used at the time.

Data on attack duration were collected in the HELP-03 and the CHANGE RCT of a C1-INH. Table 40 (Document B, page 145) showed both active treatments reduced the duration compared to placebo; however, the duration of an attack on placebo was very different across the RCTs [redacted] days in HELP-03, 3.4 days in CHANGE) so comparisons are hard to interpret. The company assumed the shortest observed duration [redacted] days for lanadelumab q4w) was used for all attacks on either lanadelumab or C1-INH treatment. The attack duration is multiplied by the mean number of attacks per cycle in the model to estimate the time in attack (days) for the purpose of estimating QALYs, and the time not in attack is simply 28 minus days in attack. Thus, the model captures a reduction in costs associated with lanadelumab's lower attack rate compared with C1-INH, and a QALY gain driven by the lower time in attack in the lanadelumab arm.

ERG commentary

The ERG are generally satisfied with the company's approach to estimating the distribution of attack severity, and applying the same distribution across the treatment arms. This seems consistent with a secondary analysis from HELP-03 which showed that lanadelumab provided a similar percentage reduction in high morbidity attacks (Figure 7, company submission Document B) as it did for all attacks. In addition, the ERG has no major concerns relating to the assumptions regarding attack duration in the model.

Mortality

Age-specific rates for the general population were applied. No disease-specific mortality was considered. While some people have a recorded cause of death of

angioedema, there were only five cases in England and Wales in 2017, according to the submission (Document B, page 145). There is a lack of robust data on excess risk, so the company assumed no excess risk. They make the case that this works against lanadelumab because seizure frequency is likely associated with mortality risk and lanadelumab is associated with biggest reduction in seizure frequency.

ERG commentary

The ERG agrees that there was insufficient data on mortality differences between treatments to model a difference over the lifetime of the patients.

5.2.7 Health-related quality of life

EQ-5D-5L data collected in the RCT

In the HELP-03 RCT the company measured quality of life using the EQ-5D-5L and the AE-QoL. Results for AE-QoL are reported in Section B.2.6 of the company submission (page 81) and are discussed further below.

EQ-5D-5L results, using the NICE DSU method of cross-walk to the EQ-5D-3L value set, were reported on page 149 of Document B and are reproduced below in Table 30 and 31:

Table 30 HELP-03 EQ-5D-5L index summary data

Treatment	Day 0	Day 98	Day 182
Pooled treatments	0.874 (n=124)	0.891 (n=117)	0.876 (n=115)
Lanadelumab 150mg q4w	0.839 (n=28)	0.869 (n=27)	0.889 (n=26)
Lanadelumab 300mg q4w	0.870 (n=28)	0.908 (n=28)	0.869 (n=28)
Lanadelumab 300mg q2w	0.888 (n=27)	0.914 (n=25)	0.874 (n=25)
Placebo	0.890 (n=41)	0.878 (n=37)	0.874 (n=36)
Key: q4w, every 4 weeks; q2w, every 2 weeks.			

Table 31 ANCOVA results for change in EQ-5D-5L scores from Day 0 to Day 182 by treatment arm, adjusted for baseline scores: ITT population

Treatment arm	EQ-5D-5L least square mean change (SD)
	Utility/index
Placebo	-0.01 (0.13)
Lanadelumab 300mg q2w	0.0 (0.13)
Lanadelumab 300mg q4w	-0.01 (0.13)
Lanadelumab 150mg q4w	0.03 (0.13)
F value	1.34
Lanadelumab total versus placebo: least square mean change (SD)	
Placebo	-0.01 (0.13)
Lanadelumab total	0.01 (0.13)
F value	0.98

Key: ANCOVA, analysis of covariance; CI, confidence interval; EQ-5D-5L, EuroQol 5-dimensional 5-level descriptive system; ITT, intent-to-treat; q2w, every 2 weeks; q4w, every 2 weeks; SD, standard deviation.

Source: HELP-03 CSR (Shire. HELP Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data])

(Tables 30 and 31 are reproduced from Document B of the company submission, page 149)

The company's interpretation was "No statistically significant differences were observed either over time or across the three lanadelumab treatment arms and placebo arm." (page 148).

The company made the case that EQ-5D suffered from "significant limitations" (page 148); the only specific support they provide for this statement is that EQ-5D was measured at three fixed time-points (Days 0, 98, and 182) and these only coincided with an attack by chance. As a result of the 807 attacks recorded in all patients in the RCT, only 2 have an associated EQ-5D completion.

The company concludes the EQ-5D data collected in the RCT have no use in the economics model.

ERG commentary

EQ-5D is an appropriate tool to use in an RCT for the purpose of measuring and valuing health states experienced by patients in each treatment arm. The ERG supports its use in HELP-03 but notes that the problem of only having very limited data while attacks were happening could have been foreseen. Apart from the issue of the fixed timing of administering EQ-5D, the nature of the disease, which sometimes involved swollen hands, would reduce the chances a patient was able to complete a written questionnaire during an attack. An alternative data collection plan could have been considered. Given the RCT protocol and results, the ERG acknowledge that the quality of life deficit patients experience during attack would have to be valued using data not collected in the RCT.

However, the ERG does not agree that this issue means the RCT data on EQ-5D should be wholly discarded. The company made the case there are three sources of quality of life loss with usual care (pages 146 to 147 of Document B): HAE attacks, psychological illness stemming from fear of attacks, and burden of iv administration of current treatments. While the ERG acknowledge that there is an issue with measuring and valuing attacks using RCT data, the company has not made a case for why EQ-5D would not capture the impacts on quality of life between attacks. (Of course, in HELP-03 no treatment was administered iv so the data provide no information on the impact of route of administration on utility.)

The ERG propose that a more plausible approach would have been to base utility values on the RCT data adjusted for the disutility of attacks where the latter was taken from a source outside of the RCT.

<u>AE-QoL data collected in the RCT</u>

As an alternative to the RCT data on EQ-5D the company note the AE-QoL data were collected. This covers four dimensions: functioning, fatigue/mood, fear/shame, and nutrition. From Table 17 in Document B (page 83), the biggest impact of lanadelumab compared to placebo was on functioning, followed by fatigue/mood. However, the company say there is no validated way to map to a utility-based data set of values.

ERG commentary

The ERG welcomes the AE-QoL as a disease-specific tool that can give greater insight into the experience of patients. It is surprising that pain was not included as a domain, given the importance patients attach to it.

The ERG acknowledges that there is no published method to map AE-QoL to EQ-5D. However, the company could have explored such an approach; while this is not the method preferred in the NICE Reference Case it can be used (with acknowledged limitations) and would have had the important advantage of having been measured in patients in the RCT used elsewhere in the economics model submitted. Given the positive results, it is surprising the company did not pursue this option.

The AE-QoL results also raise issues, however. The biggest changes were on domains that it is reasonable to expect would have been detected by EQ-5D (functioning and fatigue/mood) but no further analysis is presented to compare results in individual patients. On page 85 of Document B, commenting on the lack of a statistically significant difference on EQ-5D the company put forward the argument that it is a generic measure and can be insensitive to change in a particular disease. However, this opportunity to explore the differences with a disease-specific instrument was not taken up. The alternative hypothesis, that AE-QL is overly-sensitive to change because of the wording of the survey questions and/or the scoring method is not considered.

Data from published studies: the company's base-case

The company then carried out a systematic review of the literature for utility-based values in HAE. One study was selected for the base case with a second study used in support in sensitivity analyses.

The selected study was published in 2014 (Nordenfelt 2014).[19] Reasons for selection included that the company judged the method to be the most robust, that the values most closely matched the EQ-5D results from HELP-03, and this source was selected

independently by the American organisation, ICER, for their report on the cost-effectiveness of prophylaxis [ICER report][46]

All 629 patients in Sweden identified with HAE through health care system sources were approached and 239 replied. A registry was formed of 145 patients. For this study, 139 were contacted (1 person had died, 5 had asked not to be contacted for further research).

Two EQ-5D-5L survey documents were included, with instructions for one to be completed for 'today' and one with the patient imagining they had completed it during their last attack.

Replies were received from 107 with four returned blank. Of the 103 responses, 101 reported a score for 'today' and 78 for 'during last attack'. No further explanation was provided in the publication of why some patients did not report some values, or of any attempt to ask for the missing information. The sample was a small proportion of the overall patient population initially considered. Age is reported and seems in line with patients recruited to the RCT (average between 40 and 45 years old, range 4-89).

The average utility value for 'today' was 0.825 (+/- 0.207) and during an attack 0.512 (+/- 0.299). As would be expected this overall difference between EQ-5D today and during last attack of 0.31 covered a range from when the attack was self-assessed as having been mild (difference of 0.07), moderate (difference of 0.369) and severe (difference of 0.486)

The published paper also reports that when patients were grouped by self-reported frequency of attacks, there was a correlation between more frequent attacks and lower utility values. The Spearman correlation is reported to be -0.3 when comparing three groups: 84 patients who had between 0 and 14 attacks per month, 8 patients who had

between 15 and 29 per month, and 11 who had 30 or more attacks per month. This was reported in text but not presented visually.

In the CS, the main results for the today and 'during last attack' were used. In the base case, the utility loss for an average of all attacks was used but this was based on the average that was self-reported by the Swedish patients. The utility per cycle was a weighted average of the time with and without an attack.

In a sensitivity analysis in the CS, attack severity in the model (based on the RCT) were taken into account by applying the specific disutility for attacks of each level of severity. This changed the incremental NMB from £470,031 to £469,557.

However, the descriptions of mild, moderate and severe differed to some extent between the HELP-03 RCT and the Swedish study. In Nordenfelt (2014) [19] a moderate severity attack was described as follows:

> "Moderate: wanted intervention for symptoms during your attack or your activities of daily living were affected. For example, if your hands were swollen and you could not button your shirt, or your feet were swollen and wearing shoes was uncomfortable" (page 186 of Nordenfelt (2014)).[19]

In the HELP-03 RCT a moderate attack was described as mild to moderate limitation on activity, some assistance needed.

Nordenfelt described a severe attack as:

> "Severe: treatment or intervention was required, or you were unable to perform activities of daily living. For example, if your throat was swollen and you were having difficulty breathing, or your lips were swollen, and you could not eat" (page 186 of Nordenfelt (2014)[19]

In the HELP-03 RCT the description was marked limitation in activity, assistance required.

Second study from the literature

A second study by Aygoren-Pursun (2016)[20] was selected from the literature. This was a bespoke survey of the burden of illness in 111 HAE patients in Germany, Denmark and Spain. Answers were used by the researchers to complete an EQ-5D survey, predicting which answers respondents would have given had they completed it. Various assumptions were made, such as the ability to self-care was unaffected by HAE.

When the values from the second study were used the NMB changed from £470k to £468k.

ERG commentary

The selection of Nordenfelt from the available studies was reasonable. The way the utilities were applied seemed reasonable. However, uncertainties remain. First, while attacks evidently involve a disutility it is not clear if the values in Nordenfelt can be relied upon. The values in Aygoren-Pursun provide a cross-check but they are different e.g. for example a severe attack is valued at -0.486 in Nordenfelt compared to 0.825 when attack-free, whereas in Aygoren-Pursun it is valued at 0.08 (Document B, Table 43, page 155). Second, as noted above, the definitions of severity differ slightly. The base-case is also based on a group of self-selected Swedish patients (16% of the 629 initially identified responded) being asked to recall the experience of an attack. The reassurance that can be taken from the cross-check with Aygoren-Pursun is limited given the methods that study used when researchers completed the EQ-5D answers they think patients would have given had they completed it, based on their survey answers; for example, the assumption self-care is unaffected seems strange given that definitions of severity of attacks depends on the need for assistance.

The approach in both published studies was that severity of attack matters, whereas it seems plausible that the location of the swelling on the body matters too. The ERG asked a clarification question about this, including a request for a sensitivity analysis. The company replied that in discussion with clinicians and patient groups that the location on the body did not correlate clearly with quality of life. They said data to run a sensitivity analysis were not available.

The other issue is that the 'without attack' utility measured in the RCT is higher than the 'without attack' utility in Nordenfelt. The ERG asked a clarification question, requesting the company re-run the model with HELP-03 data representing attack free and Nordenfelt's utility values for time with attack. In reply, the company first defended their base case, saying that as Nordenfelt had to be used for attack utility values, it was consistent to also use the without attack values from that source. However, the company then described two additional scenarios (from Company Response to Clarification Questions, B12, pages 32-33).

Scenario 1 used HELP-03 data: "a regression was conducted with age included as a covariate to allow for the utility values to be adjusted over time. As the attack-free and attack utilities are taken from different sources when this scenario is utilised, the multiplier approach presented in NICE DSU TSD12[48] is adopted to adjust the attack utility for differences between both populations using the formulae outlined in Figure 7.

$$Attack\ utility\ value * \frac{HELP\ 03\ attack\ free\ utility\ value}{Nordenfelt\ attack\ free\ utility\ value}$$

Figure 7 Utility adjustment formulae

Scenario 2: This involved converting the absolute utility value 'with attack' into a decrement. The CS describes the method as follows: "The application of an absolute utility value rather than a utility decrement in the submitted model does not allow for

the impact of attacks to be adjusted over time as patients' age. Therefore, the attack-free utility value declines over time as the average age of patients increases, but the attack utility remains constant over time, resulting in an assumption that the HRQL impact of an attack declines over time. Therefore, a more appropriate approach has been adopted which involved estimating the utility decrement of an attack by subtracting the average attack-free utility value from Nordenfelt (2014)[19] from the average attack utility value and applying this decrement to the attack-free utility value in each cycle."

The model was then re-run with these scenarios included, with the following results (Table 32):

Table 32 Scenario analysis for changes in the application of utility values

Scenario	Incremental QALYs	NMB (£)
Base-case	[redacted]	£470,031
1. Age-adjusted attack-free utility values from HELP-03	[redacted]	£468,580
2. Average attack utility value applied as a decrement	[redacted]	£470,540
Scenarios 1 & 2	[redacted]	£469,137
Key: NMB, net monetary benefit; QALY, quality-adjusted life year		

(Company Response to Clarification Questions, B12, page 33)

Clearly, the impact on the NMB is minimal.

Adverse events

The CS (Document B, page 148) states rates of adverse events in the two clinical studies in the indirect comparison were low. The company state that the most frequent adverse event was injection site reactions with C1-INH, and this is covered in another part of their approach to include utility differences relating to mode of administration (see below).

ERG commentary

It would have been preferable to model injection site reactions separately for transparency, rather than in a disutility for IV versus subcutaneous administration that combines several elements (see below). However, any differences between treatments would be very unlikely to affect the NMB in an important way.

Intravenous administration and frequency of administration

The company made the case that by being on iv administration, there were several negative impacts on quality of life:

- Issues finding a usable vein or getting the infusion to work properly
- A preference for subcutaneous over iv administration in other diseases
- Use every 2-4 weeks versus twice a week is more convenient
- More frequent use is associated with a higher frequency of injection site reactions

No new data were collected to help to value this disutility. The company carried out a systematic literature review to identify relevant data and found nine studies, three of which were used in the CS. The base-case used the results of Jorgensen (2017). A sample of the UK public (n=1,645) was recruited and presented with vignette descriptions of eight health states, varying subcutaneous and iv administration; 1, 2, 4, 8, 12-week frequencies; location in home and hospital.

The values selected to represent C1-INH treatment was iv administration in hospital every 4 weeks (utility 0.836), while for lanadelumab the best match was judged to be subcutaneous delivery every 8 weeks in hospital (utility 0.86). The key figure was the difference between the two figures of 0.024. This is applied as a utility increment in the model for those on lanadelumab treatment. It should be noted that the company provided a revised version of the model in response to the clarification letter, which allowed this increment to be removed for those discontinuing lanadelumab. In the company base case it is applied to the whole cohort in the lanadelumab arm.

Holko et al.[49] carried out a survey of 127 patients with inflammatory bowel disease, varying characteristics of a hypothetical treatment and using time trade-off.

Evans et al.[50] carried out a similar exercise in 2,465 members of the public (UK, Canada, Sweden), 247 people with Type 1 diabetes and 417 with Type 2 diabetes.

The latter studies were used for sensitivity analyses (and made little difference to the NMB). Even when there was no utility benefit for treatment administration, the NMB only changed from £470k to £455k. Nevertheless, it can be noted from the company results that administration utility benefit is the key driver of the small QALY gain for lanadelumab versus C1-INH.

ERG Commentary

The company make a case for why disutility from the route and frequency of administration would be plausible; however, they provide no data on how often people have problems with iv administration, or how often injection site reactions occur.

There was no way to capture differences in utility for aspects of administration of the medicines from the clinical study programme. However, the company could have commissioned a bespoke study in HAE patients matching the license.

Having made the decision to seek data from a systematic literature review, this was adequately carried out. The comparison of methods to select a base-case study made sense. However, the Jorgensen study suffers from weaknesses. It has only been published as a poster so the full method and results have not been described. The people valuing the vignettes were members of the public and had not undergone any of the treatments being described; this would have made them dependent on the descriptions provided.

There was also a poor match for the regimes relevant to HAE with iv therapy every 4 weeks in hospital proxying iv twice a week for C1-INH, and subcutaneous every 8 weeks in hospital proxying every 2-4 weeks for lanadelumab at home. Considering C1-INH dosing is twice a week by iv infusion at home (more frequent but not in hospital) the impact on the disutility is unclear and there is uncertainty around the true difference.

5.2.8 Resources and costs

Medicines costs: lanadelumab

The company's model includes the 300mg subcutaneous dose self-administered either every 2 weeks or every 4 weeks. In line with the license, all patients are assumed to initiate on the 300mg every two weeks dose. The Summary of Product Characteristics says, "In patients who are stably attack free on treatment, a dose reduction of 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight"(Shire 2011).[27]

The medicine cost per injection was from the price agreed with Department of Health and Social Care, reduced by a confidential Patient Access Scheme discount that the company expected to agree before the meeting of the NICE Appraisal Committee. The discount applied was of [redacted].

The license allows patients to switch to every 4 weeks if the attack rate is adequately controlled. UK clinical specialists advised the company patients would be followed-up every six months so it was assumed this decision could be made at either 6 or 12 months.

To estimate the proportion who would switch, the company used data from HELP-03 which showed that after 6 months on lanadelumab 300mg every 2 weeks, [redacted] were attack free and would thus be eligible to switch to dosing every 4 weeks.

The company then assumed further switching at 12 months. Using data from HELP-03, 76.9% of patients treated every 2 weeks were attack-free between days 70 and 182

(approximately the second half of month 3, months 4, 5 and 6). The company assumed that the proportion who switched to an injection every 4 weeks rose to this level after 12 months, so an extra [redacted] of patients switched.

For the proportion switching to the 300mg dose every 4 weeks in the model, attack rates predicted from the data in lanadelumab every 4 weeks arm of HELP-03 are applied.

ERG commentary

The main issue is with the proportion of patients switching treatment at 12 months has already been discussed in Section 5.2.6 above relating the effectiveness assumptions stemming from switching. It seems reasonable to use the HELP-03 RCT data on patients who are attack-free at 6 months as an upper limit for the percentage who may switch to the lower dose at this time point. However, it is not clear why the percentage of patients attack-free in months 3, 4 and 5 should then be equated with the percentage attack-free between 6 months and month 12 – and subsequently on the lower dose for the remainder of the model time horizon.

HELP-04 is a long-term study with treatment over 132 weeks (HELP-03 is for 26 weeks), yet no data from HELP-04 seem to have been used.

As the dosing at 12 months is then carried forward for the rest of the patient's lifetime, this has a very important impact on the economics results because it halves the medicines costs for an additional 32.5% of patients on lanadelumab.

Medicines costs: C1-INH

There are two C1-INH used in the NHS in England, with the brand names Cinryze and Berinert. Cinryze has a license in HAE for prophylactic use, while Berinert has a licensed indications in HAE for treating attacks and for short-term prophylaxis. Cinryze is marketed in the UK by the same company who hold the license for lanadelumab.

Both branded types of medicine are administered intravenously, and when used as a prophylaxis both are used every 3-4 days, according to the CS (Document B, page 134).

Cinryze is licensed for 1000IU per dose. Berinert dosing was based on the opinion of six clinical specialists in HAE in the UK and was assumed to be [redacted] per kg bodyweight initially.

The model used a bodyweight of [redacted], the average in the HELP-03 study.
The company model included vial wastage for Berinert, the only medicine with a weight-based dose, using the 'method of moments' approach.

Medicines costs were taken from MIMS for C1-INH.

SUPERSEDED

The company presented a single C1-INH regime by calculating the cost as a weighted average of the two branded types of medicine. In the base-case the company assumed [redacted] on Cinryze and [redacted] on Berinert, based on hospital dispensing data for the number of vials of each branded medicine used per month. Data were for the last three months reported i.e. July, August and September 2018.

See erratum

The company presented sensitivity analyses of the impact of changing these proportions.

In situations where there is an inadequate response, clinicians reported to the company they would either increase the dose and/or frequency, but this was not modelled; the CS states this therefore underestimates the true cost of a C1-INH regime.

In a sensitivity analysis, it was assumed [redacted] This substantially increased the net benefit from £480k to £740k.

ERG commentary

Clinical advice to the ERG confirms both branded C1-INH medicines are used in the UK; there have been issues with shortages of medicines so the choice is seen as being important to ensure patients can be treated without interruption.

However, the weighted average approach used by the company requires reliable predictions of the share of each medicine. The company used data for three months to get an overall ratio of [redacted] *in terms of vials for Cinryze compared to Berinert. However, the figures for the individual months were* [redacted]*, and* [redacted]*. The total number of vials used also ranged from 2272 to 2987, which may be inconsistent with prescribing in a stable long-term prophylaxis scenario.*

In response to a clarification question from the ERG, the company provided further sensitivity analysis with a wider range than in the original submission. The results table prepared was as follows:

Table 33 Scenario analysis for changes in the percentage of patients receiving Cinryze/Berinert IV

Proportions	ICER (£/QALY)	NMB (£)
Base-case [redacted] Cinryze IV: [redacted] Berinert IV)		
[redacted] Cinryze IV: [redacted] Berinert IV)	Dominant	£568,400
[redacted] Cinryze IV: [redacted] Berinert IV)	Dominant	£408,136
[redacted] Cinryze IV: [redacted] Berinert IV)	Dominant	£247,873
[redacted] Cinryze IV: [redacted] Berinert IV)	Dominant	£87,609
Key: IV, intravenous; QALY, quality-adjusted life year		

(Company response to Clarification Questions, B14, page 34)

The company also report they considered three years of prescribing data and found the "ranges are [redacted] *for Berinert and* [redacted] *for Cinryze".*

Note the company was asked to provide scenarios with 100% on Cinryze, 0% on Berinert and with 0% on Cinryze and 100% on Berinert. They declined to do so, arguing this did not reflect clinical practice.

The ERG notes that C1-INH dosing was assumed not be increased and agrees this will likely be an under-estimate of the true NHS costs. However, it would have been preferable to have modelled this explicitly rather than leaving it unquantified as this makes it difficult to judge what the impact of including it would have been. In the sensitivity analysis described above, the [redacted] *are assumed to derive no benefit, which is unrealistic.*

SUPERSEDED

Treatment duration (discontinuation and dose switching)

The company made the case there is no evidence for a difference between lanadelumab and C1-INH in terms of rate of discontinuation. The rate used per cycle was based on 91.2% of patients in HELP-03 completing the treatment period. The discontinuation rate per cycle was thus "back-calculated" to arrive at a figure of 8.8% (i.e. 100-91.2) discontinuations after 7 cycles. This was applied to lanadelumab and C1-INH equally.

See erratum

The model assumed that if the patient is still on treatment after cycle 7 they continue on treatment until they die (no further discontinuation).

In response to a clarification question the company explained this was due to a lack of long-term data to base an assumption upon, and also the strong safety profile of lanadelumab and C1-INH (Company Response to Clarification Questions, B5, page 24).

The company went on to clarify that when patients discontinue treatment in the model (which can only occur in the first six months) they were assumed to have no further active treatment. The company acknowledge this was a simplification but argued "because the assumption of equal discontinuation and survival rates between the arms means that any subsequent therapy costs would, in all likelihood be equal between the treatment arms".

The ERG asked the company a clarification question, seeking a sensitivity analysis reflecting the NHS Commissioning Policy which specifies the following:

- Consider discontinuing C1-INH if less than 2 clinically significant attacks per week on a once weekly prophylaxis dose
- Stop treatment with C1-INH inhibitor after two months if the attack frequency has not adequately reduced.

In response, the company said, *"…clinical experts, including those interviewed for the purpose of this submission, indicated that if patients are still experiencing breakthrough attacks they are more likely to receive an increase in administration frequency, while if they are successfully controlled, i.e. they are experiencing no attacks or few of them, treatment is rarely discontinued; this is still in line with the Commissioning Policy which provides some flexibility to clinicians in their consideration of treatment discontinuation. Therefore, sensitivity analyses where a discontinuation, for either lack of effectiveness or sustained effectiveness is implemented, would not be representative of current practice as this rarely happens."*

The ERG asked an additional clarification question seeking an extrapolated estimate of the percentage of patients remaining attack free on the q2w dose over a period of six months following lanadelumab reaching steady state concentration (from day 70 in the HELP-03 trial). This was requested to provide a better approximation of the percentage of patients who might be expected to switch from q2w to q4w in the long-term. The company provided this. Their method was as follows: "[A] range of standard parametric distributions (exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma) were explored in the extrapolation of the KM data. Survival models, utilising treatment arm as a covariate were utilised in order to make efficient use of the trial data." (Company Response to Clarification Questions, B11, page 29). Results were presented in the following graph (Figure 8):

Key: q2w, every two weeks.

Figure 8 Extrapolated day 70 time to first attack analysis (lanadelumab 300mg q2w): standard parametric distributions

(Company Response to Clarification Questions, B11, page 29)
Given the perceived poor fit, the company explored proportional hazards spline models. "We explored the use of different numbers of internal knots in the model to identify whether increasing this number enhanced the fit of the model. Utilising these models allowed for greater flexibility to capture any changes in hazards as the concentration of lanadelumab continued to reach steady state." Results were presented in the following graph (Figure 9):

Key: K, knot.

Figure 9 Extrapolated day 70 time to first attack analysis (lanadelumab 300mg q2w): spline models

(Company Response to Clarification Questions, B11, page 30)

The predicted 12-month attack free rate (inferred switching rate) for each parametric form were then run in the economic model, with the following results (Table 34):

Table 34 Scenario analysis for the percentage of patients assumed attack free at the second clinical assessment point

	AIC	BIC	% attack free at second assessment	ICER (£/QALY)	NMB (£)
Base-case model	N/A	N/A	76.9%	Dominant	£470,031
Spline model with 1 internal knot	704.98	721.7	[redacted]	Dominant	£346,998
Spline model with 2 internal knots	706.8	726.32	[redacted]	Dominant	£355,200
Gompertz	707.13	721.07	[redacted]	Dominant	£415,349
Spline model with 3 internal knots	708.66	730.96	[redacted]	Dominant	£360,668
Log-normal	718.22	732.16	[redacted]	£75,297	-£33,035
Log-logistic	719.63	733.57	[redacted]	Dominant	£92,731
Generalised-gamma	719.7	736.43	[redacted]	Dominant	£46,252
Weibull	721.22	735.15	[redacted]	Dominant	£204,827
Exponential	728.03	739.18	[redacted]	Dominant	£100,933

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit.

(Company Response to Clarification Questions, B11, page 31)

The company's interpretation is that the spline with 1 knot provided best fit. They also noted the four best-fitting models on AIC and BIC produced similar predictions. Lanadelumab remained the dominant option except if the log-normal was the chosen form.

ERG commentary

The ERG agrees that there is no evidence for differences in treatment discontinuation between treatments. It could be argued that if patients see iv treatment as more burdensome then they might be more inclined to discontinue, but this is speculative and was not an argument advanced in the CS.

It was surprising the company did not use data from the HELP-04 open-label follow-up to inform their prediction of future discontinuations. The assumption of no discontinuations after cycle 7 is potentially unrealistic as it assumes no loss of efficacy. Considering the mechanism of action of lanadelumab, a case could be made for some loss of efficacy over time, but this was not considered by the company.

The original company model ignored subsequent treatment costs in the proportion discontinued in each arm, and as noted above did not adjust the attack rate for subsequent treatment received. In practice, they could be re-challenged at a later date if the disease became sufficiently severe but this is not considered.

Administration of medicines

The company took clinical advice from NHS specialists in the UK. Based on this it was assumed both treatments would be self-administered at home at zero additional cost to the NHS.

Based on the clinical advice, a sensitivity analysis was carried out where iv administration could be hospital-based. A cost of £55 was assumed for a hospital specialist nurse to administer during a 30-minute appointment.

Monitoring for adverse events

No additional monitoring costs were included in the model above routine clinical follow-up of patients with HAE.

Treatment of adverse events

Only grade 3 or 4 adverse events occurring in 2% or more of patients in the HELP-03 and the CHANGE RCTs were considered. The only event for lanadelumab was a 1% rate of increased liver enzymes and for C1-esterase inhibitors a 1.4% rate of chest discomfort was assumed.

For each of these types of event it was assumed GP consultation was required, costing £38 (based on PSSRU data).

ERG commentary

The definition of a grade 3 adverse event is that it requires hospitalization, so it is not plausible that this could be managed by a GP. However, even if the cost included was for an admission with overnight stay, this would be very unlikely to have an important impact on the NMB given the low rate and approximately equal rate across treatment arms.

Treating attacks

Based on the HELP-03 study 85% of attacks were assumed to need on-demand medication.

The company assumed a patient starting on a C1-esterase inhibitor who had an attack would also be treated with the same medicine.

When a patient on lanadelumab had an attack, the company made the case it would not be appropriate to assume lanadelumab would be used to treat the attack because it is not licensed. UK clinicians advised the company that the most widely used medicines were the two C1-esterase inhibitors (Cinryze and Berinert) and icatibant. Therefore, the company took data from HELP-03 on the proportion of patents receiving each of these three medicines during an attack and scaled them up to 100% of the patients treated.

Because different treatments for an attack were assumed based on which prophylaxis the patient was taking the costs of managing an attack differed with attacks occurring on lanadelumab costing £1,382 compared to [redacted] for an attack on a C1-esterase inhibitor.

ERG commentary
Having asked UK clinicians which medicines were used to treat an attack, the company could also have asked them about the market share; this may have been preferable to adjusting RCT data.

A proportion of patients attend A&E and can be admitted. A study of NHS resource use by HAE patients in 2011-2012 provided data comparing them to non-HAE controls (matched for age and sex from a database, plus matched on local electoral ward of residence for hospital admissions). The study provided a statistic on 'hospital visits' with HAE patients having 1.52 more of these per year compared to controls. This was compared to the number of attacks the company's model predicted a patient would experience per year on C1-esterase inhibitor prophylaxis, which was 12.6. It was estimated 11.9% of attacks required an A&E attendance (=1.52/12.6),
For hospital admissions, it was assumed every A&E attendance led to a hospital admission. An HRG code was selected, KC04 described as treating Inborn Errors of Metabolism. No explanation was provided for either of these steps.

A second study was also identified using American data. The proportions attending A&E and being admitted were similar17.4% and 10.3% with 10.7% attending a primary care doctor. In the sensitivity analysis this made very little difference to the NMB (from £470k in the base case to £460k).

ERG commentary
The paper used to obtain the excess resource use with HAE was carried out in England (and Scotland) but has only been published as a poster. Some detail is not clearly explained for two key features.

One is the way controls were selected: it was not obvious which databases were used or how one control was selected from all the possible candidates. The second key feature is the definition of the term 'visits' in the poster. The CS interprets a hospital visit as an A&E attendance AND a hospital admission, but the methods description also refers to out-patient attendances as well. It is also not clear how many patients experiencing 'a visit' went to A&E only and how many were admitted as well. As a

result, the figures estimated by the company are the highest resource use figures possible and lower estimates are equally plausible.

It was not clear how the company selected the HRG code for an admission and the cost used in the model associated with this code of £2,961 does not seem consistent with the company's own estimate that average stay is 1.38 days (Document B, Table 50, page 162). The only way these two figures can be reconciled is if all admitted patients were in intensive care for this time, which seems unlikely.

Given the ERG's skepticism about these costs, a sensitivity analysis was requested as a clarification. In response the company provided the following (Table 35):

Table 35 Results for changes in the proportion of attacks assumed to be treated and the hospitalisation cost per day (NMB)

% of attacks treated	Hospitalisation cost per day			
	£2,961 (base-case)	£2,500	£2,000	£1,500
Base-case (85%)	£470,031	£456,183	£441,150	£426,117
90%	£487,153	£473,305	£458,272	£443,239
80%	£452,866	£439,018	£423,985	£408,952
70%	£418,579	£404,731	£389,698	£374,665
60%	£384,292	£370,444	£355,411	£340,378
50%	£350,005	£336,157	£321,124	£306,092

(Company Response to Clarification Questions, B16, page 36.)

While this was some help, even the lowest figure of £1500 seems high for a stay of just over one day. The ERG cross checked this using the code to group algorithm available from NHS Digital (https://digital.nhs.uk/services/national-casemix-office/downloads-groupers-and-tools/costing-hrg4-2017-18-reference-costs-grouper), and found the hospitalization for the ICD-10 code D84.1 (defects in the complement system) maps to the root HRG code WJ11 (other problems of immunity). Whilst the name for this HRG code does not seem particularly intuitive, the short stay reference

cost for this HRG is £455. This cost is more in keeping with an admission for observation, which based on the ERGs clinical expert advice, is what would be required for the majority of HAE patients admitted for acute attacks.

5.2.9 Cost effectiveness results

CS base-case results

The CS provides the following summary results for the base case (Table 36):

Table 36 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	NMB
C1-INH	[redacted]	21.48	[redacted]					
Lanadelumab	[redacted]	21.48	[redacted]	[redacted]	0.00	[redacted]	Dominant	£470,031

(Source: CS Document B, page 170 – note the Net Monetary Benefit (NMB) was calculated assuming the value of a QALY was £30,000)

In response to a clarification question from the ERG, the company provided the following breakdown of the QALY gain (Table 37):

Table 37 Incremental QALY breakdown

Category	QALYs lanadelumab	QALYs C1-INH	Incremental QALYs
Attack free	[redacted]	[redacted]	[redacted]
During attacks	[redacted]	[redacted]	[redacted]
Treatment administration	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
Key: C1-INH, C1 esterase inhibitor; QALY, quality-adjusted life year.			

(Company Response to Clarification Questions, B17, page 37)

Over the lifetime of the patient, commencing age 41, lanadelumab is £[redacted] cheaper than C1-inhibitor in terms of NHS costs.

[redacted] of the difference in costs is explained by costs of treating attacks ([redacted] attributable to differences in treatments and [redacted] to differences in hospitalization costs. The difference in medicines costs accounts for 14%.

No difference in mortality is predicted. The model predicts undiscounted life-years of 41.62 in both treatment arms (21.48 with discounting).

Lanadelumab gains [redacted] QALYs for the patient.

Looking into the model provided by the company (sheet Results-BaseCase), the model predicts that with C1- inhibitors the patient will experience 526 attacks, of which 315 will be moderate or severe; hospital admission will be required in 62 cases. With lanadelumab, the equivalent figures are 172, 103 and 20.

Lanadelumab is predicted to avoid 42 hospital admissions, 212 moderate or severe attacks and 354 attacks of all severities. This is a 67% reduction in the number of attacks.

The model predicts that patients in the lanadelumab arm spend an additional 0.54 years of their remaining life expectancy (21.48 years, all figures discounted) in the attack-free state compared to C1-INH.

5.2.10 Sensitivity analyses

Probabilistic analysis

The probabilistic analysis showed a 0% chance the incremental the cost per QALY gained for lanadelumab versus C1-INH could be above £20k.

Deterministic analysis

The Tornado diagram provided was as follows (Figure 10):

Key: IV, intravenous; q4w, every 4 weeks; q2w, every 2 weeks; NMB, net monetary benefit; RR, rate ratio; SC, subcutaneous.

Figure 10 Results of one-way sensitivity analysis

This suggests the parameters determining the number of attacks and differences between treatments in attacks are the key variables.

Scenario analysis

The CS presented the following scenarios (Document B, page 174), reproduced in Table 38 below:

Table 38 Scenario analysis results

Model assumption	Base-case	Scenario	ICER (£/QALY)	NMB (£)
Base case			Dominant	£470,031
Probabilistic			Dominant	£471,928
Time horizon	Lifetime (60 years)	10 years	Dominant	£113,087
		20 years	Dominant	£247,023
		40 years	Dominant	£412,481
C1-INH distribution	Based on hospital dispensing data: [redacted] Cinryze IV: [redacted] Berinert IV	[redacted] Cinryze IV: [redacted] Berinert IV	Dominant	£568,400
		[redacted] Cinryze IV: [redacted] Berinert IV	Dominant	£408,136
C1-INH frequency	Administered twice per week	Administered [redacted]	Dominant	£743,269
Attack utility settings	Apply average attack disutility	Apply disutilities by attack severity	Dominant	£469,557
	Attack severity based on pooled HELP-03 data across all treatments	Apply disutilities by attack severity. Attack severity for lanadelumab based on data from treatment arms in HELP-03 and C1-INH based on Riedl (2016)[51]	Dominant	£469,982
	Apply Nordenfelt (2014) values	Apply Aygören-Pürsün (2016)[52] utility values	Dominant	£468,159
Treatment administration utility benefit	Increment: 0.024 (Jørgensen [2017])	Apply no utility benefit	Dominant	£454,565
		Increment: 0.017 (Holko, Przemyslaw [2018])[53]	Dominant	£465,520
		Increment: 0.039 (Evans [2013])[50]	Dominant	£479,696
Lanadelumab efficacy	Efficacy estimated using Poisson regression coefficient	Lanadelumab efficacy estimated by applying rate ratio from NMA to the placebo estimates	Dominant	£393,793
Self-administration	100% of patients assumed to self-administer	90% of C1-INH patients assumed to self-administer (100% for lanadelumab)	Dominant	£481,286
Treatment discontinuation	Treatment discontinuation from HELP-03 applied	No treatment discontinuation applied	Dominant	£478,533
Attack resource use	Values applied calculated from Helbert (2013)[54]	Values applied calculated from Wilson (2010)[55]	Dominant	£460,174

Key: C1-INH, C1 esterase inhibitor; ICER, incremental cost-effectiveness ratio; IV, intravenous; NMA, network meta-analysis; NMB, net monetary benefit.

Most of the scenarios considered by the company did not make an important difference to the NMB result. The incremental NMB is heavily dependent on the cost saving predicted from lanadelumab, especially in terms of treating attacks. The predicted QALY difference of [redacted], when valued at £30,000 per QALY, is equivalent to [redacted] or [redacted] of the NMB value in the base case. Thus, even quite big changes in some assumptions would have almost no impact on the results. An obvious example is the utility values used, but another example is the value attached to a QALY: if this is set to £20,000 rather than £30,000 in the base-case, the NMB only falls to £463k.

5.2.11 Model validation and face validity check

According to section B.3.10 in the CS, the model was validated by both internal and external modellers - both the formulae and labelling was reviewed. The CS does not mention if and how the VB code used to generate the average attack rates per cycle were checked for errors and consistency. However, the ERG have visually checked the code and have identified no specific issues.

According to the CS, the model extrapolations of the attack rates, shown in Fig. 20 of the CS Document B, were validated against the HELP-04 study, referring to Table 20 in the CS. They note that the six-month data from the HELP-04 study highlighted how the attack rate remained constant beyond the HELP-03 study period, supporting the long-term extrapolation of the attack rate in the model. The company were not able to offer any longer-term data to validate extrapolation beyond 12 months. Whilst the HELP-04 extension study relates only to the q2w dose, it seems reasonable to assume that the attack rate for those on the q4w dose would also remain stable over the same period. However, the longer-term efficacy remains uncertain, and there are no data to draw upon to inform the rate at which the effectiveness of lanadelumab may wane over time. The company did provide some further scenario analyses in response to the clarification letter, which explored the impact of efficacy waning and longer term discontinuation of lanadelumab. However, these involved fairly crude simplifying assumptions; i.e. they assumed all patients would lose efficacy and discontinue treatment at selected points in the future. The company did not explore the impact of applying a smaller discontinuation rate per cycle over time.

As noted previously, most patients (76.9%) were also assumed to switch to the lower q4w regimen from month 12 onwards in the model. The company assumed that these people would experience the attack rate of the q4w arm from the point of switching. The company acknowledge that whilst they do not have data on the impact of the treatment switching policy, they believe it is possibly conservative since when patients are modelled to switch to the q4w dose, the applied attack rate assumes lanadelumab must reach its steady state after the switch. In reality, the drug will already be at steady state concentrations in those who switch from q2w, and so the attack rate may not rise so markedly initially following the switch.

However, the ERG remains concerned that the long-term predicted attack rates in the model are not validated against an appropriate source, since the HELP-04 extension study did not include any patients on a 4-weekly regimen. The HELP-04 study is also of short duration, further limiting its contribution as a source of validation of the modelled attack rates.

In addition to the company's validity checks of the model, the ERG conducted its own error checks (listed in Table 39). This checklist was developed from Tappenden and Chilcott.[56] No specific problems were identified through these checks. The ERG also conducted further cell checking in the model and identified some minor bugs as listed in Table 40, but these had no significant impact on the cost-effectiveness results.

Bugs found in the model were as follows: a) the probabilistic value for four parameters was calculated using the standard deviation (an empty cell) instead of the standard error, b) The calculation of the discontinuation rate does not look up the discontinuation rate for the last five cycles in the model, and c) the utility decrements in the model are beta distributions, therefore, Excel is not able to calculate the probabilistic value due to the negative point estimate of the utility value. These bugs had no impact on the deterministic model results, and would have negligible impact on the company's probabilistic results.

Table 39 'Black box' verification checks conducted on the company submitted model

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	None
	Sum expected health state populations at any model timepoint (state transition models)	Total probability equals 1.0	None
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	None
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	None
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	None
Cost estimation	Set intervention costs to 0	ICER is reduced*	None
	Increase intervention cost	ICER is increased*	None
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	None
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	None
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter (e.g., samples from beta distribution lie in range 0\x \1, samples from lognormal distribution lie in range x[0, etc.)	None
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	None
	Amend value of each individual model parameter*	ICER is changed	None
	Switch all treatment-specific parameter values*	QALYs and costs for each option should be switched	None
ICER incremental cost-effectiveness ratio, LYG life-years gained, QALY quality-adjusted life-year * Note this assumes that the parameter is part of the total cost function and/or total QALY function			

Table 40 Minor bugs identified in the company model

	Model		
	Sheet, cell	**Value**	**Corrected value**
Administration costs	Parameters, M64	IFERROR(NORMINV(L64,C64,E64),C64)	IFERROR(NORMINV(L64,C64,**F**64),C64)
	Parameters, M65	IFERROR(NORMINV(L65,C65,E65),C65)	IFERROR(NORMINV(L65,C65,**F**65),C65)
	Parameters, M66	IFERROR(NORMINV(L66,C66,E66),C66)	IFERROR(NORMINV(L66,C66,**F**66),C66)
	Parameters, M67	IFERROR(NORMINV(L67,C67,E67),C67)	IFERROR(NORMINV(L67,C67,**F**67),C67)
Patients on treatment	Lana_Calc, N17-799	E.g. IF(B17<=7,VLOOKUP($B$17:$B$794,DrugAdminCosts!$B$61:$E$67,4),N16)	E.g. IF(B17<=7,VLOOKUP($B$17:$B$799,DrugAdminCosts!$B$61:$E$67,4),N16)
Utility decrements	Parameters, M95-97 and M99-100	Beta distributions applied to utility decrements with negative sign (point estimate lies outside the range of the beta distribution)	

5.3 Exploratory and sensitivity analyses undertaken by the ERG

This section includes additional analyses undertaken by the ERG. The specific parameters the ERG deemed important to explore are those which are subject to a uncertainty and which are key drivers of cost-effectiveness. In particular, parameters relating to the cost of treatment and the cost of attacks, which underpin the estimated cost savings for lanadelumab. The further scenarios explored, and their justification, are outlined in the Table 41. The ERG first conducted additional scenarios around the company's base case (Table 42). Following this, building on a modelling scenario that the company provided in response to the clarification letter, the ERG has adopted a preferred base case which we think better reflects the likely treatment pathway for those who discontinue lanadelumab (Table 43). This ERG base case is then subject to the full range of scenario analyses outlined in the Table 44, with the results presented in Table 45. In addition, given the uncertainty surrounding the percentage of patients switching to the lower q4w lanadelumab dose and the proportion on Berinert/Cinryze in the C1-INH arm, a two-way sensitivity analysis was conducted for these two key parameters. The results are presented in Table 46.

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Finally, Tables 47 and 48 below are provided to illustrate the importance of the high cost comparator in the case for lanadelumab. The ERG does not dispute the fact that that there is a cohort of patients who require and receive long-term prophylaxis with C1-INH in clinical practice, and acknowledges the company's positioning of lanadelumab as an option for people who would otherwise receive C1-INH prophylaxis. However, given the uncertainty surrounding eligibility for long-term C1-INH prophylaxis based on the NHS commissioning policy, the ERG does have some concern that lanadelumab could be used by a small group of patients who would otherwise manage without long-term C1-INH prophylaxis.

See erratum

A key point to note from Table 42 is the sensitivity of lanadelumab's cost savings to the proportion assumed to switch from the higher q2w dose to lower q4w dose. In the company base case this is set at 76.9% in the long-term. Holding the company's other base case assumptions constant, lanadelumab switches from being cost-saving when the proportion drops to 60%, and the ICER increases rapidly if this parameter drops any further. The cost savings are also sensitive to the proportion of the C1-INH cohort assumed to be on Berinert, although this must fall below [redacted] before the ICER for

lanadelumab rises above £20,000 per QALY (holding all else constant in the company base case). It may be unrealistic to assume that the proportional use of Berinert among those on C1-INH prophylaxis would fall this low. Lanadelumab remains cost saving across the further scenarios assessed by the ERG, but the application of the lower hospitalisation cost for acute attacks (Table 42) does knock a substantial amount off the cost saving.

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See erratum

Table 41 ERG justification for additional exploratory and sensitivity analyses

Parameter / Analysis	Base case Assumption	Scenario explored	Justification
ERG's exploratory analyses conducted on both the company's base-case and ERG base-case scenario			
Proportion of patients on lanadelumab switching to low-dose (q4w) at 12 months onwards	76.9%	[redacted]	To investigate the impact of changing the percentage of patients switching from q2w to q4w.
Proportion on Berinert	[redacted]	[redacted]	To explore the impact of the intervention cost of the comparator group by varying the proportion on Berinert/Cinryze to reflect the uncertainty around the intervention cost of the comparator group.
Alternative HRG based hospital cost	£2,961	£455	This scenario explores the impact of using alternative data for the cost of hospitalisation.
Acute attack treatment cost equal for both treatment arms	£1,382.21 (lanadelumab arm) and [redacted] (C1-INH arm)		This scenario explores the impact of assuming that patients in both treatment arms incur the same acute care drug costs.
Treat all acute attacks	85%	100%	To reflect the scenario when all attacks experienced by a patient with hereditary angioedema are treated.
ERG's exploratory analyses on ERG base-case scenario only			
Time horizon	Lifetime (60 years)	10-40 years	Look at the impact of the uncertain longer-term assumptions used in the model.

C1-INH Frequency	Administered twice per week	Administered [redacted]	To reflect that in some patients on C1-INH, some might experience an up-dose.
Attack utility settings	Apply average attack disutility	Apply disutilities by attack severity	These scenarios look at the impact of applying an alternative method/source for estimating the attack utilities.
	Attack severity based on pooled HELP-03 data across all treatments	Apply disutilities by attack severity. Attack severity for lanadelumab based on data from treatment arms in HELP-03 and C1-INH based on Riedl (2016) [51]	
	Apply Nordenfelt (2014)[19] values	Apply Aygören-Pürsün (2016)[20] utility values	
Treatment administration utility benefit	Increment: 0.024 (Jørgensen [2017])[57]	Apply no utility benefit	To reflect the impact of assuming no added benefit or due to method of injection (SC) or using alternative data for the utility benefit from SC.
		Increment: 0.017 (Holko, Przemyslaw [2018]) [49]	
		Increment: 0.039 (Evans [2013]) [50]	

Lanadelumab efficacy	Efficacy estimated using Poisson regression coefficient	Lanadelumab efficacy estimated by applying rate ratio from NMA to the placebo estimates	The impact of using an alternative estimation for the efficacy parameter.
Self-administration	100% of patients assumed to self-administer	90% of C1-INH patients assumed to self-administer (100% for lanadelumab)	This scenario investigates the impact of assuming that some patients do not self-administer, and therefore, these patients will incur an additional admin cost.
Treatment discontinuation	Treatment discontinuation from HELP-03 applied	No treatment discontinuation applied	To explore the impact of assuming all patients remain on treatment.
Attack resource use	Values applied calculated from Helbert (2013) [54]	Values applied calculated from Wilson (2010) [55]	Exploring the impact of using alternative sources for the attack resource use.
Subsequent treatment for those discontinuing	All on C1-INH remain on treatment, and those discontinuing lanadelumab receive C1-INH	One scenario assumed no subsequent treatment (placebo) and another assumed that those who discontinue lanadelumab and C1-INH receive C1-INH and no treatment, respectively.	Exploring the uncertainty surrounding the subsequent treatment for those that discontinue treatment.

Table 42 ERG's further exploratory analyses on the company base-case

		Lanadelumab		C1-INH					
Analysis	**Description**	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. Cost**	**Inc. QALY**	**Deterministic ICER**	**NMB**
Company submitted model (response to clarification)									
Base-case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£470,031
ERG explored analyses									
Proportion of patients on lanadelumab switching from q2w to q4w (lower dose)									
50%		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£393,947	-£265,430
60%		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,064	£7,976
70%		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£281,381
80%		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£554,786
Proportion on Berinert									
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£568,400
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£408,136
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£247,873
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£87,609
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£129,621	-£72,655
Alternative HRG based hospital cost (£455)[a]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£394,697
Acute attack treatment cost									

Cost per attack=£1,373.29 in both treatment arms (as per lanadelumab arm)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£430,734
Cost per attack = £1,517.65 in both treatment arms (as per C1-INH arm)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£457,241
All attacks are treated		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£521,440

[a] ICD-10 code for Hereditary Angioedema (D84.1, Defects in the compliment system) mapped to HRG WJ11Z: Other disorders of Immunity – NHS reference cost for non-elective short-stay applied.

ERG changes to the company base case

The ERG had several criticisms of the company's original model structure. Specifically, the original model assumed that 9% would discontinue to no prophylactic treatment in both arms of the model by cycle 7 (and thereafter all patients would remain on their treatment for the remaining time horizon of the model. However, the model did not appear to adjust the attack rate upwards for the proportion who discontinued treatment, and treatment specific attack rates continued to be applied to the whole cohort in the respective arms. This may lead to over-estimation of the attack cost savings associated with lanadelumab compared to C1-INH. A further criticism was that the model did not allow for patients who discontinue lanadelumab to switch to C1-INH. If patients who would otherwise be considered for C1-INH are to be offered lanadelumab, it seems logical that those who discontinue lanadelumab, for whatever reason, might then go on to receive C1-INH.

Therefore, the ERG requested changes to the model structure at the clarification stage that could address these issues. Further, given uncertainties about the long-term efficacy of lanadelumab, the ERG requested scenarios that explored the impact of longer-term discontinuation of lanadelumab and switching to C1-INH. In response, the company provided changes that allowed:

1) The attack rate for the proportion discontinuing treatment to be adjusted upwards (assuming either no treatment or switching to C1-INH).
2) Removal of the subcutaneous administration utility benefit for those who discontinued treatment with lanadelumab. Whilst this inconsistency was not apparent to the ERG at the clarification stage, it does seem appropriate if patients are assumed to switch from lanadelumab to C1-INH.
3) Scenarios exploring loss of efficacy of lanadelumab at various future time points (i.e. assuming 100% loss of efficacy and discontinuation at selected future time points).

The company presented several scenario analyses around these parameters in their clarification response (reproduced in Table 43 below). The ERG believe one of these scenarios may be more realistic than the company base case. This scenario, labelled 1B in the company's response to question B21 of the clarification letter (Table 43), assumed the following:

- 9% of patients discontinue lanadelumab and C1-INH by cycle 7 (no further discontinuation thereafter).
- Those who discontinue lanadelumab switch to and incur the attack rate and treatment costs of C1-INH
- Patients who discontinue C1-INH are managed without long-term prophylaxis and incur the attack rate of the placebo arm of HELP-03.
- The utility benefit associated with subcutaneous administration versus IV infusion is removed for the proportion discontinuing lanadelumab.

Table 43 Treatment waning and discontinuation scenarios

Waning	Waning time	Discontinuation	Inc. costs	Inc. QALYs	ICER (£/QALY)	NMB (£)
I) No treatment waning	N/A	A) No treatment following lanadelumab and C1-INH	[redacted]	[redacted]	Dominant	£447,838
		B) C1-INH following lanadelumab & no treatment after C1-INH	[redacted]	[redacted]	Dominant	£127,377
II) Lanadelumab waning	5 years	A) No treatment following lanadelumab and C1-INH	[redacted]	[redacted]	Less costly / Less effective	£3,183,367
	10 years		[redacted]	[redacted]	Dominant	£2,567,684
	20 years		[redacted]	[redacted]	Dominant	£1,632,262
	5 years	B) C1-INH following lanadelumab & no treatment after C1-INH	[redacted]	[redacted]	Dominant	£37,326
	10 years		[redacted]	[redacted]	Dominant	£57,966
	20 years		[redacted]	[redacted]	Dominant	£89,093
Key: *To apply these scenarios in the model first adjust the attack rate and utility values for discontinuation by setting cells E128 and E140 on the Controls sheet to "Yes"*						

The ERG believe that scenario 1B gets closer to the treatment pathway that patients would face if lanadelumab were to be offered on the NHS as an alternative to long-term C1-INH prophylaxis. However, the ERG believes it may bias against lanadelumab since it assumes more patients end up receiving some form of high cost prophylaxis in the lanadelumab arm; i.e. 100% versus 91% in the long-term. Therefore, the ERG assessed the impact of setting the discontinuation rate to zero in the C1-INH arm of this scenario. This seems reasonably well justified since the company note that the discontinuation rate for C1-INH was simply matched to the rate of discontinuation observed for lanadelumab in HELP-03. The company's clinical

experts, and the ERG's clinical expert, are also of the opinion that there are very few patients requiring long-term prophylaxis who cannot tolerate C1-INH. The impact of this change can be seen in row 3 of Table 44.

The ERG also identified an error in the company's revised model, in the formula used to adjust the acute attack treatment costs for the proportion switching from lanadelumab to C1-INH. The company adjustment ("Lana_Calc" worksheet, Column AW, company revised model) appeared to cost acute treatment for a proportion of attacks twice, first using the acute treatment costs for attacks on lanadelumab, and then the acute treatment costs for attacks on C1-INH. The ERG therefore modified this formula so it would only apply the difference in acute attack treatment costs to the expected attack number occurring in the proportion of patients assumed to be on C1 - INH. The impact of this change on the company's scenario 1B can be seen in row 4. In addition the ERG prefers to apply the alternative hospitalisation cost for acute attacks, identified using the ICD-10 code for hereditary angioedema (D84.1) mapped to the HRG short-stay reference cost for WJ11 (Table 44, row 5).

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Finally, as outlined in section 5.2.6 (under "Indirect comparison") for reasons of consistency the ERG has a preference for estimating the attack rates in the lanadelumab arm of the model by applying the rate ratios for lanadelumab versus placebo from the company's NMA. This approach generates in a percentage reduction in the attacks (for lanadelumab versus C1-INH) in the model which is consistent with the rate ratios for lanadelumab versus C1-INH from the NMA. However, when applying the rate ratios in this way the company's adjustment to the attack rates, for discontinuation and treatment switching, could not be applied. Therefore, the ERG modified the formulas in the model to allow for this. Row 6 in Table 44 shows the impact of these changes.

See erratum

The ERG then combined the above changes in a preferred base case for further scenarios analyses (final row of Table 44). The further scenarios in Table 45 to 48 are all conducted relative to this revised ERG base case. The ERG also ran a probabilistic analysis of this alternative base-case, which produced a similar estimate of the NMB (£348,380); incremental cost = [redacted], incremental QALY = [redacted]

An important point to note from the further scenario analyses presented in Table 45 is that, from this new reference point, the ICER for lanadelumab now becomes unfavourable when the proportion switching to the low lanadelumab dose drops to between 70% and 60%. In addition, the ICER for lanadelumab becomes unfavourable when the proportion on Berinert in the C1-INH drops to be between [redacted] and [redacted]

Given the uncertainty and sensitivity of the results to these two parameters, further two-way sensitivity analysis was conducted around the ERG base case scenario, where these two variables were varied across plausible ranges simultaneously. The results are presented in Table 46. It can be noted that at lower levels of assumed switching to the lower lanadelumab dose, the cost-effectiveness case becomes more sensitive to feasible changes in the proportion of C1-INH patients on Berinert.

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See erratum

Table 44 Base-case scenarios

	Lanadelumab		C1-INH					
Analysis	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. Cost**	**Inc. QALY**	**Deterministic ICER**	**Deterministic NMB**
Scenario 1B (company response to clarification questions 20-21)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£127,555
Scenario 1B, but assuming everyone in the C1-INH arm stays on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£433,854
Scenario 1B, with correction to the adjustment of acute attack treatment cost in those who switch from lanadelumab to C1-INH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£161,175
Scenario 1B, with the ERGs alternative hospitalisation cost for acute attacks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£55,700
Scenario 1B, but with the efficacy of lanadelumab estimated relative to the placebo arm attack rate using rate ratios from the company's NMA (includes ERG's adjustment of the	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£36,726

attack rate for discontinuation or treatment switching in the lanadelumab arm).								
ERG base-case scenario (scenario 1B including all above changes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£346,270

Table 45 Scenario analyses surrounding ERG base-case

Scenario	ERG Base-case	ICER (£/QALY)	NMB (£)
ERG base-case		Dominant	£346,270
Proportion of patients self-administering (90% of those on C1-INH)	100%	Dominant	£357,525
Utility split by severity	Average attack utility	Dominant	£345,928
Attack resource use: Wilson (2010)	Helbert (2013)	Dominant	£346,502
C1-INHs increased dosing frequency: [redacted]	2 times per week	Dominant	£622,128
Time horizon: 10 years	60	Dominant	£91,355
Time horizon: 20 years	60	Dominant	£200,862
Time horizon: 40 years	60	Dominant	£320,633
Utility data source: Aygören-Pürsün	Nordenfelt (2014)	Dominant	£346,553
Administration utility: not included	Jørgensen	Dominant	£332,152
Administration utility source: Holko	Jørgensen	Dominant	£342,153
Administration utility source: Evans	Jørgensen	Dominant	£355,095
Attack severity source: HELP-03 by treatment arm	Average attack utility	Dominant	£346,323

Assume no treatment discontinuation	Yes	Dominant	£343,298
Proportion of patients on lanadelumab switching to low-dose (q4w)	76.9%		
[redacted]		£593,681	-£362,838
[redacted]		£186,001	-£99,229
[redacted]		Dominant	£164,380
[redacted]		Dominant	£427,989
Proportion on Berinert			
[redacted]		Dominant	£444,613
[redacted]		Dominant	£284,393
[redacted]		Dominant	£124,172
[redacted]		£87,842	-£36,048
[redacted]		£344,925	-£196,269
Acute treatment costs per attack are equal between groups (=£1,373.29 as per lanadelumab arm)		Dominant	£310,393
Acute treatment costs per attack are equal between groups (= [redacted] as per C1-INH arm)		Dominant	£329,341

All attacks are treated	85%	Dominant	£384,393
Assume no treatment for people who discontinue (in both lanadelumab and C1-INH arm)	Subsequent treatment for those discontinuing lanadelumab is C1-INH and all in C1-INH arm stay on treatment.	Dominant	317,359
Assume subsequent treatment for people who discontinue lanadelumab is C1-INH and those discontinuing C1-INH receive no treatment (placebo)		Dominant	36,726

Table 46 Two-way sensitivity analyses on ERG base-case

Scenario	Base-case	ICER (£/QALY)	NMB (£)
ERG base-case		Dominant	£346,270
Proportion switching to q4w at 12 months set to [redacted]	[redacted]		
Proportion on Berinert [redacted]		Dominant	£526,332
Proportion on Berinert [redacted]		Dominant	£366,112
Proportion on Berinert [redacted]		Dominant	£205,891
Proportion on Berinert [redacted]		Dominant	£45,671
Proportion on Berinert [redacted]		£214,500	-£114,550
Proportion switching to q4w at 12 months set to 70%			
Proportion on Berinert [redacted]		Dominant	£262,723
Proportion on Berinert [redacted]		Dominant	£102,502
Proportion on Berinert [redacted]		£121,839	-£57,718
Proportion on Berinert [redacted]		£376,775	-£217,939
Proportion on Berinert [redacted]		£631,712	-£378,159
Proportion switching to q4w at 12 months set to 60%			
Proportion on Berinert [redacted]		£31,393	-£886
Proportion on Berinert [redacted]		£283,280	-£161,107
Proportion on Berinert [redacted]		£535,167	-£321,327
Proportion on Berinert [redacted]		£787,054	-£481,548
Proportion on Berinert [redacted]		£1,038,941	-£641,769
Proportion switching to q4w at 12 months set to 50%			
Proportion on Berinert [redacted]		£440,902	-£264,495
Proportion on Berinert [redacted]		£689,810	-£424,716
Proportion on Berinert [redacted]		£938,718	-£584,937
Proportion on Berinert [redacted]		£1,187,626	-£745,157
Proportion on Berinert [redacted]		£1,436,534	-£905,378

Since the ERG have some concern that lanadelumab may be used in a minority of patients who would otherwise be managed without long-term prophylaxis, the ERG assessed the impact of adding a no prophylactic treatment arm (acute treatment as required) to the model. This exploratory analysis simply adds an additional arm to the model, in which the placebo arm attack rate and no prophylactic treatment costs are applied. In addition, 100% of acute attacks are assumed to be treated in this arm of the model, to account for the possibility that all are treated at an early stage before they become severe. Furthermore, the duration of an attack is assumed to be 1.4 days as reported in the HELP-03 study for the placebo arm. The adverse event rates are assumed to be the same as in the C1-INH arm. Two alternative scenarios are also assessed with respect to the costs attached to acute attacks. The first, Table 47, assumes that the acute attack treatment costs applied in the C1-INH arm of the model also apply to attacks in the no prophylactic treatment arm, and the second (Table 48) assumes the acute attack treatment costs from the lanadelumab arm apply. These analyses are caveated by the fact that the no prophylaxis arm may fail to account for a general disutility of experiencing more regular attacks, although the utility benefit of subcutaneous administration versus IV administration is retained for lanadelumab versus no prophylaxis to account for this possibility. A further caveat is that the acute treatment costs per attack may be higher when no prophylaxis is provided. In addition, prophylaxis may also result in a small mortality benefit compared to no prophylaxis. Nevertheless, very high ICERs can be noted for both prophylactic treatments, and for the C1-INHs in particular. Thus, the case for lanadelumab, within the confines of the company's model structure, is highly dependent on comparison against long-term C1-INH prophylaxis.

Table 47 ERG base-case scenario: comparing lanadelumab and C1-INH to no long-term prophylaxis (placebo) (acute treatment cost for placebo arm is the same as for C1-INH arm)

	Placebo	C1-INH	Lanadelumab
Total costs	[redacted]	[redacted]	[redacted]
Treatment costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Acute attack treatment cost	[redacted]	[redacted]	[redacted]
Acute attack hospitalisation cost	[redacted]	[redacted]	[redacted]
Acute attack A&E costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (long-term prophylaxis vs. no long-term prophylaxis)		£7,469,932	£2,849,770

Table 48 Cost-effectiveness analysis results comparing long-term prophylaxis to no long-term prophylaxis (placebo) (acute treatment cost for placebo arm is the same as for the lanadelumab arm)

	Placebo	C1-INH	Lanadelumab
Total costs	[redacted]	[redacted]	[redacted]
Treatment costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Acute attack treatment cost	[redacted]	[redacted]	[redacted]
Acute attack hospitalisation cost	[redacted]	[redacted]	[redacted]
Acute attack A&E costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (long-term prophylaxis vs. no long-term prophylaxis)		£7,676,386	£2,936,926

5.4 Conclusions of the cost effectiveness section

The ERG review of the economic evaluation identified strengths and issues.

The submission is positioned within the license for a particular position, where a C1-INH would otherwise be used, that clinical specialists say is plausible.

The key RCT provides data on the number of attacks, which are an important factor in determining the patient's quality of life.

The company's model provides a way of extrapolating RCT data over the lifetime of the patient and converting to QALYs and NHS costs.

Costs included the costs of the medicine, as well as costs of treating and managing attacks (medicines, A&E use, hospital stay).

Quality adjusted life year estimates captured the impact of attacks on patients baseline quality of life, and also a potential gain in quality of life associated with less burdensome admistration of lanadelumab.

In costing C1-INH treatment to represent usual care some assumptions were made that the company argue were conservative e.g. the base case did not apply costs of increasing the dose.

A range of sensitivity analyses were provided that helped identify which factors were the main 'drivers' of the economics results.

However, a number of issues were also identified:

The arm of the economics model representing 'usual care' differs from the published NHS England Commissioning Policy in several ways. These include: criteria for starting prophylaxis with C1-INH; the definition of a clinically significant attack; the criteria for reducing frequency of use of C1-INH and criteria for stopping C1-INH prophylaxis. In the company's response to the ERG's clarification questions, the

company defended the base case because it said clinical practice did not fully align with the policy and clinicians anticipated the NHS policy might be revised.
In some circumstances 'usual care' may be 'no prophylaxis' for a minority of patients. The company declined to provide an ICER against this alternative, saying it did not represent the proposed positioning of lanadelumab and was outside NICE scope. The ERG constructed a 'no prophylaxis' arm based on the placebo arm of the RCT, which suggested the cost per QALY for C1-INH and for lanadelumab versus 'no prophylaxis' was likely to be above usually accepted thresholds.

The starting age in the company's model was 41, it is not clear if the results would still hold if patients were younger when they started treatment.

The company base case uses Poisson regressions fitted independently to the lanadelumab arms of HELP-03 to extrapolate attack rates in the landelumab arm of the model, whilst estimating the attack rate in the C1-INH arm relative to the predicted attack rates based on the placebo arm of HELP-03. This approach leads to a 67% reduction in attacks for landelumab versus C1-INH in the model, when the rate ratios for lanadelumab versus C1-INH from the NMA are consistent with a [redacted] reduction in attacks (after accounting for the proportion of patients assumed to be on each dose of lanadelumab in the model).

In the base case the assumption is that the effect seen can be carried forward with no subsequent waning. As lanadelumab is a monoclonal antibody, resistance is feasible and the ERG believed some exploration of waning over the lifetime horizon was appropriate.

Validation of the predictions of the model for C1-INH were confined to clinical specialist opinion in the context of an advisory board meeting. No validation was made against extrenal data on the observed use of these medicines for reductions in attacks compared to baseline, changes in doses, quality of life impacts, etc.

The model assumes that patients start on lanadelumab every 2 weeks but as the number of attacks reduces prescribers switch some patients to injections every 4 weeks instead. The company estimate this proportion to be 44.4% at 6 months, based

on the clinical studies. However, the model also assumes further switching at 12 months to bring the overall total up to 76.9%, which is carried forward for the remaining time horizon. The basis for this was the percentage of patients attack-free between Day 70 and 182 of HELP-03, when the company state drugs concentrations are in stready state. Responding to ERG clarifications questions, the company provided extrapolations of proportion of patients in steady state that would be expected to be attack free over a full six month duration, but the ERG believe uncertainty remains and this parameter is highly influenceial on the cost-effectiveness results.

C1-INH is available as two branded medicines Cinryze and Berinert. In the base case these have [redacted] and [redacted] market share respectively, but this is uncertain and results are sensitive to it. When higher rates of cynrise use are combined with other possible changes, lanadelumab can switch from being dominant to having an ICER above accepted thresholds. The ERG also asked for a comparison with each type of C1-INH individually, but the company declined to provide this.

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In the company model, the costs of treating attacks was estimated differently according to the prophylaxis received, this worked in favour of lanadelumab. The proportions of patients with attacks attending A&E and subsequently admitted are uncertain. The cost used for in-patient admissions seemed inappropriate and produced a cost that was very high for an assumed 1-day stay.

See erratum

The company chose not to use EQ-5D data from the HELP-03 RCT in the economics model because it does not capture the disutility of attacks. However, switching to an alternative source involved using lower 'without attack' values than the RCT data suggested.

The alternative study used had some strengths but the values came from a self-selected sample of Swedish patients recalling quality of life during attacks that are classified by severity scale with some differences to the RCT definitions (but applied as though they were the same).

Disutility of attacks was assumed to only depend on severity, but the location on the body may also be important. In response to an ERG clarification question the

company said patients and clinicians had told them this was less important and they could not include it in the model due to lack of data.

Disutility of iv administration was included but actually rolled several possible sources of disutility into one. The ERG's preference would have been to model them separately: for example, one element was the problem of infusion site reactions, but data are available on how common this is, and duration of utility loss could have been estimated. Instead, the study used for base-case values had several issues, the main one being the poor match between the regimes valued in utility terms and the regimes for C1-INH and lanadelumab.

6 Overall conclusions

The current submission focuses on people aged 12 years and older with HAE Type I or II who have at least one angioedema attack every 4 weeks. The proposed population is narrower than the marketing authorisation because the evidence on lanadelumab is limited to this population. The main source of evidence presented by the company is the phase III HELP-03 trial assessing lanadelumab 300mg every two weeks (27 patients) and lanadelumab 300pm every 4 weeks (29 patients) versus placebo (41 patients) and the phase III ongoing HELP-04 open label extension study. Both trials are sponsored by the company (Shire).

The ERG agrees that the evidence on clinical effectiveness from the HELP-03 trial shows that there is a beneficial effect from lanadelumab compared with placebo. During the 26-week treatment period, lanadelumab showed a significant and meaningful reduction in the number of investigator-confirmed HAE attacks compared with placebo.

The ERG also agrees that the secondary endpoints assessed in the company submission (i.e., number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period, number of moderate or severe investigator-confirmed HAE attacks during the treatment period and number of investigator-confirmed HAE attacks occurring on Day 14 to Day 182) demonstrated significant benefits for lanadelumab compared with placebo.

Results from HELP-04 (long-term extension study) showed durable responses with lanadelumab for over a 1-year treatment period.

Lanadelumab showed a well-tolerated safety profile in the HELP-03 trial and was not associated with the safety concerns of androgens and plasma-derived C1-INHs. In the long-term extension study HELP-04 the majority of AEs were reported to be mild/moderate in severity with low level of treatment discontinuation.

No other head-to-head trials assessing the effects and safety of lanadelumab versus other relevant comparators were identified. The company presents a Bayesian NMA based on two studies, HELP-03 and CHANGE. CHANGE is a phase III cross-over trial comparing C1-INH IV (11 patients) versus placebo (11 patients).

Results of the NMA showed that patients treated with 300mg lanadelumab (300mg q2w and 300mg q4w) had fewer attacks each month than patients who received placebo. Moreover, the 300mg doses of labadelumab showed an improvement in relative risk of attack compared with C1-INH IV.

Overall, the company's systematic review of clinical effectiveness evidence was well-conducted and the methods used were appropriate. There was a concern about the reliability and robustness of the results given that the key relevant study, HELP-03, was a relatively small study such that none of the sub-groups analyses were definitely investigated. This also impacted on the NMA, which included only two trials both of small sample size and of different study design with HELP-03 being a parallel 4-arm trial and CHANGE a cross-over trial. While the ERG was able to validate the NMA for basic fixed effects models, they were not able to reproduce the company's HRs or their associated SEs, which fed into the NMA.

The company developed a simple cohort model to estimate lifetime NHS costs and QALYs for lanadalumab versus C1-INH (Cinryze and Berinert) for the prevention of attacks in people with hereditary angiodema. The model was based on randomised evidence in a rare disease area, and was extrapolated over a lifetime horizon. The comparator arm was chosen based on the company's proposed positioning of lanadelumab: in those who are not controlled with or are not suitable for oral prophylactic treatment, and who would otherwise be considered for treatment with C1-INH prophylaxis.

This model has two states, alive and dead, with each cycle in the 'alive' state reflecting the proportion of time spent experiencing an attack. The predicted number of attacks in the lanadelumab arm was based on fitted estimates form Poisson regressions fitted independently to each of the relevant treatment arms of HELP-03. For the attack rate in the C1-INH arm, the company applied a rate ratio for C1-INH

versus placebo, derived from an indirect treatment comparison with lanadelumab, to the extrapolated placebo arm attack rate from HELP-03.

Key uncertainties in the model relate to:

1. The approach used to estimate attack rates in the lanadelumab arm of the model: direct regression estimates (from the q2w and q4w arms of HELP-03) or rate ratios from the NMA applied to the placebo arm attack rate from HELP-03? The ERG prefers the latter because the model then generates a percentage reduction in attacks that is consistent with the effect for lanadelumab versus C1-INH derived from the company's NMA.
2. What to assume with respect to discontinuation rates in each arm, and what treatment follows discontinuation. An important issue is whether provision of lanadelumab results in more people being on long-term prophylaxis than would be otherwise be the case if only C1-INHs are available.
3. What treatment costs to apply for acute attacks, particularly hospitalisation costs.
4. The percentage of patients assumed to switch to the less frequent q4w lanadelumab dose in the long-run. This percentage was informed by the proportion of patients remaining attack free over a period of follow-up in the HELP-03 trial. The ERG believe this to be a highly uncertain and influential parameter, which can change the conclusion of the economic evaluation from positive to negative within a plausible range.
5. The percentage of patients in the C1-INH arm assumed to be on Berinert for long-term prophylaxis as opposed to Cinryze, which is also an important parameter and becomes much more so when it interacts with changes in the proportion of lanadelumab patients switching to less frequent doses (see point above).
6. The potential relevance of a 'no prophylaxis' comparator, given the possibility of lanadelumab being considered for a small number of patients who are not suitable for or not adequately controlled on oral prohylaxis, but who otherwise manage with just on-demand treatment with C1-INH or icatibant treatment for acute attacks.

The ERG believe the above issue warrant consideration by the appraisal committee.

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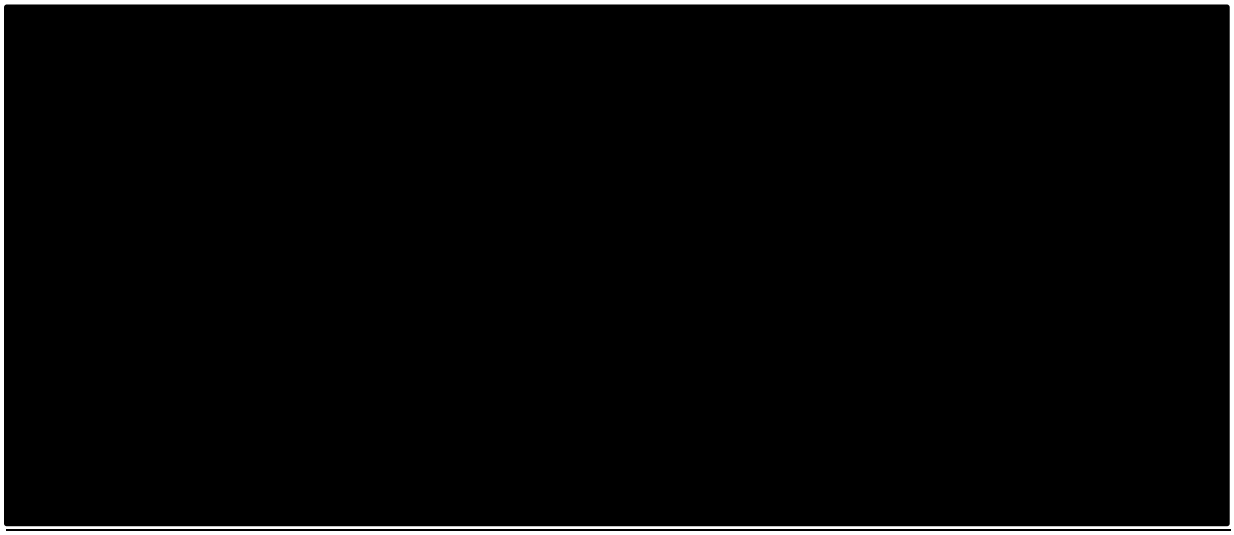
8 Appendices

Appendix 1 Results of HELP-03 and HELP-04



Key: HAE, hereditary angioedema, q2w, every 2 weeks, q4w, every 4 weeks
Source: Lanadelumab AMPC dossier (Shire. Lanadelumab AMPC dossier: Submission of Clinical and Economic Data Supporting Formulary Consideration of: TAKHZYROTM (lanadelumab-flyo). 2018 [Unpublished data]); Riedl et al. 2018 (Riedl MA BJ, Yang WH, Longhurst HJ, Magerl M, Hébert J, Martinez-Saguer I, on behalf of the HELP OLE Study investigators. Lanadelumab Reduces Hereditary Angioedema Attack Rate: Interim Findings From the HELP Open-label Extension Study. American College of Allergy, Asthma & Immunology Annual Scientific Meeting. Seattle, WA: USA, 2018 [Unpublished data])

Figure 11 Mean HAE attack rates at baseline and at interim analysis after 182 days of lanadelumab treatment in patients in the long-term extension study HELP-04 who had rolled over from the HELP-03 study.

Key: C1-INH, C1 esterase inhibitor, HAE, hereditary angioedema, LTP, long-term prophylaxis, q2w, every 2 weeks, q4w, every 4 weeks.
Source: : Lanadelumab AMPC dossier (Shire. Lanadelumab AMPC dossier: Submission of Clinical and Economic Data Supporting Formulary Consideration of: TAKHZYROTM (lanadelumab-flyo). 2018 [Unpublished data]); Riedl et al. 2018 (Riedl MA BJ, Yang WH, Longhurst HJ, Magerl M, Hébert J, Martinez-Saguer I, on behalf of the HELP OLE Study investigators. Lanadelumab Reduces Hereditary Angioedema Attack Rate: Interim Findings From the HELP Open-label Extension Study. American College of Allergy, Asthma & Immunology Annual Scientific Meeting. Seattle, WA: USA, 2018 [Unpublished data])

Figure 12 Mean HAE attack rates at baseline and at interim analysis after 182 days of lanadelumab treatment in the long-term extension study HELP-04 who had not rolled over from the HELP-03 study

Table 49 HAE attack reduction in non-rollover patients by prior therapy - HELP-04 study

	Non-rollover patients Treatment prior to Study 04 treatment				
	On demand only → 300mg q2w (n=40)	**C1-INH only → 300mg q2w (n=53)**	**Oral therapy → 300mg q2w (n=8)**	**C1-INH & oral therapy → 300mg q2w (n=2)**	**All non-rollover patients (n=103)**
Mean HAE attack rate in attacks per month (SD)					
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	2.55 (2.75)
Study 03	[redacted]	[redacted]	[redacted]	[redacted]	NA
Study 04	[redacted]	[redacted]	[redacted]	[redacted]	0.28 (0.64)

Key: C1-INH, C1 inhibitor; HAE, hereditary angioedema; q2w, every 2 weeks; NA, not applicable; SD, standard deviation.
Source: : Lanadelumab AMPC dossier (Shire. Lanadelumab AMPC dossier: Submission of Clinical and Economic Data Supporting Formulary Consideration of: TAKHZYROTM (lanadelumab-flyo). 2018 [Unpublished data]); Riedl et al. 2018 (Riedl MA BJ, Yang WH, Longhurst HJ, Magerl M, Hébert J, Martinez-Saguer I, on behalf of the HELP OLE Study investigators. Lanadelumab Reduces Hereditary Angioedema Attack Rate: Interim Findings From the HELP Open-label Extension Study. American College of Allergy, Asthma & Immunology Annual Scientific Meeting. Seattle, WA: USA, 2018 [Unpublished data])

Key: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; NE, non-estimable; Wk, week.
Source: HELP-03 CSR .(Shire. HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]

Figure 13 Time to first investigator-confirmed attack Day 70 to Day 182 visit – HELP-03 ITT Population

Key: HAE, hereditary angioedema; SD, standard deviation; SHP643, lanadelumab; Q2W, every 2 weeks; Q4W, every 4 weeks.

Source: HELP-03 CSR.(Shire. HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data])

Figure 14 Correlation between mean lanadelumab concentration and HAE attack rate over time, by treatment group

Key: BMI, body–mass index; C1-INH, C1 esterase inhibitor; CSR, clinical study report; HAE, hereditary angioedema; ITT, intent-to-treat; LTP, long-term prophylaxis.
Notes: *, Rate ratio estimate was not provided for a treatment group with only one patient in the subgroup
Source: HELP-03 CSR (Shire. HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data])

Figure 15 Forest plot of rate ratio on number of investigator-confirmed HAE attacks by patient subgroups: ITT population

Appendix 2 Adverse events in HELP-03

Table 50 Most common TEAEs (≥5% in any treatment arm) during the HELP-03 treatment period by treatment group and preferred term

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (N=56)
[redacted]				

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (N=56)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: Adverse events, AEs; n, Number of patients experiencing the event, NE, non-estimated; m, Number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.

Notes: Percentages are based on all patients in the Safety Population; patients were counted once per system organ class and once per preferred term. TEAEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. Non-HAE-attack-reported AEs include the subset of AEs identified in electronic data capture as not a reported HAE attack.

Source: HELP-03 CSR.(Shire. HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]; Banerji et al. 2018.[28]

Table 51 Treatment related TEAEs (≥5% of safety population) during the treatment period by treatment group and preferred term – HELP-03 safety population

		Lanadelumab		
Event, n (%) m	**Placebo (n=41)**	**300mg q2w (n=27)**	**300mg q4w (n=29)**	**Total (n=56)**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AEs, adverse events; n, Number of patients experiencing the event, NE, non-estimated; m, Number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.
Notes: Percentages are based on all patients in the Safety Population; patients were counted once per system organ class and once per preferred term. TEAEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. Related TEAEs are

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (n=56)
TEAEs classified as related to study drug by the investigator. Non-HAE-attack-reported AEs include the subset of AEs identified in electronic data capture as not a reported HAE attack. **Source:** HELP-03 CSR.(Shire. HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]; Banerji et al. 2018.[28]				

Table 52 Grade 3 or higher (severe) TEAEs (>2% in any treatment arm) during the treatment period by treatment group and preferred term – HELP-03 safety population

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (N=56)
[redacted]				

Key: AEs, adverse events; EDC, electronic data capture; n, Number of patients experiencing the event, NE, non-estimated; m, Number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.

Notes: Percentages are based on all patients in the Safety Population. Adverse events were classified into preferred term using Version 20.0 of MedDRA. Patients were counted once per preferred term. TEAEs are defined as AEs with onset at the time of or following the start of treatment with study; medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. Severe AEs are AEs classified as severe (Grade 3) or life threatening (Grade 4) by the investigator. Non-HAE-attack-reported AEs include the subset of AEs identified in EDC as not a reported HAE attack.

Source: HELP-03 CSR (Shire. HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]

Table 53 Grade 3 or higher (severe) treatment-related TEAEs during the treatment period by treatment group and preferred term – Safety population

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (n=56)
Any related severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]

Key: AEs, adverse events; ALT, alanine transaminase; AST, aspartate transaminase; EDC, electronic data capture; n, Number of patients experiencing the event, NE, non-estimated; m, Number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.

Notes: Percentages are based on all patients in the Safety Population; patients were counted once per preferred term. Adverse events were classified into preferred term using Version 20.0 of MedDRA; TEAEs are defined as AEs with onset at the time of or following the start of treatment with study. Medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment; Severe AEs are AEs classified as severe (Grade 3) or life threatening (Grade 4) by the investigator. Non-HAE-attack-reported AEs include the subset of AEs identified in EDC as not a reported HAE attack.

Source: HELP-03 CSR (Shire. HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]

Table 54 Serious treatment emergent adverse events during the treatment period by treatment group, and preferred term – Safety population

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (n=56)
Any serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Catheter site infection	[redacted]	[redacted]	[redacted]	[redacted]
Pyelonephritis	[redacted]	[redacted]	[redacted]	[redacted]
Meniscus injury	[redacted]	[redacted]	[redacted]	[redacted]
Bipolar II disorder	[redacted]	[redacted]	[redacted]	[redacted]

Key: AEs, adverse events; EDC, electronic data capture; n, Number of patients experiencing the event, NE, non-estimated; m, Number of events; q2w, every 2 weeks; q4w, every 2 weeks; TEAE, treatment-emergent adverse event.

Notes: Percentages are based on all patients in the Safety Population; patients were counted once per system organ class and once per preferred term. AEs were classified into system organ class and preferred term using Version 20.0 of MedDRA; TEAEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the
start of treatment. Non-HAE-attack-reported AEs include the subset of AEs identified in EDC as not a reported HAE attack.

Source: HELP-03 CSR.(Shire. HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]; Banerji et al. 2018.[28]

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

You are asked to check the ERG report from Aberdeen HTA Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Monday 11 March 2019** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Inclusion of no prophylactic treatment as a potential comparator

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 113 of the ERG report it states: *"However, given the uncertainty surrounding eligibility for long-term C1-INH prophylaxis based on the NHS commissioning policy, the ERG does have some concern that lanadelumab could be used by a small group of patients who would otherwise manage without long-term C1-INH prophylaxis."* Similar statements are made on pages 131 and 139. This is mis-leading given the additional clarity that has been provided in response to clarification questions B1 and B2 regarding the positioning of lanadelumab.	The proposed amendment is to change the wording to: *"However, given the uncertainty surrounding eligibility for long-term C1-INH prophylaxis based on the NHS commissioning policy, the ERG had some concern that lanadelumab could be used by a small group of patients who would otherwise manage without long-term C1-INH prophylaxis. However, in response to clarification B1, the company provided further clarity on the positioning of lanadelumab, that it is expected to be used in patients who would otherwise be considered for treatment with C1-INH prophylaxis. This reduces the uncertainty over the position of lanadelumab within the treatment pathway."*	Shire acknowledge that the initial statement made in the company's submission related to the positioning of lanadelumab may have resulted in some uncertainty regarding the most relevant comparator therapies to be considered. This is because the positioning was stated as follows: *"Lanadelumab is expected to be prescribed for patients with HAE whose condition is not adequately controlled with oral prophylactic treatment or for whom oral prophylactic treatment is not suitable."* In response to clarification questions B1 and B2, the positioning of lanadelumab was further clarified to remove this uncertainty. Lanadelumab is expected to be used in patients who would otherwise be considered for treatment with C1-INH prophylaxis. This	The ERG have acknowledged the company's proposed positioning of Lanadelumab, which was further clarified in the response to clarification question B1. However, the ERG have some remaining concern about its implementation in a real-world setting, since there currently seems to be lack of clarity over who is eligible for C1-INH. The concern is that the less burdensome administration of landelumab may attract more patients than would otherwise proceed with long-term C1-INH prophylaxis. However, we have changed the text to further acknowledge the company's clarified positioning on page 113: *"Given the uncertainty surrounding eligibility for long-term C1-INH prophylaxis based on the NHS commissioning policy, the ERG had some concern that lanadelumab could be used by a small group of patients who would otherwise manage without long-term C1-INH prophylaxis. In response to clarification B1, the company provided further clarity on the positioning of lanadelumab, that it is*

		prevents confusion should the NHS Commissioning Policy be revised and reduces uncertainty over the position of lanadelumab within the treatment pathway, removing no prophylactic treatment as a potentially relevant comparator.	*expected to be used in patients who would otherwise be considered for treatment with C1-INH prophylaxis. However, the ERG remains uncertain as to whether in practice this positioning could attract a number of patients who would otherwise, following consideration, not proceed with long-term C1-INH prophylaxis.*

Issue 2 Percentage of patients treated with Cinryze IV vs Berinert IV and lanadelumab q2w vs q4w

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 124 of the ERG report it states: *"An important point to note from the further scenario analyses presented in Table 45 is that, from this new reference point, the ICER for lanadelumab now becomes unfavourable when the proportion switching to the low lanadelumab dose drops to between 70% and 60%. In addition, the ICER for lanadelumab becomes unfavourable when the proportion on Berinert in the C1-*	One of the following amendments is proposed: • Additional information is provided by the ERG to support the plausibility of all of the estimates tested in scenario analysis. • The range of values is revised to be aligned with	The ERG labels their range of percentages presented for the split between Cinryze and Berinert IV as well as the percentage assumed to switch to the less frequent dose of lanadelumab in their scenario analysis as being plausible. However, the ERG provides no supportive evidence to suggest that some of these values are in fact plausible. Shire accept that each of these parameters is associated with a level of uncertainty. However, scenario analyses have been presented as part of the company submission and in response to clarification questions B11 and B14, testing a range of values that can be supported by the available data. For the percentage of patients treated with Cinryze or Berinert IV, the distribution of their use for each month in	The ERG acknowledges that the percentages on Berinert and Cinryze are uncertain. However, the ERG have flagged some concern regarding the company's justification for the percentages applied – noting that the prescribing data used may reflect treatment for acute attacks or short-term prophylaxis, and not just long-term prophylaxis. Since it is Cinryze that is licenced for long-term prophylaxis, and Berinert is used off-license in this indication, the prescribing proportions may look different if restricted to the population

INH drops to be between [redacted] and [redacted]. *Given the uncertainty and sensitivity of the results to these two parameters, further two-way sensitivity analysis was conducted around the ERG base case scenario, where these two variables were varied across plausible ranges simultaneously. The results are presented in Table 46. It can be noted that at lower levels of assumed switching to the lower lanadelumab dose, the cost-effectiveness case becomes more sensitive to feasible changes in the proportion of C1-INH patients on Berinert."* A similar statement is made on page 78. This is mis-leading as the ERG describe these values as "plausible", "possible" and "feasible" without providing substantive evidence to support this.	the available evidence • The words "plausible", "possible" and "feasible" are removed from the text	the past 3 years from the Hospital Pharmacy Audit data demonstrates ranges of [redacted] for Berinert IV and [redacted] for Cinryze. This range is much narrower than the range of [redacted] presented in Table 42 of the ERG report, which appears to not be based on any additional evidence. For the percentage of patients assumed to switch to the less frequent dose of lanadelumab, this is based on the proportion of patients who remain attack free on the q2w dose once lanadelumab concentration has reached a steady state. This is consistent with the SPC and marketing authorisation and was supported by the opinion of six UK clinical experts, who stated that they [redacted] In response to clarification question B11 a range of plausible values were presented based on several extrapolations of the day 70 time to first attack data. These values ranged from [redacted] with the best fitting curves consistently providing estimates above 70%. Again, this range is narrower than the range of [redacted] presented in Table 42 of the ERG report, which appears to not be based on any additional evidence.	in question. With respect to the proportion switching and remaining on the q4w regimen, the ERG outlined the arguments for dropping this to [redacted] (in sensitivity analysis) on page 78 of our report. This is an approximation of the percentage that might be expected to be attack free over a 6 month period when stable on the q4w regimen (based on figure 6 in the company submission). Whilst the ERG do not believe this is a factual inaccuracy, we have removed the term plausible and feasible applied to the proportions on Berinert and Cinryze on page 124, to acknowledge the fact that we do not know exactly what is feasible for the specific indication of long-term Prophylaxis.

Issue 3 Switching from lanadelumab q2w to q4w

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 78 of the ERG report it states: *"It is of note that no patients in the open label extension (HELP-04) were put on q4w. Rather, all patients who were originally on q4w moved on to q2w. If patients and/or clinicians are motivated to minimise the attack rate, then it remains to be seen how acceptable and feasible it will be to move this percentage of patients to the lower dose which incurs a higher average attack rate.* *An alternative way of looking at this could be to assume that the percentage who remain attack free over a period of 6 months on q4w to be the proportion more likely to accept this dose in the longer term. This might then put the percentage on q4w at around 50% in the long-run (approximated from the survival curves in Figure 6 of the CS).* The following implications made in the ERG report are not accurate: • That patients switched from	The first paragraph should be deleted as it is mis-leading. The second paragraph should either be deleted or re-phrased to the following: *"An alternative way of looking at this could be to assume that the percentage who remain attack free over a period of 6 months on q4w to be the proportion more likely to accept this dosing regimen in the longer term. This might then put the percentage on q4w at around 50% in the long-run (approximated from the survival curves in Figure 6 of the CS). However, this approach has significant limitations as it relies on the assumption that patients who are treated with the q4w dosing regimen at the start of the HELP-03 trial are equivalent to patients who remain attack free for six months while receiving the q2w regimen and then switch to the q4w regimen. The*	It is incorrect to state that patients switch to a lower dose as the dose is effectively the same (300mg) while it is the frequency of administration that changes. Dose and dosing regimen/frequency should not be used interchangeably. The first paragraph implies that patients may have switched from the q4w to the q2w frequency in HELP-04 due to the preference of the treating clinicians, and that this somehow supports the idea that patients may not switch from the q2w to the q4w frequency in practice. However, the trial was designed so that all patients switched onto the q2w frequency regardless of their prior therapy, attack rate etc. and therefore does not provide any evidence contrary to the assumptions made in the company's base-case analysis. This statement also fails to acknowledge the fact that the SPC and marketing authorisation explicitly state that patients who are stably attack free on treatment should switch to the q4w frequency. The second paragraph fails to acknowledge the limitations with the suggestion that the time to first attack data for q4w patients in HELP-03 could be used to inform the percentage of patients who switch dosing regimen. This approach relies on the	We acknowledge the company's concern that reference to the treatment regimen explored in HELP-04 is not relevant to the question of treatment switching, and so have removed the offending sentence from our report. We have also replaced "lower dose" with "*less frequent q4w lanadelumab regimen*". Regarding the second paragraph. We have added an acknowledgement to the company's point that patients who switch from q2w to q4w because they are attack free, may fair better on the q4w dose than the average patient in HELP-03: *"However, the ERG acknowledge that patients who switch from q2w to q4w because they are attack free, may also be more likely to remain attack free on the q4w regimen than the average patient in HELP-03. This is because patients who switch may be lower risk than the average patient given that they have remained attack-free for six months. The ERG therefore apply* [redacted] *as a lower limit*

q4w to q2w in HELP-04 for reasons other than the design of the trial • That the time to first attack curves for q4w provide a better estimate of the proportion who will remain on this treatment in the long-run	*patients who switch are more likely to remain attack-free as they will be lower risk patients given they have been attack-free for six months, and because lanadelumab will have reached a steady state concentration in these patients prior to switching."*	assumption that patients who are treated with the q4w frequency at the start of the HELP-03 trial are equivalent to patients who remain attack free for six months while receiving the q2w frequency and then switch to the q4w frequency. The patients who switch are more likely to remain attack-free as they will likely be lower risk patients given they have been attack-free for six months, and because lanadelumab will have reached a steady state concentration in these patients prior to switching.	*in additional sensitivity analysis"*

Issue 4 References to the NHS England Commissioning Policy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages xxii – xxiii of the ERG report it states: *"The arm of the economics model representing 'usual care' differs from the published NHS England Commissioning Policy for C1-INH in several ways. These include: criteria for starting prophylaxis with C1-INH; the definition of a clinically significant attack; the criteria for reducing frequency of*	The last sentence should be re-phrased to state. *"In the company's response to the ERG's clarification questions, the company defended the base case in the following manner. Firstly, they noted the limited data that exists from the trial to present robust results for each relevant sub-group who would align with the Commissioning Policy. However, they noted that results from HELP-03 demonstrated there were no statistically significant differences in the treatment effect between sub-*	The company's response to clarification question B1 did note that clinical experts are not supportive of the current criteria and that the NHS England Commissioning Policy may be reviewed in the future. However, this information was not used to defend the company's base-case analysis as the ERG have suggested, but simply to provide context to the policy. The company's response did not claim that clinical practice did not align with the policy. The justification that was provided in response to question B1, was firstly that there was limited data from the trial to present robust results for each relevant sub-group who would align with the Commissioning Policy. However, results from HELP-03 demonstrated there were no statistically significant differences in treatment effect between	The ERG accept the proposed amendment.

use of C1-INH and criteria for stopping C1-INH prophylaxis. In the company's response to the ERG's clarification questions, the company defended the base case because it said clinical practice did not fully align with the policy and clinicians anticipated that NHS policy was likely to be revised." Similar statements of made on pages 69 and 133 These statements do not accurately reflect the company's response to the ERG's clarification questions.	*groups and the scenario analysis presented in response to clarification question B1 demonstrated that lanadelumab becomes more cost-effective in patients with higher baseline attack risks. Secondly, they noted that based on clinician feedback, patients are more likely to receive an increase in administration frequency of C1-INH if they are experiencing breakthrough attacks and that treatment is rarely discontinued. They noted that this is still in line with the Commissioning Policy which provides some flexibility to clinicians in their consideration of treatment discontinuation."*	sub-groups and the scenario analysis presented in response to question B1 demonstrated that lanadelumab becomes more cost-effective in patients with higher baseline attack risks. Secondly, while the Commissioning Policy lists some options for considering treatment discontinuation, clinical experts, including those interviewed for the purpose of this submission, indicated that if patients are still experiencing breakthrough attacks they are more likely to receive an increase in administration frequency, while if they are successfully controlled, i.e. they are experiencing no attacks or few of them, treatment is rarely discontinued; this is still in line with the Commissioning Policy which provides some flexibility to clinicians in their consideration of treatment discontinuation. Therefore, sensitivity analyses where discontinuation, for either lack of effectiveness or sustained effectiveness is implemented, would not be representative of current practice as this rarely happens. In addition, given the variability in manner in which C1-INH can be up-dosed, this practice was not included in the base-case analysis which is likely to be a conservative assumption given this may significantly under-estimate the costs of C1-INH.	

Issue 5 Critique of lanadelumab attack rate methods

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 79 of the ERG report it states:	These statements should be removed as they	The ERGs claim that the percentage reduction in the attack rate estimated from	The ERG does not agree that this is a factual inaccuracy. We do not imply

"The ERG have concerns regarding the company's approach of applying the rate ratio for C1-INH versus placebo (from the indirect comparison) to estimate the C1-INH attack rate in the model, whilst using the treatment specific regression based attack rates from HELP-03 in the lanadelumab arm. This creates an inconsistency between the model based estimate of the percentage reduction in attacks for lanadelumab versus C1-INH, and the rate ratios for lanadelumab versus C1-INH from the indirect treatment comparison; i.e. the company base case predicts a 67% reduction in the attack rate, while the indirect comparison generates rate ratios consistent with a 52% reduction in attacks (after accounting for the proportion assumed to be on each dose of lanadelumab)." Similar statements are made on pages xxiii, xxvi, 123, 134 and 139. The implication that the Poisson regressions for lanadelumab are not consistent with the output of the indirect treatment comparison is mis-leading.	suggest there are issues with the Poisson regression method which do not exist.	the Poisson regression is inconsistent with the indirect treatment comparison is mis-leading and implies the regression is flawed, when in-fact the two results are consistent. The indirect treatment comparison utilises data across the full trial duration to estimate one rate ratio which is then applied to the placebo curve, assuming proportional hazards. The Poisson regression predicts the number of attacks in each cycle, allowing for any changes in the attack rate over time to be captured. The analysis conducted in HELP-03 using data from Day 70-182 indicates that lanadelumab becomes more effective when concentrations have reached a steady state, with the rate ratio against placebo falling from 0.131 to 0.085 for the q2w dose and from 0.267 to 0.194 for the q4w dose compared to the Day 0-182 analysis. Therefore, we would expect the Poisson regression to more accurately capture this change over time. However, the rate ratio from the indirect treatment comparison was used to estimate the attack rate for C1-INH patients over time out of necessity as there was insufficient data from the CHANGE trial to allow for the estimation of an additional Poisson regression.	that the Poisson regressions for lanadelumab are inconsistent with the output from the indirect comparison. We make the point that the company's overall approach results in a percentage reduction in attacks for landelumab versus C1-INH that is inconsistent with the available comparative evidence from their indirect treatment comparison. We also noted that the company could have retained their approach for lanadelumab and consistency with the indirect comparison by applying their estimated rate ratio for C1-INH versus lanadelumab in the model.

Issue 6 Disutility based on location of attack

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page xxiv of the ERG report it states: *"Disutility of attacks was assumed to only depend on severity, but the location on the body may also be important. In response to an ERG clarification question the company said patients and clinicians had told them this was less important and they could not include it in the model due to lack of data."* A similar statement is made on page 67. This is mis-leading as the primary reason for not presenting an analysis based on the location of an attack was the absence of any data to inform it.	The proposed amendment is to change the wording to: *"Disutility of attacks were applied in the model based on severity classifications (mild, moderate and severe) rather than location of attack. In response to an ERG clarification question the company said the reason for this was that no utility data was available which categorised attacks by location rather than severity. It was also noted that clinical experts and patient groups had highlighted that the location of attacks does not necessarily correlate with impact on quality of life and that other factors seem to be more important such as discomfort and impact on daily activities."*	This statement implies that the primary rationale for not presenting a scenario based around the location of attacks was based on the company's view on the importance of location as a driver of quality of life. However, the key reason for not presenting such a scenario was the absence of any utility data to inform it.	The ERG accept the proposed amendment for clarity. Pages xxiv and 67 amended in the erratum.

Issue 7 Issues raised with route of administration utility increment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page xxiv of the ERG report it states: *"Disutility of iv administration was*	The proposed amendment is to change the wording to: *"Disutility of iv administration was*	The ERG note that they would have preferred an analysis which modelled the different possible sources of disutility	The ERG do not believe this represents a factual inaccuracy.

also included but rolled several possible sources of disutility into one. The ERG's preference would have been to model them separately: for example, one element was the problem of infusion site reactions, but data are available on how common this is, and duration of utility loss could have been estimated. Instead, the study used for base-case values had several issues, the main one being the poor match between the regimes valued in utility terms and the regimes for C1-INH and lanadelumab." Similar statements are made on pages 90, 92 and 136. This fails to acknowledge the lack of data available to split up the different possible sources of disutility and the potential for the mis-match in dosing regimens between clinical practice and the study to result in a conservative estimate of the utility gain.	*also included but rolled several possible sources of disutility into one. The ERG's preference would have been to model them separately: for example, one element was the problem of infusion site reactions, but data are available on how common this is, and duration of utility loss could have been estimated. Instead, the study used for base-case values had several issues, the main one being the poor match between the regimens valued in utility terms and the regimens for C1-INH and lanadelumab. However, it should be acknowledged that there was a lack of data available to allow for these sources of disutility to be separated out. It should also be noted that the differences between the regimens in the study used to inform this disutility compared to the regimens for lanadelumab and C1-INH may result in the value from the study being a conservative estimate of the utility benefit."*	separately. The company agree that this would have been preferable, however, the ERG fail to acknowledge the absence of any data to allow for such an approach. By only including one disutility value and not adding a separate value for the problem of infusion site reactions this has avoided the risk of double-counting utility. The ERG also note that the treatment regimens outlined in the Jørgensen study do not align perfectly with the administration of lanadelumab and C1-INH. However, given there is strong evidence to suggest a utility benefit associated with a less frequent subcutaneous treatment over a more frequent intravenous therapy, and no data exists specific to lanadelumab, the value from the Jørgensen study was considered the most appropriate to quantify this benefit. There is also no acknowledgement that the health states in the Jørgensen study present a scenario where IV therapy is administered twice as frequently as SC therapy (every 8 weeks vs every 4 weeks), whereas C1-INHs are administered at least 4–8 times more frequently than lanadelumab, meaning this study potentially provides a conservative estimate of the utility benefit.	

Issue 8 Patients eligible for lanadelumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 68 of the ERG report is states: *"The company's proposed positioning is in patients who have tried oral prophylaxis (attenuated androgens and anti-fibrinolytics) with inadequate results and patients for whom oral prophylaxis is not clinically appropriate.* *Only 8% of patients in HELP-03 match this proposed positioning (and 14% in the CHANGE RCT of C1-INH used in the indirect comparison)."* The 8% and 14% figures do not capture the true percentage of patients in the trials who meet the proposed positioning.	The proposed amendment is to change the paragraph to: *"The company's proposed positioning is in patients who would otherwise be considered for treatment with C1-INH prophylaxis, which is currently prescribed for patients who fail or are intolerant of oral prophylaxis or for those in whom oral prophylaxis is contraindicated.* *Only 8% of patients in HELP-03 had received prior oral therapy (and 14% in the CHANGE RCT of C1-INH used in the indirect comparison), and it is unclear in how many patient's oral prophylaxis is not clinically appropriate."*	The 8% and 14% figures quoted by the ERG reference the percentage of patients who received oral therapy prior to trial enrolment in HELP-03 and CHANGE respectively. However, these percentages do not capture the full positioning of lanadelumab. In addition, the positioning of lanadelumab was further clarified in response to clarification questions B1 and B2. Lanadelumab is expected to be used in patients who would otherwise be considered for treatment with C1-INH prophylaxis, and therefore these percentages may not appropriately capture this population.	The ERG have amended the text as follows: *"In the original submission, the company proposed use of lanadelumab after oral prophylaxis had been tried and not adequately controlled attacks or patients were intolerant or contraindicated. In the response to clarification questions, this was re-stated as being when the patient would otherwise be a candidate for prophylaxis with a C1-INH.* *Only 8% of patients in HELP-03 had received prior oral therapy (and 14% in the CHANGE RCT of C1-INH used in the indirect comparison), and it is unclear in how many patient's oral prophylaxis is not clinically appropriate."* Note, the ERG has two concerns about the company's revised positioning. First, were NICE to accept lanadelumab with this restriction it is not clear how this could be monitored or applied in any given case. Immediately after lanadelumab became available it would be relatively obvious which

			patients would have been C1-INH candidates. However, five years into the future with lanadelumab having achieved a high market share, it would no longer be obvious who was a candidate for a medicine last used as prophylaxis in the past. The second concern is that while the company might position lanadelumab in this way, doctors may still consider prescribing the medicine for use where a C1-INH would be desirable but was ruled out e.g. due to likely poor adherence to treatment or previous intolerance.

Issue 9 Baseline attack risk analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 69 and 70 of the ERG report it states: *"With these caveats they then re-ran the Poisson model successively excluding patients with baseline attack below a threshold level of attacks that was steadily increased. They report the following results in Table 29.* *This shows that for higher baseline levels of attacks,*	The proposed amendment is to change the wording to: *"With these caveats they then re-ran the Poisson model successively excluding patients with baseline attack below a threshold level of attacks that was steadily increased. They report the following results in Table 29.* *This shows that for higher baseline levels of attacks, lanadelumab*	In response to clarification question B1, functionality was added to the model to allow for the user to filter patients in HELP-03 based on their baseline attack risk and re-estimate the Poisson regression results in that sub-set of patients. As the same Poisson regression covariates were utilised in the model it is clear what assumptions were made about relative effectiveness.	The ERG accept the company's proposed amendment.

lanadelumab becomes more cost-effective compared to C1-INH. *It was not clear what sample size each row of the table was based on or what was assumed about relative effectiveness when (as the company pointed out earlier) very few – if any – of the patients in either RCT in the indirect comparison would meet the NHS England criteria."* This is incorrect as the model makes it clear what sample size each row of the table was based on and what was assumed about relative effectiveness.	*becomes more cost-effective compared to C1-INH."*	In addition, the data-set of patients from HELP-03 included in the model is also included in the model on the sheet "Attack numbers" in cells A4:E651. When patients are filtered based on the baseline attack risk specified by the user, the data that is utilised is presented in these cells, making it clear what sample size each row of Table 29 in the ERG report was based on.	

Issue 10 Covariates included in Poisson regression

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 76 of the ERG report it states: *"The company however, did not include any justification for how other potential covariates (other than the baseline attack rate and the attack rate at previous cycle) were excluded or justification for why no other terms were included*	The proposed amendment is to change the wording to: *"The company provided justification in response to clarification question B7 for how other potential covariates (other than the baseline attack rate and the attack rate at previous cycle) were excluded or for why no other terms were included in the analysis. The company noted that the regression including baseline*	The justification for not including additional covariates was provided in response to clarification question B7. The covariates utilised in the Poisson regression analysis were selected with the aim of choosing covariates which helped meet the decision	The ERG do not agree that this is a factual inaccuracy. The company did not provide any details on other covariates considered. Therefore, the ERG does not know which other potential covariates were explored and how/why they were excluded.

in the analysis." This is mis-leading as justification for why no other terms were included in the analysis was provided in response to clarification question B7.	*attack risk and the number of attacks in the previous cycle as covariates provides a good fit to the observed data, and therefore the addition of more covariates was judged to be of limited merit.*	problem for this appraisal by providing a good fit to the clinical trial data and an accurate prediction of the number of attacks experienced in each model cycle. The regression including baseline attack risk and the number of attacks in the previous cycle as covariates provides a good fit to the observed data, and therefore the addition of more covariates was judged to be of limited merit.	

Issue 11 Validation of C1-INH outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page xxiii of the ERG report it states: *"Validation of the predictions of the model for C1-INH were confined to clinical specialist opinion in the context of an advisory board meeting. No validation was made against external data on the observed use of these medicines for reductions in attacks compared to baseline, changes in doses, quality of life impacts, etc."* No suggested source of data is provided to inform such a validation exercise.	The proposed amendment is to change the wording to: *"Validation of the predictions of the model for C1-INH were confined to clinical specialist opinion in a series of one-to-one interviews with six UK clinical experts given the absence of any additional data source to validate the CHANGE study."*	The implication from the statement in the ERG report is that validation against external data was possible in these areas. However, no such data exists, and the ERG did not provide any suggestions. Therefore, although Shire agree that it would be useful to conduct such a validation exercise, it should be made clear that this was not possible.	The ERG do not believe this to be a factual inaccuracy. The ERG's position is that it is not unreasonable to expect the company to have anticipated this issue and to have initiated some data collection for the purposes of submitting evidence to HTA agencies such as NICE

Issue 12 Hospitalisation costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page xxiv of the ERG report it states: *"The cost used for in-patient admissions seemed inappropriate and produced a cost that was very high for an assumed 1-day stay (excluding drug costs)."* Similar statements are made on pages 103-104 and 135. "*This cost is more in keeping with an admission for observation, which based on the ERGs clinical expert advice, is what would be required for the majority of HAE patients admitted for acute attacks."* There is no certainty around the code used to record HAE patient admissions and it would be misleading to select one estimate in the absence of certainty.	The proposed amendment is to change the wording on page 104 to: "This cost is more in keeping with an admission for observation, which based on the ERGs clinical expert advice, is what would be required for the majority of HAE patients admitted for acute attacks. However, there is still uncertainty around the code used to record hospital admissions due to HAE attacks and the true cost could lie within the range defined by the ERG and the company's values."	The company had used the HRG code KC04, corresponding to treating Inborn Errors of Metabolism, while the ERG used an ICD-10 code D84.1 (defects in the complement system) which maps to the root HRG code WJ11 (other problems of immunity). As there is uncertainty around which code is in actual practice used to record hospital admission for HAE patients, it would be more correct to highlight this uncertainty and clarify that the ERG assumption may be a conservative one and the true value may be between the two figures provided.	This is not a factual inaccuracy. The company do not report how they identified the HRG code or what effort they made to verify it.

Issue 13 Mapping AE-QoL to EQ-5D

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 84 of the ERG report it states: *"The ERG acknowledges that there is no published method to map AE-QoL to EQ-5D. However, the company could have explored such an approach; while this is not the method preferred in the NICE Reference Case it can be used (with acknowledged limitations) and would have had the important advantage of having been measured in patients in the RCT used elsewhere in the economics model submitted. Given the positive results, it is surprising the company did not pursue this option."* Further limitations with this proposed approach are not noted.	The proposed amendment is to change the wording to: *"The ERG acknowledges that there is no published method to map AE-QoL to EQ-5D. The ERG also recognise that any mapping exercise requires the assumption that EQ-5D domains represent the experience of patients well which is unlikely to be the case. Additionally, the AE-QoL data is unlikely to be useful for inclusion within the model as it is not collected when patients are experiencing attacks, and therefore suffers the some of the same issues as the EQ-5D. Therefore, despite the positive results, it is unlikely that this data would have been appropriate for use within the model."*	Shire agree that as a disease specific tool the AE-QoL may provide greater insight into the experience of patients relative to the EQ-5D. However, although the ERG outline some issues in potentially mapping AE-QoL to EQ-5D some additional ones are missing. Firstly, mapping requires the assumption that EQ-5D domains represent the experience of patients well which is unlikely the case. Secondly, the AE-QoL data is still not useful for inclusion within the model as it is not collected when patients are experiencing attacks, and therefore suffers the some of the same issues as the EQ-5D.	The ERG do believe this represents a factual inaccuracy. The company has made the case to the ERG that this involves accepting EQ-5D domains represent the experience of patients and that this is unlikely to be the case. The ERG is surprised by this as the company's RCT included EQ-5D as an endpoint measured. In addition the company's model includes utility values from other published sources based on EQ-5D measured directly in one case or via a crude mapping exercise in the other case. The company did not present any evidence that EQ-5D does not represent the patient's experience, other than in terms of the timing of the measurement of EQ-5D in the RCT which only coincided with an attack on rare occasions (the ERG accepts this point). Indeed, the process of mapping

			from AE-QoL to EQ-5D could have uncovered evidence of aspects detected on the disease-specific scale that were to seen in EQ-5D. However, the company presents no evidence this was attempted

Issue 14 CIC marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page xxi of the ERG report it states: *"In the company base case lanadelumab dominated C1-INH prophylaxis, with a substantial cost saving [redacted]) being the main driver of a high incremental net monetary benefit (£470k at a threshold of [redacted] per QALY)."* Throughout the ERG report the NMB values should also be marked as CIC as using the NMB would allow the calculation of the incremental cost. On page 123 of the ERG report it states: *"The ERG also ran a probabilistic analysis of this alternative base-case, which produced a similar estimate of the NMB (£348,380); incremental cost [redacted], incremental QALY [redacted]."*	The proposed amendment is to amend the CIC marking in the following way: "In the company base case lanadelumab dominated C1-INH prophylaxis, with a substantial cost saving [redacted]) being the main driver of a high incremental net monetary benefit [redacted] at a threshold of £30,000 per QALY)." The incremental NMB values should be marked as CIC throughout the report. On page 123 of the ERG report: "The ERG also ran a probabilistic analysis of this alternative base-case, which produced a similar estimate of the NMB [redacted]); incremental cost = [redacted], incremental QALY [redacted]."	Confidentiality marking is not applied appropriately in these instances.	Proposed amendments accepted. However, based on discussions with NICE, it is the ERGs understanding that the total and incremental QALYs are now all CiC, and ICERs and NMB are not CiC. Thus the ERG changes reflect these subsequent changes to CiC mark-up.

On page xxii of the ERG report it states: *"Scenario analyses provided by the company demonstrated a substantial increase in incremental NMB when the dosing frequency of C1-INH was [redacted] (assuming no change in efficacy),"* On page 94 of the ERG report it states: "*In a sensitivity analysis, it was assumed [redacted] This substantially increased the net benefit from [redacted] to [redacted]* On page 96 of the ERG report it states: *"In the sensitivity analysis described above, the [redacted] are assumed to derive no benefit, which is unrealistic."*	On page xxii of the ERG report: "Scenario analyses provided by the company demonstrated a substantial increase in incremental NMB when the dosing frequency of C1-INH was [redacted] (assuming no change in efficacy), On page 94 of the report: "In a sensitivity analysis, it was assumed [redacted]. This substantially increased the net benefit from [redacted] to [redacted] On page 96 of the report: "In the sensitivity analysis described above, the [redacted] are assumed to derive no benefit, which is unrealistic."		

Issue 15 ACIC marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 93 of the ERG report it states: *"As the dosing at 12 months is then carried forward for the rest of the patient's lifetime,*	The proposed amendment is to amend the text in the following way: "*As the dosing at 12 months is then carried*	Confidentiality marking is not applied appropriately in	Based on discussions with NICE, the ERG understand that AIC marking is to be removed from the proportion switching to the lower frequency q4w

this has a very important impact on the economics results because it halves the medicines costs for an additional 32.5% of patients on lanadelumab." The % of patients should be marked as ACIC.	*forward for the rest of the patient's lifetime, this has a very important impact on the economics results because it halves the medicines costs for an additional 32.5% of patients on lanadelumab"*	these instances.	regimen at 6 and 12 months throughout the report. Therefore, no change has been made to percentage reported on page 93. Note, the ERG have removed the AIC markings from the company base case proportion on q4w at 6 months and 12 months, whenever it appears on any of the erratum pages produced. Following instructions from NICE, we have also changed the proportion on Berinert to be AiC rather than CiC where it appears in the erratum pages. However, erratum pages have not been produced specifically to deal with subsequent changes to the CiC/AiC mark-up. These changes will need to be made directly to the ERG report before it is made public.

Issue 16 Exclusion of phase 1b lanadelumab study from the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page xvii of the ERG report, it states: "*These data were not included in the economic model because,*	Please consider adding further detail and context here to read: "*These data were not included in the economic model because, according to the company,*	To clarify the exact number of patients in the phase 1b study and provide clear rationale as to why this study wasn't	Not factually inaccurate. The proposed revision is not accepted.

according to the company, they are superseded by the HELP-03 trial and few participants received the relevant lanadelumab dose." The number of patients and the relevant dose are not provided here so the context is unclear.	*they are superseded by the HELP-03 trial and only 5 patients received the relevant lanadelumab 300mg dose*."	included in the model.	

Issue 17 Relative efficacy of two lanadelumab treatment arms

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page xix of the ERG report, it states: "*From the evidence provided by the HELP-03 study, lanadelumab has been shown to benefit patients with HAE during the 26-week treatment period when compared with placebo. This is especially true for participants treated with the 300mg q2w dose*." Currently, this suggests that the lanadelumab 300mg q2w dose is substantially better than the 300mg q4w dose, but HELP-03 does not show significant differences in efficacy between the two arms. Furthermore, for all primary and secondary endpoints, both these 300mg arms show a significant improvement compared with placebo (both p<0.001).	Please consider amending the text to read: *From the evidence provided by the HELP-03 study, lanadelumab has been shown to benefit patients with HAE during the 26-week treatment period when compared with placebo. This is true for participants treated with both the 300mg q2w and the 300mg q4w dose*."	To avoid any misinterpretation that the lanadelumab 300mg q2w is significantly better than the q4w dose.	Revision accepted

Issue 18 Rationale for not quality assessing the phase 1b lanadelumab study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 14 of the ERG report, it states: "*The company did not provide a quality assessment of the DX-*	Please expand on the text to provide rationale as follows: "*The company did not provide a quality assessment of the DX-2930-02 study, because this study was not used for the economic model*	To provide rationale as to why the study was not quality assessed.	Not factually inaccurate. The proposed revision is not accepted.

2930-02 study." The text currently does not explain why the quality assessment was not conducted; adding this will give the reader some context and understanding as to why this was not conducted.	*due to the very small patient numbers in the trial receiving the relevant lanadelumab dose*."		

Issue 19 Rationale for not using HELP-04 extension study in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 15 of the ERG report, it states: "*The company explains that data from HELP-04 were not used to populate the economic model as the study is currently ongoing. However, interim 6-month results of HELP-04 are presented in section B.2.6 of Document B*." The text currently does not explain why HELP-04 was not used in the model and this would benefit from further explanation.	Please consider amending the text to read: "*The company explains that data from HELP-04 were not used to populate the economic model for the following reasons: the study is currently ongoing; HELP-04 is not a simple extension study but involves switching all patients to the lanadelumab 300mg q2w dose; HELP-04 does not provide outcomes for the q4w dose; and the results for the q2w dose are consistent with HELP-03 so would have a negligible impact on the results*."	Provide the full explanation as to why HELP-04 was not used in the economic model.	The ERG statement is not factually inaccurate. The ERG have adequately described details of the HELP-04 study in the ERG report. The proposed revision is not accepted.

Issue 20 Relevance of both lanadelumab 300mg treatment arms to decision problem

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 57 of the ERG report, it states: "*However, HELP-03 is a relative small study with only 27 participants in the arm of interest, 300mg q2w*." Currently, the text suggests that only the 300mg q2w arm of HELP-03 is of interest; however, the 300mg q4w arm is also of interest, which is also used in the model, and is a dose of interest as per the SmPC. The 300mg q4w arm includes a further 29 patients, which should be clarified here.	Please expand on this by stating: "*However, HELP-03 is a relatively small study with only 56 participants in the arms of interest, 300mg q2w (27 patients) and 300mg q4w (29 patients).*"	To clarify that both the lanadelumab 300mg q2w arm and the 300mg q4w arm are of interest, as both are stated in the SmPC, and both arms are used in the economic model. Although 300mg q2w is the recommended starting dose, 300mg q4w can be used long-term in patients who are stably attack free on treatment, as per the SmPC.	The proposed revision is accepted.

Issue 21 Presentation of NMA results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In table 20 on page 54 of the ERG report NMA results are presented with lanadelumab 300 q4w labelled as the reference treatment. This presents the	The table headers should be amended to clarify presentation of the treatment comparisons.	The NMA results submitted were calculated for lanadelumab 300 q4w relative to each alternative treatment. The presentation of results in	Change accepted (see erratum)

comparisons the wrong way around. This also applies to the following tables 22, 23, 25 and 26.	As an example, table 20 row 1 presents treatment group = placebo, ref = 300 q4w and rate ratio = [redacted]. This presentation implies that placebo reduces the attack rate relative to lanadelumab 300 q4w which is incorrect. The correct result is that lanadelumab reduced the rate of attacks relative to placebo. The same principle applies to all rows of tables 20, 22, 23, 25 and 26	these tables implies that the relative effect was calculated for each alternative treatment relative to lanadelumab 300 q4w which is incorrect.	
In the header of table 21 on page 54 of the ERG report it states: "*SE log HR used in NMA (already adapted using Woods equations)*" The Woods method was only used to estimate the standard error of the log hazard in the placebo arm of HELP03. The standard error of the log hazard ratio for each dose of lanadelumab compared to placebo was calculated using a standard formula. The same point applies to table 24	The table header and any associated text should be revised to clarify the presentation of the results.	The presentation of the NMA input data does not accurately reflect how these data were derived. The standard error of the log hazard in the placebo arm in HELP03 was derived using the Woods equations. The standard errors for the log hazard ratio for each dose of lanadelumab compared to placebo were calculated using a standard formula as documented on page 32 in appendix D of the CS. se(log HR) = $\sqrt{(1/E_t + 1/E_p)}$ where E_t is the number of events in the treatment arm and E_p is the number of	Change accepted. The header has been amended to: SE log HR used in NMA (Placebo adapted using Woods equations) (3)

		events the placebo arm	
On page 58 of the ERG report it states: "*The ERG has been able to verify the results of the NMA for the outcome Attack Rate if the RR and the SE's provided are accepted. Using additional information provided by the company the 'Time to First attack' for 0-182 and 70-182 days have also been checked. The additional information included the R code and the data used, which enabled the ERG to see that the SEs originally given were the Woods et al.-adapted SEs - not original SEs from the HR models which have not been provided in any form. The ERG derived raw HRs the 'Time to first event' variables based on the basic KM data provided at clarification and did them incorporate into NMA models just for investigation.*" This description is ambiguous and confusing as it mixes up the different approaches taken for the attack rate and time to first attack endpoints	Please revise the text to clarify the approach taken for time to first attack endpoints as follows: *"The ERG has been able to verify the results of the NMA for the outcome Attack Rate if the RR and the SEs provided are accepted. The 'Time to First attack' for 0-182 and 70-182 days have also been checked. The company reported that for the time to first attack endpoints, the standard error of the log hazard in the placebo arm in HELP-03 was derived using the Woods equations. The standard errors for the log hazard ratio for each dose of lanadelumab compared to placebo were calculated using a standard formula (see CS appendix D1, page 32). The ERG derived raw HRs for the 'Time to first event' variables based on the basic KM data provided at clarification and incorporated them into NMA models just for investigation."*	For the time to first attack endpoints, the standard errors were derived as described above. The standard error of the log hazard in the placebo arm in HELP03 was derived using the Woods equations. The standard errors for the log hazard ratio for each dose of lanadelumab compared to placebo were calculated using a standard formula as documented on page 32 in appendix D of the CS, not using the Woods equations.	Text has been amended as follows: "*The ERG has been able to verify the results of the NMA for the outcome Attack Rate if the RR and the SEs provided are accepted. The 'Time to First attack' for 0-182 and 70-182 days have also been checked. The company reported that for the time to first attack endpoints, the standard error of the log hazard in the placebo arm in HELP-03 was derived using the Woods equations. However, the standard errors for the log hazard ratio for each dose of lanadelumab compared to placebo were calculated using a standard formula (see CS appendix D1, page 32) that is using the original count data thus countering the need to adjust for the correlation between multiple arms. The ERG was not able to verify these values provided. Note, the components used to estimate the Placebo SE, were based on the 150 q4w and 300 q4w arms of Help-03. The 150 arm is not relevant to this submission. The ERG originally asked for this to be based on the 300 q42w and 300 q4w arms, but was not provided .The ERG were able to derive raw HRs for the 'Time to first event' variables based on the basic KM data provided at clarification and incorporated them into NMA models*

			just for investigation"

Issue 22 Licence wording

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Table 28, page 63 of the ERG report it states: "*The license is for use in patients aged 12 and above with HAE types 1 and 2 as long-term prophylaxis*." The licence does not state the HAE types.	Please change to read: "The licence is for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older."	The information regarding the product licence should be accurate.	Not factually inaccurate. The proposed revision is not accepted.

Issue 23 HELP-04 description

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page xvi of the ERG report it states: "*Participants will receive their last dose on day 350 (maximum of 26 doses) and will then be followed-*	Please change to read: "*Non-rollover participants will receive their last dose on day 350 (maximum of 26 doses) and will then be followed-up for four weeks*."	The follow up time for other patients is longer than 350 days.	The proposed revision is accepted

up for four weeks." The sentence does not clarify that this is for non-rollover patients only.			

Issue 24 Minor text inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 11 of the ERG report it states: "*In addition, the company searched health technology assessment and trial registry websites, as well as several conference proceedings from 2016 to 2019*." The date ranges given for these searches in the ERG report is incorrect and does not match with the details presented in Appendix D of the CS.	Shire requests that the ERG change this to: "*In addition, the company searched health technology assessment and trial registry websites, as well as several conference proceedings from 2016 to 2018*."	To aid in both the accuracy and clarity of the document.	This is a typographical error, which does not affect results and conclusions. The proposed revision is not accepted.
On page xvii of the ERG report it states: "*Lanadelumab was favoured compared with placebo for all secondary endpoints in HELP-03*." This statement fails to acknowledge that Lanadelumab was significantly more effective for all secondary endpoints compared to placebo.	Shire requests that the ERG change this to: "*Lanadelumab was significantly superior to placebo in all secondary endpoints in HELP-03*".	To aid in both the accuracy and clarity of the document.	The ERG statement is not factually inaccurate. The proposed revision is not accepted.
On page 29 of the ERG report it states: "*Data for the primary endpoint analysis are presented in Table 12 and Figure 4, Document A of the CS , which are reproduced by the*	Shire requests that the ERG change this to: "*Data for the primary endpoint analysis are presented in Table 12 and Figure 4, Document B of the CS , which are*	To aid in both the accuracy and clarity of the document.	Minor typographical error. The proposed

ERG as Table 9 and Figure 3 below." The table and figure numbers presented in the ERG report are relevant for Document B of the CS not Document A.	*reproduced by the ERG as Table 9 and Figure 3 below*."		revision is not accepted
On page 40 of the ERG report it states: "*A summary of TEAEs during the 26-week treatment period is presented in Table 24, Document B, of the CS and reproduced by the ERG as Table 14 below*." Table 14 in the ERG report was created using data from Table 3 of the ERG clarification questions responses submitted by Shire and not from Table 24 of the CS.	Shire requests that the ERG change this to: "*A summary of TEAEs during the 26-week treatment period is presented in Table 3, of the clarification question document and reproduced by the ERG as Table 14 below*."	To aid in both the accuracy and clarity of the document.	The proposed revision is accepted (The Table was initially presented in Doc B but then the errors were corrected in the clarification response)
On Page 41 of the ERG report it states: *"No placebo participants experienced an adverse event of special interest (AESI), pre-defined as hypersensitivity reactions and disordered coagulation, and only five lanadelumab participants experienced eight AESIs.*" The values in the ERG report are taken from Table 24, Document B, of the CS and do not match up with values presented in Table 14 of the ERG report.	Shire requests that the ERG change this to: "*No placebo participants experienced an adverse event of special interest (AESI), pre-defined as hypersensitivity reactions and disordered coagulation, and only four lanadelumab participants experienced six AESIs.*"	To aid in both the accuracy and clarity of the document.	The ERG statement is taken from the company wording on page 116 of Doc B "No patients in the placebo treatment arm experienced and AESI and the rates of AESIs were low in the lanadelumab treatment arms, as only five patients (6.0%) experienced a

			total of eight AESIs." No revision needed.
On Page 41 of the ERG report it states: "*Ten (11.9%) lanadelumab-treated and two (4.9%) placebo-treated patients had at least one treatment-emergent antidrug antibody (ADA)-positive sample during the treatment period; all antibody titres were low (range: 20–1,280)."* The values in the ERG report are taken from Table 30, Document B, of the CS and do not match up with the values presented in Table 9 of the ERG clarification questions responses submitted by Shire.	Shire requests that the ERG change this to: "*Five (8.9%) lanadelumab-treated and two (4.9%) placebo-treated patients had at least one treatment-emergent antidrug antibody (ADA)-positive sample during the treatment period; all antibody titres were low (range: 20–1,280)*."	To aid in both the accuracy and clarity of the document.	The ERG statement refers to the company's wording on page 117 of Doc B, which contained errors. The proposed revision is accepted.
On page 43 of the ERG report is states: "*During the treatment period, eight patients treated with 300mg lanadelumab and two (4.9%) patients receiving placebo had at least one treatment-emergent antidrug antibody (ADA)-positive samples*." The values in the ERG report are taken from Table 30, Document B, of the CS and do not match up with the values presented in Table 9 of the ERG clarification questions responses submitted by Shire.	Shire requests that the ERG change this to: "*During the treatment period, five (8.9%) patients treated with 300mg lanadelumab and two (4.9%) patients receiving placebo had at least one treatment-emergent antidrug antibody (ADA)-positive samples*."	To aid in both the accuracy and clarity of the document.	Proposed revision is accepted
On page 44 of the ERG report it states: "*Over half (56.4%) of the lanadelumab doses were self-administered by patients, 20.8% at home (655/3157 doses) 357% and in clinic (1127/3157 doses)*." A decimal point is missing in the ERG report for the percentage of patients who administered lanadelumab in the clinic	Shire requests that the ERG change this to: "*Over half (56.4%) of the lanadelumab doses were self-administered by patients, 20.8% at home (655/3157 doses) 35.7% and in clinic (1127/3157 doses).*"	To aid in both the accuracy and clarity of the document.	The proposed revision is accepted
On page 44 of the ERG report it states: "*The company presents a summary of TEAEs in the HELP-04 study,*	Shire requests that the ERG change this to: "*The company presents a summary of*	To aid in both the accuracy and	The sentence is not factually

and these are reproduced by the ERG as Table 15 below." No table number or location is given in the ERG report for the summary of TEAEs in the HELP-04 study presented in the CS.	*TEAEs in the HELP-04 study in Table 31, Document B, of the CS, and these are reproduced by the ERG as Table 15 below.*"	clarity of the document.	inaccurate. The proposed revision is not accepted
On page xvii of the ERG report, it states: "*No significant differences were observed between landelumab and placebo for EQ-5D-5L scores over the HELP-03 treatment period , although significant improvements in AE-QoL scores were observed for lanadelumab from Day 0 to Day 182 (total AE-QoL score least square mean change placebo -4.71 (SD 18.64); lanadelumab -19.47 (SD 18.59), p<0.001*" The p-value is quoted incorrectly and should be changed from p<0.001 to p<0.01.	Please update to: "*No significant differences were observed between lanadelumab and placebo for EQ-5D-5L scores over the HELP-03 treatment period, although significant improvements in AE-QoL scores were observed for lanadelumab from Day 0 to Day 182 (total AE-QoL score least square mean change placebo -4.71 (SD 18.64); lanadelumab -19.47 (SD 18.59), p<0.01*"	To aid in both the accuracy and clarity of the document.	The proposed revision is accepted
On page xviii and page 43 of the ERG report, it states: "*Similarly, the most commonly reported treatment related TEAEs in the 300 mg lanadelumab arms were* [redacted])." The rate of injection site pain was incorrectly stated in the ERG report, and the rate for injection-site bruising is also incorrect, which was an error made by the company in the responses to the ERG clarification questions. As such, please can we ask that this is corrected from [redacted]).	Please update to: "*Similarly, the most commonly reported treatment related TEAEs in the 300 mg lanadelumab arms were* [redacted]	To aid in both the accuracy and clarity of the document.	The proposed revision is accepted
On page xviii of the ERG report, it states: "*Overall,* [redacted] *patients in lanadelumab treatment arms and ,* [redacted] *patients in the placebo arm had related TEAEs*." The text is unclear and could suggest that the lanadelumab data refer to all lanadelumab arms (i.e., including the 150mg arm), not the	Please can the text be changed to: "*Overall, ,* [redacted] *patients in the 300mg lanadelumab treatment arms and ,* [redacted] *patients in the placebo arm had related TEAEs*."	To aid in both the accuracy and clarity of the document.	Not factually inaccurate. The proposed revision is not accepted

two 300 mg arms that it does actually refer to.			
In Table 1 on page 7 of the ERG report, it states: "*The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) granted a positive opinion on 18 October 2018 with marketing authorisation expected in December 2018*." Although this was correct at the time of submission writing, the EMA approval has since been granted, and this took place in November and not December.	Please can the text be changed to: "*The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) granted a positive opinion on 18 October 2018 with marketing authorisation received in November 2018*."	To aid in both the accuracy and clarity of the document.	The proposed revision is accepted
On page 35 of the ERG report, it states: "*The company states that patients treated with lanadelumab in HELP-04 reported a median of 100% attack-free days (mean 97.4%) for a median of 10.5.0 days (mean 125.7 days).”* This is a typographical error that should be corrected	Please change to read "*The company states that patients treated with lanadelumab in HELP-04 reported a median of 100% attack-free days (mean 97.4%) for a median of 105.0 days (mean 125.7 days)*"	To aid in both the accuracy and clarity of the document.	The proposed revision is accepted
On page 35 of the ERG report, it states: "*The number and percentage of attack-free days per month was similar for rollover and non-rollover patients (106 and 103, mean 97.3% and 97.6%, respectively)*." The numbers that are quoted were the number of evaluable patients for these outcomes, and not the numbers of attack-free days.	Please change to read: "*The number and percentage of attack-free days per month was similar for rollover and non-rollover patients (mean: 27.2 and 27.3 days; median: 28 and 28 days; percentage: 97.3% and 97.6%, respectively)”.*	To aid in both the accuracy and clarity of the document.	The proposed revision is accepted
On page 40 of the ERG report, it states: "*In the company submission all adverse events (AEs) analyses were performed using the safety population (56 patients in the lanadelumab group and 41 patients in the placebo group).”* The text is currently unclear as it does not specify which lanadelumab groups it refers to. Given that the overall safety population was 84 patients including the 150mg dose, it would be	Please amend to read: "*In the company submission all adverse events (AEs) analyses were performed using the safety population (84 patients in the lanadelumab group and 41 patients in the placebo group)*."	To aid in both the accuracy and clarity of the document.	Not factually inaccurate. The submission <u>does not</u> focus on the 150mg arm. This is clearly state in the ERG report.

helpful to present this overall number here and then below, go on to focus only on the two 300mg arms (which total 56 patients). Indeed, the ERG report does go on to explain the exclusion of the 150mg group in the second paragraph of section 4.2.4.			The proposed revision is not accepted.
On page 40 of the ERG report it states: "*The company reports that 41 AEs occurred in 23 patients (24.3%) during the pre-treatment period*." Currently, the data presented here is for the lanadelumab arms only, but given that this is not explicitly specified here, and that it follows on from a sentence relating to the overall safety population in the ERG report, it would be more appropriate to present the data for AEs across all patients in the safety population (i.e., lanadelumab and placebo groups).	Please change to read: "*The company reports that 61 AEs occurred in 32 patients (25.6%) during the pre-treatment period.*"	To aid in both the accuracy and clarity of the document.	Not factually inaccurate. The proposed revision is not accepted
On page 135 of the ERG report it reads: "*The basis for this was the percentage of patients attack-free between Day 70 and 182 of HELP-03, when the company state drugs concentrations are in stready state. Responding to ERG clarifications questions, the company provided extrapolations of proportion of patients in steady state that would be expected to be attack free over a full six month duration, but the ERG believe uncertainty remains and this parameter is highly influenceial on the cost-effectiveness results.* *C1-INH is available as two branded medicines Cinryze and Berinert. In the base case these have , [redacted] and [redacted] market share respectively, but this is uncertain and results are sensitive to it. When higher rates of cynrise use are combined with other possible changes, lanadelumab can switch from being dominant to having an ICER above accepted thresholds*." Cinryze is also misspelled on page xix	Please change to read: "*The basis for this was the percentage of patients attack-free between Day 70 and 182 of HELP-03, when the company state drugs concentrations are in steady state. Responding to ERG clarifications questions, the company provided extrapolations of proportion of patients in steady state that would be expected to be attack free over a full six month duration, but the ERG believe uncertainty remains and this parameter is highly influential on the cost-effectiveness results.* *C1-INH is available as two branded medicines Cinryze and Berinert. In the base case these have [redacted] and [redacted] market share respectively, but this is uncertain and results are sensitive to it. When higher rates of*	To aid in both the accuracy and clarity of the document.	Typos have been corrected. Note also Cic has been changed to AiC as instructed by NICE.

There are some spelling mistakes that would require correcting.	*Cinryze use are combined with other possible changes, lanadelumab can switch from being dominant to having an ICER above accepted thresholds*." Also please correct spelling of Cinryze throughout the document.		
On page 92 of the ERG report it reads: "*The Summary of Product Characteristics says, "In patients who are stably attack free on treatment, a dose reduction of 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight"(Shire 2011)."* The reference provided (Shire 2011) relates to Cinryze, not to lanadelumab.	Please update reference to refer to lanadelumab SPC (reference 29)	To aid in both the accuracy and clarity of the document.	Minor mistake (wrong reference). Revision is not considered necessary.

Aberdeen HTA Group

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

Erratum

Completed March 20, 2019

Contains [redacted]

This document is intended to replace pages xvi, xvii, xviii, xix, xxi, xxii, xxiii, xxiv, 7, 35, 40, 41, 43, 44, 54, 55, 56, 57, 58, 67, 68, 70, 78, 94, 96, 113, 114, 123, 124, and 135 of the original ERG assessment report for *Lanadelumab for preventing recurrent attacks of hereditary angioedema,* which contained a few inaccuracies. The amended pages follow in order of page number below.

1.1.5 Other relevant factors

The company notes that, unlike attenuated androgens, lanadelumab does not impact on a woman's ability to have children as there is no associated risk of virilisation to the female foetus. The company also note that lanadelumab is not based on human or animal products. Both factors are relevant to direct or indirect discrimination, either on the basis of sex or religion.

1.2 Summary of clinical effectiveness evidence submitted by the company

The main evidence presented by the company for the effectiveness of lanadelumab is from the HELP-03 trial. HELP-03 was an international phase 3 multicentre, randomised, double-blind, placebo-controlled trial that evaluated SC lanadelumab for long-term prophylactic (LTP) treatment of acute attacks in 125 patients with Type I or II HAE. Participants were randomised to receive placebo (n=41) or one of three lanadelumab groups: 150mg every four weeks (n=28), 300mg every four weeks (n=29) and 300mg every two weeks (n=27). Because the current licence for lanadelumab is for the 300mg dose, the company did not present data for the 150mg dose in the CS. The primary efficacy endpoint of HELP-03 was the number of investigator-confirmed HAE attacks during the 26-week treatment period.

Participants who completed HELP-03 were given the option to enter the ongoing open-label extension study, HELP-04, and those participants who consented to join HELP-04 were termed rollover patients (n=109). Rollover patients (n=109) received their first 300mg SC lanadelumab dose on Day 0 and then did not receive another dose until their first HAE attack, at which point they received 300mg lanadelumab every two weeks thereafter. HELP-03 participants who chose not to participate in HELP-04 were followed-up for eight weeks. Patients who did not participate in HELP-03 were also invited to enrol in HELP-04. These non-rollover patients (n=103) included some people who were receiving another prophylactic therapy. Non-rollover participants received 300mg SC lanadelumab every two weeks regardless of their first HAE attack. Non-rollover participants will receive their last dose on day 350 (maximum of 26 doses) and will then be followed-up for four weeks. The interim 6-month results are presented in section B.2.6, Document B of the CS. Data from HELP-04 were not used to populate the economic model.

A Phase Ib study, DX-2930-02 was presented as supporting evidence to inform the indirect treatment comparison (ITC). This was a multicentre, randomised, double-blind, multiple-ascending dose study that compared SC lanadelumab with placebo/on-demand standard care in 37 people. There were four lanadelumab groups: Lanadelumab 30mg q2w (n=4), Lanadelumab 100mg q2w (n=4), Lanadelumab 300mg q2w (n=5), Lanadelumab 400mg q2w (n=11). These data were not included in the economic model because, according to the company, they are superseded by the HELP-03 trial and few participants received the relevant lanadelumab dose.

The key results of the clinical effectiveness evidence indicate that in HELP-03 both lanadelumab 300mg treatment groups met the primary endpoint and showed statistically significant and clinically meaningful reductions (>50% HAE attacks) in the number of attacks during the treatment period compared with placebo. Compared with placebo, lanadelumab 300mg q2w and 300mg q4w reduced investigator-confirmed attacks by 86.9% and 73.3%, respectively ($p<0.001$ for both). All rollover patients in HELP-04 continued to experience a reduction in mean attack rate from baseline over 182 days. Lanadelumab rollover patients experienced an [redacted] total reduction in attacks per month from baseline, while placebo rollover patients experienced a reduction of [redacted] in mean attack rate from baseline. Non-rollover patients who received landelumab 300mg q2w in HELP-04 also showed reductions in the number of HAE attacks per month over 6 months (182 days), irrespective of previous LTP. The baseline mean of [redacted] attacks per months decreased to [redacted] attacks per month, corresponding to a reduction in attack rate of [redacted]

Lanadelumab was favoured compared with placebo for all secondary endpoints in HELP-03. No significant differences were observed between lanadelumab and placebo for EQ-5D-5L scores over the HELP-03 treatment period, although significant improvements in AE-QoL scores were observed for lanadelumab from Day 0 to Day 182 (total AE-QoL score least square mean change placebo [redacted] lanadelumab [redacted]

Generally, lanadelumab was well-tolerated in HELP-03 in terms of adverse events and in keeping with the known safety profile. A total of 4 patients across the lanadelumab groups experienced four serious TEAEs compared with none in the

placebo group. According to the company, none of these events was considered related to the lanadelumab treatment. One patient in the lanadelumab 300mg q2w arm and three patients in the lanadelumab 300mg q4w treatment arm were hospitalised due to AEs. The company did not consider these events treatment-related. No placebo participants experienced an adverse event of special interest (AESI), pre-defined as hypersensitivity reactions and disordered coagulation, and only 5 lanadelumab participants experienced eight AESIs.

The most frequently reported TEAEs were [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients), [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients), [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients), [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients) and [redacted] of lanadelumab-treated patients compared with [redacted] in the placebo-treated arm). Similarly, the most commonly reported treatment related TEAEs in the 300 mg lanadelumab arms were [redacted] Overall, [redacted] patients in lanadelumab treatment arms and [redacted] patients in the placebo arm had related TEAEs. Ten (11.9%) lanadelumab-treated and two (4.9%) placebo-treated patients had at least one treatment-emergent antidrug antibody (ADA)-positive sample during the treatment period; all antibody titres were low (range: 20–1,280). One patient in the placebo arm and one patient in the lanadelumab 300mg q4w arm discontinued treatment due to a TEAE. No deaths were reported in the study. Adverse events were not used by the company to inform the economic model.

The only study eligible for comparison with HELP-03 was CHANGE, which tested C1-INH IV against placebo using a cross-over design. The ERG agrees with the company that currently this is the only available source of evidence. A Bayesian NMA of fixed effect models was performed using data from the HELP-03 study and the CHANGE cross-over study. The outcomes assessed in the NMA were attack rate and time to first attack after Day 0 and Day 70. The treatment comparisons showed that patients treated with lanadelumab (300mg q2w and 300mg q4w) had lower

attack rates than patients receiving placebo and an improvement in the relative risk of attack compared with those treated with C1-INH IV. In particular, for patients treated with lanadelumab 300mg q2w compared with those receiving placebo, the attack rate ratio [redacted] which indicates a [redacted] attack rate reduction. For patients treated with lanadelumab 300mg q4w compared with those receiving placebo, the rate ratio was [redacted] which indicates a [redacted] attack rate reduction. Similarly, the rate ratio for lanadelumab 300mg q2w compared with C1-INH IV is [redacted] which indicates that patients treated with lanadelumab had a [redacted] reduction in attack rate compared with patients treated with C1-INH IV. The rate ratio for lanadelumab 300mg q4w compared with C1-INH IV was [redacted] which corresponds to a [redacted] reduction in attack rate compared with patients receiving C1-INH IV. For patients treated with C1-INH IV compared with those receiving placebo the rate ratio was [redacted]

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

From the evidence provided by the HELP-03 study, lanadelumab has been shown to benefit patients with HAE during the 26-week treatment period when compared with placebo. This is true for participants treated with both the 300mg q2w and the 300mg q4w dose. There is also some evidence that lanadelumab is also more effective than the only other comparison treatment C1-INH IV from the CHANGE study. The ERG is satisfied that the methods used to assess both the HELP-03 trial itself and the indirect comparison with CHANGE using NMA are appropriate; however, whether this evidence could be considered sufficient still needs to be determined.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's economic case positioned the medicine within its marketing authorisation, in those who are not controlled with or are not suitable for oral prophylactic treatment. They further noted that they expect lanadelumab to be used in patients who would otherwise be considered for treatment with C1-INH prophylaxis. On this basis, the company made the case that oral prophylaxis was not a relevant comparator, and focused on comparison with intra-venous C1-INH prophylaxis. The C1-INH comparator was a weighted average of two branded medicines available on the NHS in England: Cinryze (IV) and Berinert (IV). The proportion on each

attacks. Costs of acute attacks included drug treatment costs, hospitalisation costs and accident and emergency costs. Fixed proportions of attacks were assumed to require treatment and hospitalisation, but the drug treatment costs for acute attacks did vary by treatment arm. [redacted]. However, lanadelumab is not indicated for treating acute attacks so the company used data on the treatment of attacks in the HELP-03 RCT, excluding treatments that would not be used in the NHS.

In terms of lifetime costs of medicines, the modelling assumed that 44.4% and 76.9% of those in the lanadelumab arm would switch from the q2w regimen to the less frequent regimen (q4w) from month 6 and month 12 respectively. These are the proportions of patients who remained attack free on lanadelumab 300mg q2w over 6 months, and between day 70 and day 182 of the HELP-03 study, respectively. The assumption being that those who remain attack free on the more frequent regimen (q2w) will be switched in clinical practice to the less frequent regimen (q4w). It was assumed that the proportion on the less frequent regimen would remain stable beyond 12 months at 76.9%. It was also assumed that a small proportion of patients (8.8%) would discontinue treatment by month seven in both arms of the model, based on the observed proportion in HELP-03. However, the original model only used this discontinuation proportion to adjust the treatment costs, and not the attack rates applied in the model. Beyond cycle seven, it was assumed all patients would remain on their assigned prophylactic treatment for life. Longer term discontinuation due to loss of efficacy wasn't explored in the company's originally submitted economic model.

In the company base case lanadelumab dominated C1-INH prophylaxis, with a substantial cost saving [redacted] being the main driver of a high incremental net monetary benefit (£470k at a threshold of £30,000 per QALY). [redacted] of the difference in costs is explained by costs of treating attacks [redacted] attributable to differences in treatments and [redacted] to differences in hospitalization costs). The difference in prophylaxis medicine costs accounts for [redacted] The reported QALY gain for lanadelumab was modest in comparison [redacted] with >70% being attributable to the utility increment for subcutaneous administration and the remainder due to less time spent with attacks.

The company model predicts that over a lifetime, patients on C1-INH will experience 526 attacks, of which 315 will be moderate or severe, and 62 will require hospitalisation. With lanadelumab, the equivalent figures are 172, 103 and 20. This equates with a 67% reduction in the number of attacks experienced.

The company provided results of one-way sensitivity analysis which showed the NMB to be most sensitive to uncertainty surrounding the parameter estimates for the covariates included in the Poisson regressions for the placebo arm and the lanadelumab q4w arm of HELP-03. These inputs are key determinants of the predicted attack rate in the respective arms of the model. Scenario analyses provided by the company demonstrated a substantial increase in incremental NMB when the dosing frequency of C1-INH was [redacted] assuming no change in efficacy), and a sizeable reduction in NMB when the attack rate in the lanadelumab arm was estimated by applying rate ratios from the indirect comparison to the predicted attack rate in the placebo arm of HELP-03. Further scenario analyses provided by the company in response to clarification questions further illustrated the sensitivity of the incremental NMB to the percentage of patients assumed to switch to the less frequent (q4w) lanadelumab regimen, and the percentage of the C1-INH cohort assumed to be on Berinert.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG identified several issues with the company's original model and base case analysis.

- The initial model structure provided by the company did not appear to account for expected changes in attack rates for those discontinuing treatment (on lanadelumab or C1-INH prophylaxis), did not allow for treatment switching (from lanadelumab to C1-INH), and did not explore the potential impact of longer-term loss of efficacy and discontinuation in the lanadelumab arm. The ERG therefore requested some structural changes to the model that would allow these issue to be explored.
- The arm of the economics model representing 'usual care' differs from the published NHS England Commissioning Policy for C1-INH in several ways. These include: criteria for starting prophylaxis with C1-INH; the definition of a clinically significant attack; the criteria for reducing frequency of use of C1-INH and criteria for stopping C1-INH prophylaxis. In the company's response to the ERG's clarification questions, the company defended the base case in the following manner. Firstly, they noted the

limited data that exists from the trial to present robust results for each relevant sub-group who would align with the Commissioning Policy. However, they noted that results from HELP-03 demonstrated there were no statistically significant differences in the treatment effect between sub-groups and the scenario analysis presented in response to clarification question B1 demonstrated that lanadelumab becomes more cost-effective in patients with higher baseline attack risks. Secondly, they noted that based on clinician feedback, patients are more likely to receive an increase in administration frequency of C1-INH if they are experiencing breakthrough attacks and that treatment is rarely discontinued. They noted that this is still in line with the Commissioning Policy which provides some flexibility to clinicians in their consideration of treatment discontinuation.

- The ERG also have some concern, given the NHS commissioning policy for C1-INH, that in certain circumstances 'usual care' may involve 'no prophylaxis' for a minority of patients. The company declined to provide an ICER against this alternative, saying it did not represent the proposed positioning of lanadelumab and was outside NICE scope. For illustrative purposes the ERG explored the impact of constructing a 'no prophylaxis' arm based on the placebo arm of the RCT, which suggests the cost per QALY for C1-INH and for lanadelumab versus 'no prophylaxis' is likely above usually accepted thresholds.
- The company base case uses the Poisson regressions fitted independently to the lanadelumab arms of HELP-03 to extrapolate attack rates in the landelumab arm of the model, whilst estimating the attack rate in the C1-INH arm relative to the predicted attack rates based on the placebo arm of HELP-03. This approach leads to a 67% reduction in attacks for landelumab versus C1-INH in the model, when the rate ratios for lanadelumab versus C1-INH from the NMA are consistent with a [redacted] reduction in attacks (after accounting for the proportion of patients on each dose of lanadelumab).
- The assumption that 76.9% of the patients in the lanadelumab arm will remain on the less frequent regimen (q4w) from month 12 onwards appears speculative to the ERG, and was not thoroughly tested in the sensitivity analysis originally provided in the company submission.
- C1-INH is available as two branded medicines Cinryze and Berinert. In the base case these have [redacted] and [redacted] market share respectively, but this is uncertain and results are

sensitive to changes in the distribution, particularly if applied in combination with other changes.

- Validation of the predictions of the model for C1-INH were confined to clinical specialist opinion in the context of an advisory board meeting. No validation was made against external data on the observed use of these medicines for reductions in attacks compared to baseline, changes in doses, quality of life impacts, etc.
- In the company model, the costs of treating attacks was estimated differently according to the prophylaxis received; this worked in favour of lanadelumab. The proportions of patients with attacks attending A&E and subsequently admitted are uncertain. The cost used for in-patient admissions seemed inappropriate and produced a cost that was very high for an assumed 1-day stay (excluding drug costs).
- The company chose not to use EQ-5D data from the HELP-03 RCT in the economics model because it does not capture the disutility of attacks. However, switching to an alternative source involved using lower 'without attack' values than the RCT data suggested. The alternative study used had some strengths, but the values came from a self-selected sample of Swedish patients recalling quality of life during attacks that are classified by severity scale with some differences to the RCT definitions (but applied as though they were the same). Disutility of attacks were applied in the model based on severity classifications (mild, moderate and severe) rather than location of attack. In response to an ERG clarification question the company said the reason for this was that no utility data was available which categorised attacks by location rather than severity. It was also noted that clinical experts and patient groups had highlighted that the location of attacks does not necessarily correlate with impact on quality of life and that other factors seem to be more important such as discomfort and impact on daily activities.
- Disutility of iv administration was also included but rolled several possible sources of disutility into one. The ERG's preference would have been to model them separately: for example, one element was the problem of infusion site reactions, but data are available on how common this is, and duration of utility loss could have been estimated. Instead, the study used for base-case values had several issues, the main one being the poor match between the regimes valued in utility terms and the regimes for C1-INH and lanadelumab.

CS, Document B, pages 13-14, and this table is reproduced by the ERG as Table 1 below.

Table 1 Technology being appraised

UK approved name and brand name	Lanadelumab (brand name: Takhzyro; alternative identifier: DX-2930; ATC code: B06AC05)
Mechanism of action	Fully human monoclonal antibody (immunoglobulin G1/ κ-light chain) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. [29] Lanadelumab provides sustained inhibition of plasma kallikrein-induced proteolysis of high-molecular-weight kininogen (HMWK), which produces cleaved HMWK (cHMWK) and bradykinin, a potent vasodilator that increases vascular permeability resulting in HAE attacks and associated swelling and pain. Patients with HAE due to C1-INH deficiency or dysfunction have increased plasma kallikrein activity, both during and in between HAE attacks. In inhibiting active plasma kallikrein proteolytic activity and subsequently limiting bradykinin generation, lanadelumab directly addresses the mechanism of HAE attacks. [29] Furthermore, lanadelumab is highly selective and binds active kallikrein without binding similar proteins (e.g. other serine proteases the pre-kallikrein zymogen, factor X1a and tissue kallikrein 1 gene). [29]
Marketing authorisation/CE mark status	The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) granted a positive opinion on 18 October 2018 with marketing authorisation received in November 2018. [29, 30, 32] Lanadelumab was designated as an orphan medicinal product on 9 October 2015 and reviewed under EMA's accelerated assessment programme. [33]
Indications and any restriction(s) as described in the summary of product characteristics (SPC)	The indication is: [29] Lanadelumab is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.

Attack-free days

The company defined an attack free day as "*a calendar day with no investigator-confirmed HAE attack*" for HELP-03 and "no HAE attack on a particular day" for HELP-04. In comparison with [redacted] of patients in the placebo arm, [redacted] of patients in the lanadelumab 300mg q2w arm and [redacted] of patients in the lanadelumab 300mg q4w arm were attack-free until the Day 182 visit in HELP-03. (Shire. HELP Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]) [28]The mean percentage of attack-free days was higher for both lanadelumab 300mg treatment arms [redacted] in the q2w group; [redacted] in the q4w group) in comparison with placebo [redacted] (Shire. HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). Clinical Study Report. 2017 [Unpublished data]) Similar trends were observed for attack-free days after Day 14.

The company states that patients treated with lanadelumab in HELP-04 reported a median of 100% attack-free days (mean 97.4%) for a median of 105.0 days (mean 125.7 days). The number and percentage of attack-free days per month was similar for rollover and non-rollover patients (mean: 27.2 and 27.3 days; median: 28 and 28 days; percentage: 97.3% and 97.6%, respectively). The median duration of the attack-free period was shorter for rollover patients than non-rollover patients (88.3 versus 164.5 days). (Riedl MA BJ, Yang WH, Longhurst HJ, Magerl M, Hébert J, Martinez-Saguer I, on behalf of the HELP OLE Study investigators. Lanadelumab Reduces Hereditary Angioedema Attack Rate: Interim Findings From the HELP Open-label Extension Study. American College of Allergy, Asthma & Immunology Annual Scientific Meeting. Seattle, WA: USA, 2018 [Unpublished data])

Number of high-morbidity investigator-confirmed HAE attacks

The company defined high-morbidity attacks as "*any attack that had at least one of the following characteristics: severe, resulted in hospitalisation (except hospitalisation for observation <24 hours), haemodynamically significant (systolic blood pressure <90, required IV hydration, or was associated with syncope or near-*

Adverse reactions

In the company submission all adverse events (AEs) analyses were performed using the safety population (56 patients in the lanadelumab group and 41 patients in the placebo group). The company reports that 41 AEs occurred in 23 patients (24.3%) during the pre-treatment period. The majority of AEs during the treatment period were mild to moderate in severity (98.5% in HELP-03 and 98.2% in HELP-04) and were managed with supportive care. The ERG agrees with the company that in general lanadelumab was well tolerated and there was no evident dose response toxicity.

4.2.4 Adverse events - HELP-03

Safety analyses for AEs were performed using the HELP-03 safety population. The company defines treatment-emergent adverse events (TEAEs) as "*events with an onset date on or after the start of study treatment, or those that worsened after the start of study treatment.*" The company explains that, because HAE-attack-reported AEs included investigator-confirmed HAE attacks, the safety data presented in the CS are for non-HAE-reported AEs only. Non-HAE-attack reported AEs were defined as "*the subset of AEs identified in electronic data capture (EDC) as not a reported HAE attack (all AEs excluding HAE-attack-reported events).*"

The company presents AEs data in Tables 24-30, Document B of the CS. At clarification, in response to a question from the ERG, the company provided an updated version of these tables, removing the lanadelumab 150mg q4w dose, which is not considered in the current licence for lanadelumab. A summary of TEAEs during the 26-week treatment period is presented in Table 3, of the clarification question document and reproduced by the ERG as Table 14 below. A higher percentage of people in the lanadelumab arms reported TEAEs than in the placebo arm but the ERG agrees with the company that, overall, lanadelumab was well tolerated. The proportion of people with severe TEAEs was comparable across treatment groups. A total of four patients across the lanadelumab arms experienced four serious TEAEs compared with none in the placebo arm. According to the company, none of these events were considered related to the lanadelumab treatment. One patient in the lanadelumab 300mg q2w arm and three patients in the lanadelumab 300mg q4w treatment arm were hospitalised due to AEs. These events were not considered treatment related by the company. No placebo participants experienced an adverse event of special interest (AESI), pre-

defined as hypersensitivity reactions and disordered coagulation, and only five lanadelumab participants experienced eight AESIs. Five (8.9%) lanadelumab-treated and two (4.9%) placebo-treated patients had at least one treatment-emergent antidrug antibody (ADA)-positive sample during the treatment period; all antibody titres were low (range: 20–1,280). One patient in the placebo arm and one patient in the lanadelumab 300mg q4w arm discontinued treatment due to a TEAE. No deaths were reported in the study.

Appendix 2 of this report. The most frequently reported TEAEs were [redacted] [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients), [redacted] [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients), [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients), [redacted] [redacted] of lanadelumab 300mg-treated patients compared with [redacted] of placebo-treated patients) and [redacted] of lanadelumab-treated patients compared with [redacted] in the placebo-treated arm). Similarly, the most commonly reported treatment related TEAEs in the 300 mg lanadelumab arms were [redacted] [redacted] [redacted] [redacted] Overall, [redacted] patients in lanadelumab treatment arms and [redacted] patients in the placebo arm had related TEAEs (see Table 51 in Appendix 2 for more details).

In Table 26, Document B, of the CS, the company presents a summary of Grade 3 or higher (severe) TEAEs, which occurred in >2% of participants during the treatment period. These data are reproduced by the ERG as Table 52 in Appendix 2. [redacted] patients had [redacted] severe TEAEs in the two 300mg lanadelumab arms and [redacted] patients had [redacted] severe TEAEs in the placebo arm. For Grade 3 or higher treatment-related TEAEs, [redacted] patient in the lanadelumab 300mg q4w arm had [redacted] events of severe related TEAEs (alanine transaminase [ALT] and aspartate transaminase [AST] increased), and [redacted] patient in the placebo arm had [redacted] of injection site reaction (see Table 53 in Appendix 2).

Serious treatment emergent AEs during the treatment period are presented in Table 29, Document B of the CS and reproduced by the ERG as Table 54 in Appendix 2 of this report. Overall, [redacted] patients treated with 300mg lanadelumab [redacted] experienced [redacted] serious emergent AEs during the treatment period compared with none of those treated with placebo. According to the company, none of these events was considered related to the study treatment.

During the treatment period, five (8.9%) patients treated with 300mg lanadelumab and two (4.9%) patients receiving placebo had at least one treatment-emergent antidrug

antibody (ADA)-positive samples. The company reports that antibody titres were low (range, 20-1,280) and the formation of ADAs did not impact on the safety and efficacy of the clinical response.

Adverse events observed in the HELP-04 extension study

The company states that, at the time of the HELP-04 interim analysis, rollover and non-rollover patients had received a median of 15 (range 1 to 26) doses of lanadelumab. Over half (56.4%) of the lanadelumab doses were self-administered by patients, 20.8% at home (655/3157 doses) 35.7% and in clinic (1127/3157 doses). TEAEs were reported by 85.8% of all patients. A higher proportion of patients in the non-rollover group had TEAEs considered related to lanadelumab by the investigator (51.5%) compared with rollover patients (33.0%). The majority (98.2%) of TEAEs were mild to moderate in severity. Five patients (2.4%; four non-rollover and one rollover) withdrew from the study due to TEAEs. Two non-rollover patients withdrew due to hypersensitivity AESIs (oedema, wheals and joint pain; and rash at site of injection and slight swelling under the eyes). The company explains that neither event was serious, but one event was classified as treatment-related and severe because it coincided with a HAE attack and ongoing disease. One non-rollover patient withdrew due to a treatment-related injection site reaction (papules), also classified as a hypersensitivity AESI. One non-rollover patient withdrew due to elevated ALT and AST. The company claims that this event was unrelated to the study drug. One rollover patient withdrew due to upper gastrointestinal bleeding and pneumonia following ingestion of a caustic substance. Eight (3.8%) patients had an investigator-reported AESI (four rollover [8 events] and four non-rollover [5 events], and six of these events were considered to be treatment related. The company presents a summary of TEAEs in the HELP-04 study, and these are reproduced by the ERG as Table 15 below.

Table 20 'Attack Rate': NMA HRs derived by the ERG (in red using WinBUGS), compared with the results reported by the company

Reference	Treatment group	ERG median	ERG 2.5%	ERG 97.5%	Submitted results using R
Placebo	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300 q2w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300 q4w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 150 q4w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
C1-INH IV	300 4w	[redacted]	[redacted]	[redacted]	[redacted]

Table 20 above shows that the NMA attack rates and credible intervals calculated by the ERG are virtually identical to those obtained by the company.

4.7 Time to first attack for days 0-182 (based on Table 14, Appendix D of the CS)

Tables 21 and 24 below are the original HR estimates submitted by the company for time to first attack for 0-182 days and for 70-182 days, respectively. In red are the estimates derived by the ERG using the basic Kaplan Myer (KM) data supplied by the company after clarification (i.e., allowing the ERG to produce the raw HRs).

Table 21 'Time to first event (0-182 days)' estimates for use in the NMA

Treatment group	Original HRs	Ln HR(1)	ERG Raw HRs	ERG Ln HRs (2)	SE log HR used in NMA (Placebo adapted using Woods equations) (3)
Lanadelumab 300mg q2w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 150mg q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo					[redacted]
C1-INH IV	Binary data from Table 12, Appendix D of the CS				

Using original submitted HRs (1) in Table 21 to verify the results given in Figure 15, Appendix D of the CS. As above only the fixed effects model are presented.

Table 22 'Time to first event (0-182 days)' NMA HRs derived by the ERG (in red using WinBUGS), compared with the company results. Based on the original submitted HRs [Table 21 (1)] and SE log HR [Table 21 (3)].

Reference	Treatment group	ERG median	ERG 2.5%	ERG 97.5%	Submitted results using R
Placebo	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg q2w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg q4w	300 4w	[redacted]	[redacted]	[redacted]	
Lanadelumab 150mg q4w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
C1-INH IV	300 4w	[redacted]	[redacted]	[redacted]	[redacted]

Table 22 shows that the NMA HRs and credible intervals are virtually identical between the ERG's results and those obtained by the company.

In Table 23 below the estimates were derived by the ERG using the KM data (i.e., the raw HRs). The original SE(Ln HR) estimates were used in Table 23.

Table 23 'Time to first event (0-182 days)' NMA HR's [Table 21 (2)] derived by the ERG (in red using WinBUGS), compared with the company results using the ERG derived LnHR's and SE log HR [Table 21 (3)].

Reference	Treatment group	ERG median	ERG 2.5%	ERG 97.5%	Submitted results as above	Comments
Placebo	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	
Lanadelumab 300mg q2w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	Slightly different
Lanadelumab 300mg q4w	300 4w	[redacted]	[redacted]	[redacted]		
Lanadelumab 150mg q4w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	Slightly different
C1-INH IV	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	

Although there are some differences, these do not alter the impact of HELP-03 with the second trial, CHANGE.

4.8 Time to first attack for days 70-182 (based on Table 15, Appendix D of the CS)

In Table 24, the ERG has used the original submitted HRs (1) in order to verify Figure 27, Appendix D of the CS. Table 25 shows that the ERG's results are slightly different, but largely comparable, with the company's results.

Table 24 'Time to first event (70-182 days)' estimates for the NMA

Treatment group	Original HR's	Ln HR(1)	ERG Raw HRs	ERG Ln HR's (2)	SE log HR used in NMA (already adapted using Woods et al's equations) (3)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg q2w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 150mg q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C1-INH IV	Binary data from Table 12 Appendix D of the CB				

Table 25 'Time to first event (70-182 days)' NMA HR's HRs derived by the ERG (in red using WinBUGS), compared with the company results. Based on the original submitted HRs [Table 24 (1)] and SE log HR [Table 24 (3)].

Reference	Treatment group	ERG median	ERG 2.5%	ERG 97.5%	Submitted results Figure 27
Placebo	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg q2w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg q4w	300 4w	[redacted]	[redacted]	[redacted]	
Lanadelumab 150mg q4w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]
C1-INH IV	300 4w	[redacted]	[redacted]	[redacted]	[redacted]

As final check, using the KM data received from the company, the ERG derived raw HRs [Table 24 (2)] for the 'time to first attack 70-182 days', while using the same SE(Ln|HR) [Table 24 (3)]. These were used in the NMA and the resulting estimates presented in Table 26 and compared with the results in Figure 27, Appendix D of the CS.

Table 26 'Time to first event (70-182 days)' NMA HRs derived by the ERG (in red using WinBUGS) [Table 24 (2)], compared with the company results using the ERG derived LnHR's [Table 24 (3)],

Reference	Treatment group	ERG median	ERG 2.5%	ERG 97.5%	Submitted results as above	Comments
Placebo	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	Similar
Lanadelumab 300mg q2w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	Very different [a]
Lanadelumab 300mg q4w	300 4w	[redacted]	[redacted]	[redacted]		
Lanadelumab 150mg q4w	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	Some difference
C1-INH IV	300 4w	[redacted]	[redacted]	[redacted]	[redacted]	Similar

Using the raw HRs for the 'time to first attack 70-182 day' has the impact of changing the company significant result to now be non-significant (see [a] in Table 26 above).

4.9 Conclusions of the clinical effectiveness section

The evidence from HELP-03 shows that lanadelumab provides protection from attacks for patients with HAE during the 26-week treatment period. However, HELP-03 is a relative small study with only 27 participants in the arm of interest, 300mg q2w. While this is sufficient for detecting significant difference with respect to 'attack rate' and 'time to first event', the company states (and the ERG is in agreement with the company) that there was insufficient information for more detailed and/or more robust assessment. The company attempted several sub-group analyses all of which were non-significant. However, due to their sample sizes these subgroup analyses are at risk of Type II errors. The models for testing the outcome variables were simple, with the company stating in their clarification response that this was because of the small sample sizes (for example they did not include covariates that often are/should be considered, like age and gender).

The ERG has been able to verify the results of the NMA for the outcome Attack Rate if the RR and the SEs provided are accepted. The 'Time to First attack' for 0-182 and 70-182 days have also been checked. The company reported that for the time to first attack endpoints, the standard error of the log hazard in the placebo arm in HELP-03 was derived using the Woods equations. However, the standard errors for the log hazard ratio for each dose of lanadelumab compared to placebo were calculated using a standard formula (see CS appendix D1, page 32) that is using the original count data thus countering the need to adjust for the correlation between multiple arms. The ERG was not able to verify these values provided. Note the components used to estimate the Placebo SE, were based on the 150 q4w and 300 q4w arms of Help-03. The 150 arm is not relevant to this submission. The ERG originally asked for this to be based on the 300 q42w and 300 q4w arms, but was not provided .The ERG were able to derive raw HRs for the 'Time to first event' variables based on the basic KM data provided at clarification and incorporated them into NMA models just for investigation. However, the method section in the Shire Clinical Study report – DX-2930-03, states that HRs were derived from a GLM for count data, assuming a Poisson distribution with a log link function and Pearson chi-squared scaling of SEs to account for potential over-dispersion. The model included fixed effects for treatment group (categorical) and the normalised baseline attack rate (continuous). The logarithm of time in days each patient was observed during the treatment period was used as an offset variable in the model. The baseline attack rate and time offset variable were not provided to the ERG, and so could not be replicated. None-the-less this approach seems sensible. Indeed, Banerji et al., 2018[28] indicates that the HELP-03 participants receiving 300mg every 2 weeks had fewer attacks 12 months prior to screening suggesting some baseline adjustment to be valid. In addition, these results are linked to the CHANGE cross-over study, through the NMA. The impact of the cross-over would have automatically adjusted for all baseline variables, again suggesting that the adjustment for HELP-03 is a reasonable approach.

Providing the Committee is prepared to accept the company submission in terms of the HR estimates and their precision (already adapted using equations from Woods et al., 2010[43]), the ERG is happy to accept the company's NMA results. However, the Committee should be aware that the providence of the precision estimates for the rate ratios and HRs is not something the ERG has been able to validate. While some attempt has been made to account for the differing study designs of Help-03 and CHANGE this remains a source of concern to the ERG.

The company explained their choice with reference to four factors:

- There are limits on data availability as HAE is an orphan disease (presumably in EMA regulatory terms, although this is not specified)
- The main treatment effect in the RCT programme is a reduced number of attacks
- "The evidence available from the trial data and the literature on the impact of HAE on health-related quality of life (HRQL) and resource use" – this seems to refer to the number of attacks being the main determinant of HRQL and NHS costs
- The need to capture attack severity and the subsequent impact on HRQL and resource use. This was not fully explained and, as the brief description of the model above shows, attack severity was not explicitly modelled.

ERG commentary

The ERG was content with a cohort-level approach over a patient-level approach given the limited RCT data and the lack of a clear argument why the latter might give a different or more precise ICER to help the Appraisal Committee reach a recommendation.

The ERG asked the company to explain the decision to only use attack frequency (ERG clarification questions B13). The company answered that the location of the attack does not necessarily correlate with the patient's quality of life, based on discussions with clinical experts and patient groups. A scenario analysis is not possible due to the lack of data on this issue.

Further issues that the ERG identified with the company's model included its failure to account for changes in attack rates for those discontinuing treatment (on lanadelumab or C1-INH prophylaxis), failure to allow for treatment switching (from lanadelumab to C1-INH), and failure to explore the impact of potential for longer-term loss of efficacy and discontinuation in the lanadelumab arm. The company assumed that an equal proportion (9%) of patients would discontinue treatment in both arms of the model by cycle 7 (based on HELP-03), and that thereafter all

patients would remain on their respective treatment for the entire duration of the model. However, the proportion discontinuing treatment were only accounted for in the estimation of treatment costs. Their attack rate was not adjusted upwards for lack of treatment or lower efficacy treatment, and a utility increment associated with lanadelumab's subcutaneous mode of administration over IV infusion continued to be applied for the full cohort. The ERGs clinical expert believed a C1-INH would be the most appropriate treatment option for those who discontinue treatment with lanadelumab, whilst those (rarely) discontinuing C1-INH would have an uncertain treatment pathway, perhaps with just on-demand treatment C1-INH or icatibant treatment for acute attacks. Therefore, the ERG requested some structural changes to the model at the clarification stage, which would allow these issues to be explored more fully. These were subsequently provided by the company.

5.2.3 Population

The population considered in the company's model was a sub-set of the licensed indication. The license is for use in patients aged 12 and above with HAE types 1 and 2 as long-term prophylaxis.

The HELP-03 study, which formed the basis of the label, recruited patients who had at least one attack every four weeks during the run-in period. The company report that clinicians attending the NICE Scoping workshop had commented this was in line with their expectations of patients they would consider for prophylaxis
In the original submission, the company proposed use of lanadelumab after oral prophylaxis had been tried and not adequately controlled attacks or patients were intolerant or contraindicated. In the response to clarification questions, this was re-stated as being when the patient would otherwise be a candidate for prophylaxis with a C1-INH.

Only 8% of patients in HELP-03 had received prior oral therapy (and 14% in the CHANGE RCT of C1-INH used in the indirect comparison), and it is unclear in how many patient's oral prophylaxis is not clinically appropriate. However, the company noted that within the RCT there were no significant differences in efficacy between sub-groups of patients based on previous treatment history. Therefore, they used the ITT population for HELP-03, irrespective of previous treatment history. The company report they were supported by their clinical specialist advisors who said there was no reason why lanadelumab would be more or less effective after oral prophylaxis.

Table 29 Results by baseline attack risk

Baseline attack risk (per 28 day cycle)	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB (£)
≥ 1 attack	[redacted]	[redacted]	Dominant	£408,206
≥ 2 attack	[redacted]	[redacted]	Dominant	£447,432
≥ 3 attack	[redacted]	[redacted]	Dominant	£489,232
≥ 4 attack	[redacted]	[redacted]	Dominant	£495,161
≥ 5 attack	[redacted]	[redacted]	Dominant	£543,225
≥ 6 attack	[redacted]	[redacted]	Dominant	£640,106
≥ 7 attack	[redacted]	[redacted]	Dominant	£766,649
≥ 8 attack	[redacted]	[redacted]	Dominant	£856,445
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality adjusted life years,				

Source: Company Response to Clarification Questions, page 21

This shows that for higher baseline levels of attacks, lanadelumab becomes more cost-effective compared to C1-INH.

The analysis also appears to be based on all attacks, when the clarification question asked for the NHS England definition of clinically significant attacks to be applied. The 2016 NHS England Commissioning Policy defines an attack as being clinically significant if it is potentially life-threatening (on the head or neck) or if causes pain/disability such that usual activities cannot continue. In their response to a clarification question (Response to Clarification Questions B9, page 27), the company argue "the definition used in the Commissioning Policy would probably include the majority of attacks experienced by patients as, based on discussion with clinicians

clarification request, the company therefore fitted several standard parametric survival curves to the available time to event data, but ultimately selected a spline model with one internal knot as providing the best statistical and visual fit to the data (see Figures 8 and 9 in Section 5.2.8). They then used this to estimate the proportion expected to be attack free in steady lanadelumab concentration over a [redacted] period [redacted] and used this to represent the percentage assumed to be on the less frequent q4w lanadelumab regimen in a scenario analysis. They also provided scenarios where they applied the percentage attack free from all other fitted curves they assessed (presented and discussed further under section 5.2.8 on resource use and costs).

The ERG is satisfied that the selected spline model does provide a good statistical and visual fit to the observed time to attack data. However, the ERG has remaining concerns with respect to the rationale for assuming this extrapolated six month attack free percentage (on q2w) equates with the percentage of patients expected to accept and be on the less frequent regimen (q4w) over the remaining time horizon of the model. The assumption appears speculative to the ERG, without firm evidence to support it. If patients and/or clinicians are motivated to minimise the attack rate, then it remains to be seen how acceptable and feasible it will be to move this percentage of patients to the less frequent regimen which incurs a higher average attack rate.

An alternative way of looking at this could be to assume that the percentage who remain attack free over a period of [redacted] to be the proportion more likely to accept this dosing regimen in the longer term. This might then put the percentage on q4w at around [redacted] in the long-run (approximated from the survival curves in Figure 6 of the CS). However, the ERG acknowledge that patients who switch from q2w to q4w because they are attack free, may also be more likely to remain attack free on the q4w regimen than the average patient in HELP-03. This is because patients who switch may be lower risk than the average patient given that they have remained attack-free for six months. The ERG therefore apply [redacted] as a lower limit in additional sensitivity analysis.

Indirect comparison

The next step was to carry out an indirect comparison against C1-INH. This produced consistent estimates of the relative rates of attacks for C1-INH, lanadelumab q4w and lanadelumab q2w versus placebo, and versus each other. The rate ratio compared to

Both branded types of medicine are administered intravenously, and when used as a prophylaxis both are used every 3-4 days, according to the CS (Document B, page 134).

Cinryze is licensed for 1000IU per dose. Berinert dosing was based on the opinion of six clinical specialists in HAE in the UK and was assumed to be [redacted] per kg bodyweight initially.

The model used a bodyweight of [redacted], the average in the HELP-03 study.
The company model included vial wastage for Berinert, the only medicine with a weight-based dose, using the 'method of moments' approach.

Medicines costs were taken from MIMS for C1-INH.

The company presented a single C1-INH regime by calculating the cost as a weighted average of the two branded types of medicine. In the base-case the company assumed [redacted] on Cinryze and [redacted] on Berinert, based on hospital dispensing data for the number of vials of each branded medicine used per month. Data were for the last three months reported i.e. July, August and September 2018.

The company presented sensitivity analyses of the impact of changing these proportions.

In situations where there is an inadequate response, clinicians reported to the company they would either increase the dose and/or frequency, but this was not modelled; the CS states this therefore underestimates the true cost of a C1-INH regime.

In a sensitivity analysis, it was assumed [redacted] This substantially increased the net benefit from £470k to £743k.

Note the company was asked to provide scenarios with 100% on Cinryze, 0% on Berinert and with 0% on Cinryze and 100% on Berinert. They declined to do so, arguing this did not reflect clinical practice.

The ERG notes that C1-INH dosing was assumed not be increased and agrees this will likely be an under-estimate of the true NHS costs. However, it would have been preferable to have modelled this explicitly rather than leaving it unquantified as this makes it difficult to judge what the impact of including it would have been. In the sensitivity analysis described above, [redacted] *are assumed to derive no benefit, which is unrealistic.*

Treatment duration (discontinuation and dose switching)

The company made the case there is no evidence for a difference between lanadelumab and C1-INH in terms of rate of discontinuation. The rate used per cycle was based on 91.2% of patients in HELP-03 completing the treatment period. The discontinuation rate per cycle was thus 'back-calculated' to arrive at a figure of 8.8% (i.e. 100-91.2) discontinuations after 7 cycles. This was applied to lanadelumab and C1-INH equally.

The model assumed that if the patient is still on treatment after cycle 7 they continue on treatment until they die (no further discontinuation).

In response to a clarification question the company explained this was due to a lack of long-term data to base an assumption upon, and also the strong safety profile of lanadelumab and C1-INH (Company Response to Clarification Questions, B5, page 24).

The company went on to clarify that when patients discontinue treatment in the model (which can only occur in the first six months) they were assumed to have no further active treatment. The company acknowledge this was a simplification but argued "because the assumption of equal discontinuation and survival rates between the arms means that any subsequent therapy costs would, in all likelihood be equal between the treatment arms".

5.3 Exploratory and sensitivity analyses undertaken by the ERG

This section includes additional analyses undertaken by the ERG. The specific parameters the ERG deemed important to explore are those which are subject to a uncertainty and which are key drivers of cost-effectiveness. In particular, parameters relating to the cost of treatment and the cost of attacks, which underpin the estimated cost savings for lanadelumab. The further scenarios explored, and their justification, are outlined in the Table 41. The ERG first conducted additional scenarios around the company's base case (Table 42). Following this, building on a modelling scenario that the company provided in response to the clarification letter, the ERG has adopted a preferred base case which we think better reflects the likely treatment pathway for those who discontinue lanadelumab (Table 43). This ERG base case is then subject to the full range of scenario analyses outlined in the Table 44, with the results presented in Table 45. In addition, given the uncertainty surrounding the percentage of patients switching to the less frequent lanadelumab regimen (q4w) and the proportion on Berinert/Cinryze in the C1-INH arm, a two-way sensitivity analysis was conducted for these two key parameters. The results are presented in Table 46.

Finally, Tables 47 and 48 below are provided to illustrate the importance of the high cost comparator in the case for lanadelumab. The ERG does not dispute the fact that that there is a cohort of patients who require and receive long-term prophylaxis with C1-INH in clinical practice, and acknowledges the company's positioning of lanadelumab as an option for people who would otherwise receive C1-INH prophylaxis. Given the uncertainty surrounding eligibility for long-term C1-INH prophylaxis based on the NHS commissioning policy, the ERG had some concern that lanadelumab could be used by a small group of patients who would otherwise manage without long-term C1-INH prophylaxis. In response to clarification B1, the company provided further clarity on the positioning of lanadelumab, that it is expected to be used in patients who would otherwise be considered for treatment with C1-INH prophylaxis. However, the ERG remains uncertain as to whether in practice this positioning could attract a number of patients who would otherwise, following consideration, not proceed with long-term C1-INH prophylaxis.

A key point to note from Table 42 is the sensitivity of lanadelumab's cost savings to the proportion assumed to switch from the q2w regimen to the less frequent regimen (q4w). In the company base case this is set at 76.9% in the long-term. Holding the company's other base case assumptions constant, lanadelumab switches from being cost-saving when the

proportion drops to 60%, and the ICER increases rapidly if this parameter drops any further. The cost savings are also sensitive to the proportion of the C1-INH cohort assumed to be on Berinert, although this must fall below [redacted] before the ICER for lanadelumab rises above £20,000 per QALY (holding all else constant in the company base case). It may be unrealistic to assume that the proportional use of Berinert among those on C1-INH prophylaxis would fall this low. Lanadelumab remains cost saving across the further scenarios assessed by the ERG, but the application of the lower hospitalisation cost for acute attacks (Table 42) does knock a substantial amount off the cost saving.

of discontinuation observed for lanadelumab in HELP-03. The company's clinical experts, and the ERG's clinical expert, are also of the opinion that there are very few patients requiring long-term prophylaxis who cannot tolerate C1-INH. The impact of this change can be seen in row 3 of Table 44.

The ERG also identified an error in the company's revised model, in the formula used to adjust the acute attack treatment costs for the proportion switching from lanadelumab to C1-INH. The company adjustment ("Lana_Calc" worksheet, Column AW, company revised model) appeared to cost acute treatment for a proportion of attacks twice, first using the acute treatment costs for attacks on lanadelumab, and then the acute treatment costs for attacks on C1-INH. The ERG therefore modified this formula so it would only apply the difference in acute attack treatment costs to the expected attack number occurring in the proportion of patients assumed to be on C1 -INH. The impact of this change on the company's scenario 1B can be seen in row 4. In additon, the ERG prefers to apply the alternative hospitalisation cost for acute attacks, identified using the ICD-10 code for hereditary angioedema (D84.1) mapped to the HRG short-stay reference cost for WJ11 (Table 44, row 5).

Finally, as outlined in section 5.2.6 (under "Indirect comparison"), for reasons of consistency the ERG has a preference for estimating the attack rates in the lanadelumab arm of the model by applying the rate ratios for lanadelumab versus placebo from the company's NMA. This approach generates in a percentage reduction in the attacks (for lanadelumab versus C1-INH) in the model which is consistent with the rate ratios for lanadelumab versus C1-INH from the NMA. However, when applying the rate ratios in this way the company's adjustment to the attack rates, for discontinuation and treatment switching, could not be applied. Therefore, the ERG modified the formulas in the model to allow for this. Row 6 in Table 44 shows the impact of these changes.

The ERG then combined the above changes in a preferred base case for further scenarios analyses (final row of Table 44). The further scenarios in Table 45 to 48 are all conducted relative to this revised ERG base case. The ERG also ran a probabilistic analysis of this alternative base-case, which produced a similar estimate of the NMB (£348,380); incremental cost [redacted] incremental QALY = [redacted]

An important point to note from the further scenario analyses presented in Table 45 is that, from this new reference point, the ICER for lanadelumab now becomes unfavourable when the proportion switching to the lower frequency q4w lanadelumab regimen drops to between 70% and 60%. In addition, the ICER for lanadelumab becomes unfavourable when the proportion on Berinert in the C1-INH arm drops to between [redacted] and [redacted]

Given the uncertainty and sensitivity of the results to these two parameters, further two-way sensitivity analysis was conducted around the ERG base case scenario, where these two variables were varied across ranges simultaneously. The results are presented in Table 46. It can be noted that at lower levels of assumed switching to the less frequent lanadelumab regimen (q4w), the cost-effectiveness case becomes more sensitive to changes in the proportion of C1-INH patients on Berinert.

on the clinical studies. However, the model also assumes further switching at 12 months to bring the overall total up to 76.9%, which is carried forward for the remaining time horizon. The basis for this was the percentage of patients attack-free between Day 70 and 182 of HELP-03, when the company state drugs concentrations are in steady state. Responding to ERG clarifications questions, the company provided extrapolations of proportion of patients in steady state that would be expected to be attack free over a full six month duration, but the ERG believe uncertainty remains and this parameter is highly influential on the cost-effectiveness results.

C1-INH is available as two branded medicines Cinryze and Berinert. In the base case these have [redacted] and [redacted] market share respectively, but this is uncertain and results are sensitive to it. When higher rates of Cinryze use are combined with other possible changes, lanadelumab can switch from being dominant to having an ICER above accepted thresholds. The ERG also asked for a comparison with each type of C1-INH individually, but the company declined to provide this.

In the company model, the costs of treating attacks was estimated differently according to the prophylaxis received; this worked in favour of lanadelumab. The proportions of patients with attacks attending A&E and subsequently admitted are uncertain. The cost used for in-patient admissions seemed inappropriate and produced a cost that was very high for an assumed 1-day stay.

The company chose not to use EQ-5D data from the HELP-03 RCT in the economics model because it does not capture the disutility of attacks. However, switching to an alternative source involved using lower 'without attack' values than the RCT data suggested.
The alternative study used had some strengths but the values came from a self-selected sample of Swedish patients recalling quality of life during attacks that are classified by severity scale with some differences to the RCT definitions (but applied as though they were the same).

Disutility of attacks was assumed to only depend on severity, but the location on the body may also be important. In response to an ERG clarification question the

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft questions for clinical expert

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

1. Nature of the disease

1.1 How does the disease usually progress over time?

People are born with this disease, so adults, children and young people are treated in clinical practice. Some patients have symptoms early in life and this often becomes worse around the age of puberty. Symptoms are often exacerbated by stress and for some women, hormonal fluctuations. The condition is hereditary, but the severity of symptoms is variable, even within people from the same family. Treatment is individualised with the aim to reduce symptoms and, ideally, become symptom-free. Acute attacks are exacerbated by stress, some predictable (for example exams, surgery and dental treatment) and some unpredictable (for example “good stress” life events, such as weddings and holidays). Some patients have frequent attacks, while others will have long periods without an attack. The pattern of attacks can change over a patient’s own lifetime.

1.2 How often are patients monitored? Does this depend on the frequency of acute attacks?

Generally, patients should be monitored every 6 months, and may be seen more regularly during periods with more frequent attacks. Sometimes people who are stable (i.e. no symptoms) do not attend every monitoring appointment and are therefore seen 0 to 1 times in a year. Monitoring frequency may depend on treatment; for example, patients treated with danazol are seen at least every 6 months to monitor liver function. It may also depend on individual-specific needs.

1.3 Would an acute attack be treated differently depending on the prophylactic treatment used? For an acute attack that requires hospitalisation, how long is a typical inpatient stay (or range)?

Treatment can potentially differ depending on the prophylactic treatment used. If C1-INH is being used as a long-term prophylactic treatment it may also be used to treat an acute attack, with or without add-on icatibant. Some centres prefer to use C1-INH to treat throat swellings, while icatibant is used for swelling to other locations. There is some variation in practice regarding how acute attacks are treated, but hospitalisations these days are very rare, if patients have access to acute treatment at home. When a patient does attend hospital, for example for laryngeal swelling, and the attack is treated adequately, the hospital stay is usually over 24 hours. When an inpatient hospitalisation is required, it is typically for 1 or 2 days. If acute laryngeal swelling is not caught early, it can result in a stay in intensive care.

2. Treatment pathway and current treatment options

2.1 In whom would prophylactic treatment be considered? What prophylactic treatments are currently used in the NHS? If C1-inhibitor (C1-INH) is used, does current practice follow the NHS England commissioning policy for C1-INH?

Patients who have regular swelling and those at risk of severe swelling would be considered to benefit from long-term prophylactic treatment. In clinical practice, many patients have oral prophylactic treatment, such as attenuated androgens. Generally, treatment has improved over time but there remains limited options. Women who are of child-bearing age may be reluctant to take androgens, and androgens would not typically be given to young people. For patients taking androgens, the dose is titrated to the minimum effective level to minimise the risk of side effects. C1-INH is used in line with the NHSE commissioning policy. It is primarily used as short-term prophylaxis (for example before surgery). Only a few patients take C1-INH as a long-term prophylactic treatment, and this decision requires agreement and review by a multidisciplinary team outside the patient's own specialised service.

2.2 Lanadelumab is expected to be licensed for any patients aged 12 years and older to prevent recurrent attacks of HAE. What's the expected positioning of lanadelumab in clinical practice? Would you expect to use lanadelumab instead of oral prophylactic treatment or later in the pathway? How would this differ to the NHSE commissioning policy for C1-INH?

Ideally, as well as using lanadelumab as an alternative to C1-INH, it would be a treatment option earlier in the treatment pathway, as an alternative to long-term oral prophylactics. There is a lack of effective long-term treatment options; androgens (oral prophylaxis) are helpful but are not a gold standard. In clinical practice, the expected positioning of lanadelumab would be for patients that need long-term prophylactic treatment.

2.3 The trial only included patients with type I and II disease with at least 1 attack in the preceding 4 weeks. Would you expect to use lanadelumab for any other patients in clinical practice?

Most patients (around 98%) have type 1 or 2 hereditary angioedema, and one attack in the past 4 weeks is a moderate burden of disease, therefore the trial adequately reflects the population that is generally seen in clinical practice.

2.4 The trial included around 44% of participants who had not previously had any long-term prophylactic treatment. Would you expect to use lanadelumab in this group in clinical practice?

Potentially yes, we would see patients who have not had previous long-term prophylactic treatment. It is not known why prophylactic treatment was not used. The available treatment options have side-effects and some are not effective, so some patients may choose to have no prophylactic treatment, monitor their condition and use treatment only for acute attacks. Some patients would prefer no treatment even if they were having regular and moderately debilitating attacks.

2.5 **PRIORITY**: Is C1-INH the most appropriate comparator? How often is Berinert used in clinical practice as a prophylactic rather than acute treatment? Approximately what proportion (or range) would have Berinert

vs. Cinryze to prevent attacks? Is ‘no prophylactic treatment’ a relevant comparator?

The ideal position of lanadelumab would be in place of current oral prophylactic treatments (such as androgens), however there is currently no trial evidence for these. Therefore, the comparator could be C1-INH or no prophylactic treatment. There is variation in the use of available C1-INH. Some centres mainly use Cinryze because of a home care arrangement provided by the manufacturer, other centres use Berinert, and some are starting to move to Ruconest. It is difficult to assess clinical practice across all treatment centres but it is plausible that there is a 50/50 split in the use of Cinryze and Berinert. Off-label Berinert for long-term prophylaxis is used in clinical practice and this has been agreed with commissioning. It is believed that the majority of prescriptions for C1-INH is likely to be for treatment for acute attacks, though a small number of patients will receive lots of C1-INH as long-term prophylaxis. In one service, it is estimated that less than 40% are on long-term prophylaxis.

2.6 Are all C1-INH given intravenously in clinical practice, or is there any off-label subcutaneous administration? Will all patients self-administer treatment at home?

C1-INH may be used off-label and administered subcutaneously because this route is licensed in some places. This may be due to individual patient needs, for example because of lack of reliable venous access. However, most administration is intravenous.

2.7 In clinical practice, would dose reductions be used for any current prophylactic treatments?

Patients are monitored regularly, and doses are titrated down to the lowest level that achieves symptom control for the individual patient. The aim of treatment is to control symptoms and reduce the number of acute attacks. One swelling per year is an indication that treatment is working well, though not perfectly; practice may have become willing to accept imperfect results due to the lack of effective treatments currently available.

3. Experience with lanadelumab

3.1 Do you have any clinical experience with lanadelumab? Please describe

No experience with lanadelumab.

3.2 **PRIORITY**: Is it clinically plausible that long-term dose reductions in lanadelumab will be used? If so, in approximately what proportion (or range) would you expect this to happen? Is there any other evidence (for example from other subcutaneous prophylactics) that may support this?

There is a lack of data, but long-term dose reductions are clinically plausible. Generally, the starting treatment dose (once every 2 weeks) would be used to achieve symptom control and then a dose reduction in line with the SPC would be considered. This potentially could continue long-term but would be tailored to the needs of the individual patient. Dosing is an iterative process and long-term dose reductions are currently achieved with oral prophylactic treatments in most patients.

3.3 Is it clinically plausible to assume that lanadelumab would not lose its effectiveness over time?

It is plausible that lanadelumab would not lose its effectiveness for most patients but, like other biological therapies, it is likely there will be a small proportion of patients with disease who might develop secondary non-response (approx. 5 to 10%).

4. Subsequent prophylactic treatment

4.1 In clinical practice, what prophylactic treatment would be used if preventative C1-INH is stopped? Is it plausible that a patient would receive no prophylactic treatment after C1-INH?

If long-term treatment with C1-INH is stopped no prophylactic treatment would be used, because at this point other oral prophylactic treatments would have been tried, and there are no alternative treatments available.

4.2 In clinical practice, what treatment is likely to be used if lanadelumab is stopped? Is it plausible that C1-INH would be used?

If lanadelumab was stopped, it is likely that prophylactic C1-INH would be started.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **Tuesday 30 April 2019** at **5pm**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Shire which is now part of Takeda**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Positioning of lanadelumab	
Given that the marketing authorisation is broad, and the trial population differs from the population in the NHS England commissioning policy, is the company's positioning of lanadelumab as a long-term prophylactic treatment after oral therapy appropriate?	The Company believes the positioning is appropriate. According to the current treatment pathway in England and Wales, the majority of patients with HAE receive oral prophylactic therapy; a smaller proportion of patients is eligible for long-term prophylactic (LTP) treatment with C1-INH. Those patients currently eligible for LTP with C1-INH represent a population with a high unmet need as they are either experiencing a high number of attacks per month, or are not suitable for oral prophylactic treatment. They also have the treatment burden of having to administer IV infusions 2-4 times a week. Lanadelumab has the potential to achieve a higher reduction of attacks and even attack-free status and fulfil the need of this population for whom C1-INH treatment is the only alternative. Furthermore, lanadelumab is administered via subcutaneous injection every two or four weeks. The same criteria currently used to select patients eligible for LTP with C1-INH would be used to select patients eligible for lanadelumab treatment. Should these criteria change in the future, the cost-effectiveness of lanadelumab and a positive NICE recommendation would still be applicable; for example, if the future attack threshold is lowered, since we demonstrate cost-effectiveness against C1-INH in a population experiencing a minimum of two attacks per month, the data in the Company Submission would still be valid.
Given that the trial included people who were having fewer attacks than the NHS England commissioning policy criteria for long-term prophylactic C1-INH, is the	Although the population in England expected to receive lanadelumab may have a higher number of acute attacks at baseline than the trial population, the efficacy of lanadelumab is not expected to vary based on the baseline attack rate; as confirmed by clinical experts during the technical engagement TC. Subgroup analyses performed within the HELP-03 trial showed a significant reduction in the mean HAE attack rate in the lanadelumab arm compared to placebo for the subgroups defined by potential indicators of severity: attack number at baseline, previous long-term prophylactic treatment received, and history of laryngeal attacks. These sub-group analyses

trial generalisable to the proposed positioning of lanadelumab in NHS practice in England?	provide strong evidence that these characteristics are not treatment effect modifiers. They are reported in more detail in Appendix E of the Company Submission and in Appendix **A** below. Although the small number of patients experiencing a higher number of attacks in HELP-03 represents a significant limitation, a scenario analysis presented as part of the Company response to Clarification Questions (Table 10 on page 25 of Clarification Questions document) demonstrated how lanadelumab is actually more cost-effective (saves more costs and generates more QALYs) in this scenario, as the number of attacks at baseline is increased. Despite the limitations, this scenario analysis indicates that using the HELP-03 data in the model produces conservative results and that in a more severe population, such as the population currently suitable for C1-INH in England, the benefits of lanadelumab may be even larger. The updated scenario analysis using the revised Company's base case is reported in Appendix C **– Scenario analysis on baseline attack risk based on Company's revised base case**
In people for whom long-term oral prophylactic treatment is not controlling the disease, or those for whom it is not suitable, does long-term oral prophylactic treatment ever become suitable again over time?	
Issue 2: Comparator	
What is the most appropriate comparator? a. In NHS clinical practice in England, for people for whom long-term	The majority of patients with HAE in the UK receive long-term prophylactic treatment with attenuated androgens (e.g. danazol); these are used outside their licenced indication and their historical use is not accompanied by any robust

prophylactic treatment with C1-INH is an option, what proportion of people have C1-INH and what proportion choose not to have it? b. Given that lanadelumab is given subcutaneously, would it lead people to switch from no long-term prophylactic treatment to treatment with lanadelumab? c. In clinical practice, would lanadelumab be used as an alternative to long-term oral prophylactics, long-term C1-INH or both?	evidence. The Company is not aware of any evidence that would allow a robust comparison between lanadelumab and attenuated androgens. A smaller proportion of patients are eligible for long-term prophylactic treatment with C1-INH and clinical experts during the technical engagement TC clarified that negligible patient numberss eligible for C1-INH decline treatment. Therefore, it was agreed that 'no treatment' is not an appropriate comparator. On this basis, the only appropriate comparator is long-term prophylactic treatment with C1-INH as lanadelumab would be used as an alternative to this treatment, consistent with the Company positioning and NICE recommendation. The Company do not regard attenuated androgens to be a relevant comparator and no evidence exists to allow for a robust comparison against them. [redacted] 1 presents the latest results, using revised assumptions from the company's original base-case based on feedback from the ERG and NICE; [redacted]. The details of the revised based case assumptions are reported in Appendix B – Revised Company's base case. [redacted] The results demonstrate that lanadelumab is a cost-effective treatment option compared to C1-INH – the relevant comparator for this appraisal given the company's positioning. Therefore, focus should be placed on the comparison against C1-INH.

Table 1: Revised company base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	NMB
C1-INH	[redacted]	21.48	[redacted]					
Lanadelumab	[redacted]	21.48	[redacted]	[redacted]	0.00	[redacted]	Dominant	£424,788
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: C1-INH, C1 esterase inhibitor; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALY, quality-adjusted life year.

What C1-INH treatments are used in clinical practice for long-term prophylaxis?

a. What proportion of patients use Berinert?

b. What proportion of patients use Cinryze?

We are aware that there is variation across the country on the use of Berinert or Cinryze as long-term prophylaxis for HAE. In the Company's submission and economic analysis, published data based on IQVIA Hospital Pharmacy Audit data has been provided, and an average of the last three months of reported data informed the base case values; we believe this provides the most robust estimate of the use of Berinert and Cinryze in UK clinical practice. Data for each month over the past three years from the Hospital Pharmacy Audit data provides ranges of [redacted] for Berinert and [redacted] for Cinryze. As the results in Table 2 demonstrate, lanadelumab remains cost-saving even when the maximum and minimum percentages from this data-set are applied.

Table 2: Scenario analysis for changes in the percentage of patients receiving Cinryze/Berinert IV

Proportions	ICER (£/QALY)	NMB (£)
Base-case ([redacted] Cinryze IV: [redacted] Berinert IV)	Dominant	£424,788
([redacted] Cinryze IV: [redacted] Berinert IV)	Dominant	£346,887
([redacted] Cinryze IV: [redacted] Berinert IV)	Dominant	£715,400

Issue 3: Long-term dose reduction for lanadelumab	
When using long-term prophylactic treatment in clinical practice, when is it appropriate to reduce the dosing frequency? a. Using current treatments (long-term oral therapy and intravenous C1-INH), is the dosing frequency titrated down to the lowest level that achieves control of symptoms?	As clinical experts can confirm, titrations for oral androgens and C1-INH are fundamentally different. With oral androgens, the aim is to find a good balance between effectiveness and side effects and down-titration to the minimum effective dose is common; with C1-INH, up-titration is more common to control attack occurrences. Based on feedback from six UK clinicians we are not aware of any down-titration lower than the licensed dose for C1-INH, although we are aware a proportion of patients are up-dosed, as confirmed by clinical experts during technical engagement TC. In the Company Submission, we have conservatively assumed licensed dose in the base case model.
Are lower dosing frequencies of prophylactic treatment expected to continue in the long-term? a. Is it clinically plausible that around 77% of patients continue to have a lower dosing frequency of lanadelumab after 1 year? b. Are any further changes to dosing (for example,	The SPC of lanadelumab states that the lower dosing frequency may be considered in patients who are stably attack-free on treatment. From the HELP-03 trial data, the proportion of patients expected to be attack-free once lanadelumab has achieved steady-state is 77%. Clinical experts at the technical engagement TC confirmed that it is plausible that this proportion of patients would be prescribed lanadelumab every four weeks. Although the patients who would receive lanadelumab in UK clinical practice would likely be more severe patients based on the UK clinical commissioning policy for C1-INH, the 77% is expected to be representative for these patients based on an analysis of the steady state time to first attack data from HELP-03. Figure 1 and **Figure 2** present time for first attack data for the lanadelumab every 2 weeks (q2w) and placebo arms from HELP-03 respectively from day 70 onwards (once lanadelumab has achieved steady state), split by patients baseline attack risk (<3

increasing the frequency) expected in the long-term? If so, approximately what proportion will need to switch back to a higher dosing frequency, and for how long?	attacks vs >3 attacks). These results demonstrate no differences between the less severe and more severe group in the percentage of patients remaining attack-free in the lanadelumab q2w arm, while differences appear to exist in the placebo group, where the more severe group is less likely to be attack-free. Therefore, these figures provide further evidence that

lanadelumab is highly effective in more severe patients and that the results from the ITT population in HELP-03 are broadly generalisable to the population of interest.

Figure 1: Lanadelumab q2w day 70-182 time to first attack Kaplan-Meier data (by baseline attack risk)

Figure 2: Placebo day 70-182 time to first attack Kaplan-Meier data (by baseline attack risk)

In the economic model, attack-free patients move onto the 4-weekly lanadelumab dosing frequency; some of these would subsequently experience further attacks, requiring them to go back to the 2-weekly frequency; however, at the same time some of the 23% of patients receiving the 2-weekly frequency would become attack-free and would therefore switch to the 4-weekly frequency. For this reason, we expect this proportion to remain approximately constant, even if switches continue to occur in both directions.

Issue 4: Subsequent prophylactic treatment and continued treatment effect	
In clinical practice, what long-term prophylactic treatment is used if C1-INH is stopped?	Clinical experts at the technical engagement TC confirmed that C1-INH treatments are rarely stopped because in severe patients, achieving a sub-optimal response is still beneficial and no other option is currently available. This is also in line with the ERG preferred base case. Those patients still experiencing a high number of attacks despite treatment with C1-INH, are likely to have their dose increased until control is achieved. In the revised company base case model reported in Table 1, we have conservatively assumed no dose increases in the C1-INH arm.
In clinical practice, what long-term prophylactic treatment is likely to be used if lanadelumab is stopped?	Clinical experts at the technical engagement TC confirmed that this would be C1-INH. This has been reflected in the company's revised base case as reported in Table 1.
Is it clinically plausible that lanadelumab would not lose its effectiveness over time?	As part of the clarification questions responses dated 01/02/19, the Company provided some explanation and scenario analyses around the loss of effectiveness with lanadelumab over time. Lanadelumab remained dominant in all scenarios explored, except for an extreme scenario where 100% of patients experience lack of response at 5 years and patients were assumed to receive no treatment afterwards, which is not reflective of clinical practice. Even in this scenario lanadelumab was less costly than C1-INH, although less effective, and the NMB was positive. As explained in the Company response to Clarification Questions B6 and B21, in HELP-03 the overall incidence of anti-drug antibodies (ADAs) in treated subjects was just 9.6% (12/125). Furthermore, the development of ADAs did not have an impact on treatment efficacy and did not result in discontinuation. For this reason, we believe assuming that 100% of

patients will experience loss of effectiveness after only five years is extremely unlikely and the 5-year scenario should be considered unrealistic.

This is also in line with the opinion of the clinical experts participating in the technical engagement TC who stated that they would expect no more than 5-10% of patients to develop a non-response to lanadelumab. The clinical experts also indicated that any loss in effectiveness may be overcome by having a treatment break.

The revised Company's base case does not account for treatment lack of response based on feedback from NICE after the technical engagement TC.

In response to a request from NICE regarding discontinuation data from the HELP-04 study, interim data (data from 26 May 2016 to 1 September 2017) is provided in Table 3 below, showing that most patients (92.9%) remained in the study. These data are supportive and consistent with the HELP-03 data and in line with the discontinuation rate already used in the model (91.2%).

Table 3: HELP-04 discontinuation data

	Rollover Subjects	**Non-rollover subjects**	**Total**
Number of Subjects Treated	109	103	212
Completed study	0 (0%)	2 (1.9%)	2 (0.9%)
Ongoing (active study participation)	102 (93.6%)	95 (92.2%)	197 (92.9%)
Number of subjects who did not complete study	7 (6.4%)	6 (5.8%)	13 (6.1%)

Appendix A – Subgroup analyses from HELP-03

In the HELP-03 study, subgroup analyses based on various baseline characteristics were planned for the primary efficacy endpoint. As shown in Figure 3, for subgroups with an adequate number of patients to fit into the Poisson regression model for HAE attack rate analysis, all estimated least squares (LS) mean HAE attack rate ratios in comparison to placebo were <1, consistently favouring the three lanadelumab treatment arms.

Consistent with the primary efficacy outcome for the ITT population, the 95% CIs for percentage reduction in the investigator-confirmed HAE attack rate across subgroups with an adequate number of patients was below 1, which is equivalent to a significantly lower attack rate for the lanadelumab treatment arm compared to placebo in the respective subgroup in an unadjusted comparison.

For subgroups with inadequate numbers of patients or low numbers of observed clinical events for the HAE attack rate model, any inferential conclusions regarding the HAE attack rate in comparison to placebo cannot be supported. However, a reduction in the LS mean HAE attack rate was consistently observed compared to placebo for all subgroups (except the ‘other race’ subgroup) for all three lanadelumab treatment arms. This treatment effect was also observed in subgroups with low number of patients. Notably, the magnitude of the treatment effect across all subgroups was most profound and consistent in the 300mg q2w arm.

Figure 3: Forest plot of rate ratio on number of investigator-confirmed HAE attacks by patient subgroups: ITT population

Key: BMI, body–mass index; C1-INH, C1 esterase inhibitor; CSR, clinical study report; HAE, hereditary angioedema; ITT, intent-to-treat; LTP, long-term prophylaxis.
Notes: *, Rate ratio estimate was not provided for a treatment group with only one patient in the subgroup
Source: HELP-03 CSR

Appendix B – Revised Company's base case

As part of the technical engagement stage, NICE have indicated their preference for the economic analysis. Table 4 below reports this information together with an explanation of the revised Company's base case and rationale.

Table 4 - Revised Company's base case

Preferred approach as indicated by NICE	Company's revised base case	Explanation of Company's position
No treatment waning for lanadelumab	No treatment waning for lanadelumab	In line with NICE preference and clinical opinion
Analyses including both treatment discontinuation options 1) Patients stopping lanadelumab switch to C1-INH, those on C1-INH will continue to have this and 2) Patients stopping lanadelumab switch to C1-INH, those on C1-INH switch to no treatment. All patients in comparator arm stay on treatment. No utility benefit from subcutaneous lanadelumab after it is stopped	Patients stopping lanadelumab switch to C1-INH, those on C1-INH will continue to have this No utility benefit from subcutaneous lanadelumab after it is stopped	Proposed analysis 2 is effectively the same as analysis 1 as all patients in comparator arm (i.e. C1-INH) stay on treatment. This is also in line with the ERG base case and the opinion of clinical experts participating in the technical engagement TC who confirmed that C1-INH are rarely stopped because in severe patients achieving a sub-optimal response is still beneficial and no other option is currently available.
It would be useful to present analyses using longer-term discontinuation data from HELP-04	Discontinuation from HELP-03	In the model, it is expected that the majority of patients would switch to the 4-weekly dose after one year, therefore data from HELP-04,

		which was designed with the 2-weekly dosing only, are of less relevance to the model population. In addition, we have reported discontinuation data from the HELP-04 study as part of our response to Issue 4 which show consistency with the data already used in the model.
Correct acute attack costs for patients switching from lanadelumab to C1-INH	Correct acute attack costs, attack rate and utility benefit associated with treatment administration for patients switching from lanadelumab to C1-INH	In line with NICE preference
Lower hospitalisation costs for acute attacks	Lower hospitalisation costs for acute attacks	In line with NICE preference
Use NMA data for both arms	HELP-03 data for lanadelumab arm	The ERG outlined that their preference for estimating the attack rate in the lanadelumab arm of the model is applying the rate ratios for lanadelumab versus placebo from the company's NMA in order to be consistent with the approach adopted to estimate the attack rate for C1-INH patients. However, we maintain that the approach of estimating the attack rate in the lanadelumab arm using the Poisson regression coefficients provides the best option for estimating more precisely the number of attacks experienced in each cycle. The indirect treatment comparison utilises data across the full trial duration to estimate

		one rate ratio which is then applied to the placebo curve, assuming proportional hazards. The Poisson regression predicts the number of attacks in each cycle, allowing for any changes in the attack rate over time to be captured. The analysis conducted in HELP-03 using data from Day 70-182 indicates that lanadelumab becomes more effective when concentrations have reached a steady state, with the rate ratio against placebo falling from 0.131 to 0.085 for the q2w dose and from 0.267 to 0.194 for the q4w dose compared to the Day 0-182 analysis. Therefore, we would expect the Poisson regression to more accurately capture this change over time. However, the rate ratio from the indirect treatment comparison was used to estimate the attack rate for C1-INH patients over time out of necessity as there was insufficient data from the CHANGE trial to allow for the estimation of an additional Poisson regression

Appendix C – Scenario analysis on baseline attack risk based on Company's revised base case

Table 5: Model results by baseline attack risk

Baseline attack risk (per 28 day cycle)	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB (£)
≥ 1 attack	[redacted]	[redacted]	Dominant	424,854
≥ 2 attack	[redacted]	[redacted]	Dominant	426,523
≥ 3 attack	[redacted]	[redacted]	Dominant	428,257
≥ 4 attack	[redacted]	[redacted]	Dominant	428,275
≥ 5 attack	[redacted]	[redacted]	Dominant	430,364
≥ 6 attack	[redacted]	[redacted]	Dominant	434,621
≥ 7 attack	[redacted]	[redacted]	Dominant	439,300
≥ 8 attack	[redacted]	[redacted]	Dominant	440,760

Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality adjusted life years,

Appendix D - Company identified inaccuracies/changes in technical report submitted to NICE ahead of technical engagement TC

- Replace any references to long-term prophylaxis in the report or any further discussion with the specific treatment: a) LTP with oral treatment, b) LTP with C1-INH, c) LTP with either oral treatment of C1-INH.
- Issue 3 Q5a should be modified to consider each treatment separately and ask how titration works rather than focusing on down-titration
- Issue 4 Q9 should be amended to make it less vague and add more useful scenarios
- Issue 4, the two issues of subsequent therapy changes and treatment waning are explained and presented separately
- Page 6 of the technical report “The company suggests that the use of C1-INH in practice may not be in line with the NHS England commissioning policy.” This was challenged under Issue 4 of the factual accuracy review of the ERG report and had been accepted by ERG
- Issue 1 Q2: the question implies that the NHS England commissioning policy only permits use of C1-INH in patients who have 2 or more significant attacks per week over 8 weeks but fails to acknowledge that patients can also receive treatment if they are considered unsuitable for oral treatment
- Q6a and Q6b inaccurately represent how the switch to lower dose is used in the model: the company model does not assume that the lower frequency is maintained throughout a lifetime for those patients who switch at 1 year; we have explained that among the 77% of patients who are attack free at steady-state and switch to the 4-weekly frequency, some would subsequently experience further attacks, requiring to go back to the 2-weekly dose; however, at the same time some of the 23% of patients receiving the 2-weekly frequency would become attack-free and would therefore switch to the 4-weekly dose. For this reason, we expect this proportion to remain constant, even if switches continue to occur in both directions
- Page 3 “The company’s base case assumption of no subsequent treatment if Lanadelumab is stopped is not realistic” fails to acknowledge the analyses provided during clarification question

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- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of

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About you

Your name	**Sinisa Savic**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Immunology and Allergy CRG**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Positioning of lanadelumab	
Given that the marketing authorisation is broad, and the trial population differs from the population in the NHS England commissioning policy, is the company's positioning of lanadelumab as a long-term prophylactic treatment after oral therapy appropriate?	**No.** **Lanadelumab (Lana) has a potential to transform how we manage patients with the HAE. Up to this point we had very few options to offer for long-term prophylaxis (LTP). Although attenuated androgens (AA) (for example danazol) are widely used in the UK, these medication are likely to be inferior to Lana in efficacy and tolerance. The use of AA is also limited to specific age groups (not recommended for children and young adults) and often have unacceptable side-effect profile in women of child bearing age. Therefore proposing to use Lana only after oral therapy failed might limit the use of this medication to the most severe spectrum of the disease, when in reality far more patients could benefit.**
Given that the trial included people who were having fewer attacks than the NHS England commissioning policy criteria for long-term prophylactic C1-INH, is the trial generalisable to the proposed positioning of lanadelumab in NHS practice in England?	**Yes.** **The minimum attack frequency to enter the trial was 1/month. However there were many patient who had more frequent attacks prior to entering the trial. In addition there was a proportion of patents who were on long-term prophylaxis with pC1-INH, who stopped the treatment to enter the trial. The primary outcome of the study was not affected by frequency of attacks or the type of previous prophylaxis used.**
In people for whom long-term oral prophylactic treatment is not controlling the disease, or those for whom it is not suitable, does long-term oral prophylactic treatment ever become suitable again over time?	**The severity of HAE varies during a life-time of an individual patient. There are number of known and unknow factors which will influence this. Therefore the need for LTP will also need to be assessed on a regular basis. Furthermore, in the women of post-menopausal**

	age, the frequency of HAE-related attacks can decrease significantly, and the use of AA might be more acceptable.
Issue 2: Comparator	
What is the most appropriate comparator? a. In NHS clinical practice in England, for people for whom long-term prophylactic treatment with C1-INH is an option, what proportion of people have C1-INH and what proportion choose not to have it? b. Given that lanadelumab is given subcutaneously, would it lead people to switch from no long-term prophylactic treatment to treatment with lanadelumab? c. In clinical practice, would lanadelumab be used as an alternative to long-term oral prophylactics, long-term C1-INH or both?	**a. To qualify for LTP with C1Inh in England patients have to be experiencing more than 2 moderate to severe attacks per week. This is extremely high burden of the disease and therefore patients are highly motivated to go on to the treatment and continue to comply. However, there might be an occasional person in whom IV access is problematic, which makes this treatment option difficult to administer.** **b. yes** **c. please see my previous answer under 1. There are number of patients who have significantly high burden of the disease, in whom AA are not effective or cause unacceptable side-effects, but do not qualify for LTP with C1Inh. Such patients would benefit greatly from having access to Lana**
What C1-INH treatments are used in clinical practice for long-term prophylaxis? a. What proportion of patients use Berinert? b. What proportion of patients use Cinryze?	**Not entirely sure, this will vary between hospitals, but likely to be used in equal proportions**
Issue 3: Long-term dose reduction for lanadelumab	
When using long-term prophylactic treatment in clinical practice, when is it appropriate to reduce the dosing frequency? a. Using current treatments (long-term oral therapy and intravenous C1-INH), is the dosing	**As already mentioned, HAE activity varies over a life-time of an individual and influenced by a variety of factors. Therefore truly individualised approached to therapy is needed. This stipulates regular follow up to assess burden of the diseases, to enquire about change in circumstances that might affect this and on-going effectives of therapy. As part**

frequency titrated down to the lowest level that achieves control of symptoms?	**of this process titrating of LTP (either AA, or IV C1Inh) to minim required to maintain symptomatic control is regularly undertaken.**
Are lower dosing frequencies of prophylactic treatment expected to continue in the long-term? a. Is it clinically plausible that around 77% of patients continue to have a lower dosing frequency of lanadelumab after 1 year? b. Are any further changes to dosing (for example, increasing the frequency) expected in the long-term? If so, approximately what proportion will need to switch back to a higher dosing frequency, and for how long?	**a. this is possible based on some preliminary data from HELP-03 study, but impossible to predict accurately at this stage** **b. it is likely that few patient will require higher frequency of administration at the times when HAE become more active. Again this is difficult to predict accurately and sensually a perioded of treatment between of 3-6 months is necessary before making any further adjustments**
Issue 4: Subsequent prophylactic treatment and continued treatment effect	
In clinical practice, what long-term prophylactic treatment is used if C1-INH is stopped?	There are currently no alternatives available
In clinical practice, what long-term prophylactic treatment is likely to be used if lanadelumab is stopped?	C1-INH
Is it clinically plausible that lanadelumab would not lose its effectiveness over time?	Yes as it is the case with all other biological therapies, some patients will develop secondary non-response. It is difficult to predict what proportion will be affected, but unlikely to be large.

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About you

Your name	**Laura Szutowicz**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**HAE UK Patient Support and Advocacy Charity**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Positioning of lanadelumab	
Given that the marketing authorisation is broad, and the trial population differs from the population in the NHS England commissioning policy, is the company's positioning of lanadelumab as a long-term prophylactic treatment after oral therapy appropriate?	Lanadelumab does seem to be appropriate for long term prophylaxis for patients, however what must be taken into consideration is the variability of the condition which is described in the next answer.
Given that the trial included people who were having fewer attacks than the NHS England commissioning policy criteria for long-term prophylactic C1-INH, is the trial generalisable to the proposed positioning of lanadelumab in NHS practice in England?	The level of control shown across the study does hold good from patients have relatively few attacks to those having more frequent attacks. However, the variability of this condition must be recognised; patients often experience more frequent attacks during period of hormonal or emotional instability eg puberty, exam time, other transitional changes. They can also experience more frequent or more severe attacks because of underlying infection/inflammatory processes. There is therefore a need for a review period to be built into prescribing practice. For example, this product may be very appropriate for a person taking exams and then progressing to University. Their time of stress may lessen during their University time and they may in any case experience fewer attacks, but the increased stress of first time job may increase the rate of attacks. It may be that the clinician and patient consider other forms of management, eg extending the period between doses at some times and reducing it at others.
In people for whom long-term oral prophylactic treatment is not controlling the disease, or those for whom it is not suitable, does long-term oral prophylactic treatment ever become suitable again over time?	As above, because of the mutability of the condition, the patient may revert to oral prophylaxis and find it manages their attacks well when it has failed in the past.

Issue 2: Comparator	
What is the most appropriate comparator? a. In NHS clinical practice in England, for people for whom long-term prophylactic treatment with C1-INH is an option, what proportion of people have C1-INH and what proportion choose not to have it? b. Given that lanadelumab is given subcutaneously, would it lead people to switch from no long-term prophylactic treatment to treatment with lanadelumab? c. In clinical practice, would lanadelumab be used as an alternative to long-term oral prophylactics, long-term C1-INH or both?	a) our patient surveys show the vast majority of those eligible, say, 85% opt for C1-INH; the ones who do not have it usually are unable to carry out the venepuncture and self-administer for some reason (eg lack of venous access, needle phobia). b) People managing their condition with Icatibant on demand may well find that if their attacks are well controlled and that the administration is similar to Icatibant that they will find Lanadelumab of benefit rather than having to use many syringes of shorter acting product? c) Ideally, this should be offered as part of the range of products available to be discussed between patient and doctor. There is a significant cohort of patients who actually fall outside the NHS England Commissioning Policy for C1-INH but are still eligible for various benefits because their HAE affects more than 50% of daily living, for example the patient who has severe abdominal attacks once a week and is bedridden with excruciating pain, vomiting and diarrhoea for several days. Or, as suggested above the patient who for a short period could benefit from this type of treatment to get them through a few stressful months but who may subsequently revert to oral prophylaxis or other methods of management..
What C1-INH treatments are used in clinical practice for long-term prophylaxis? a. What proportion of patients use Berinert? b. What proportion of patients use Cinryze?	I am not sure of exact figures, and the recent shortage/unavailability of Cinryze which had a knock on effect on Berinert supplies has probably slewed this. Lack of, or restriction on supply is a cause of grave concern to my members.
Issue 3: Long-term dose reduction for lanadelumab	
When using long-term prophylactic treatment in clinical practice, when is it appropriate to reduce the dosing frequency? a. Using current treatments (long-term oral therapy and intravenous C1-INH), is the dosing frequency titrated down to the lowest level that achieves control of symptoms?	As I am not a clinician I cannot comment on these questions but as suggested above I think a review period should be built in to this type of prescribing because of the very mutable condition we are dealing with. The clinical studies show that good control is still enabled by dose reduction after an initial period of stabilisation. It should be a subject for discussion between patient and clinician, and practice modified to suit the circumstance.

Are lower dosing frequencies of prophylactic treatment expected to continue in the long-term? a. Is it clinically plausible that around 77% of patients continue to have a lower dosing frequency of lanadelumab after 1 year? b. Are any further changes to dosing (for example, increasing the frequency) expected in the long-term? If so, approximately what proportion will need to switch back to a higher dosing frequency, and for how long?	Unable to comment
Issue 4: Subsequent prophylactic treatment and continued treatment effect	
In clinical practice, what long-term prophylactic treatment is used if C1-INH is stopped?	Unable to comment
In clinical practice, what long-term prophylactic treatment is likely to be used if lanadelumab is stopped?	Unable to comment
Is it clinically plausible that lanadelumab would not lose its effectiveness over time?	Unable to comment

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About you

Your name	**Rachel Annals**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Patient and HAE UK representative**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Positioning of lanadelumab	
Given that the marketing authorisation is broad, and the trial population differs from the population in the NHS England commissioning policy, is the company's positioning of lanadelumab as a long-term prophylactic treatment after oral therapy appropriate?	**I believe lanadelumab should have broader use. I have severe frequent attacks of HAE, two attacks per week, so I would fit the NHS commissioning policy for treatment, but I know others who suffer one attack per week and struggle with day to day life because of this. Whilst I understand that lanadelumab cannot be available for every HAE patient, I think we would be automatically excluding so many other severely affected patients by following the current protocol.**
Given that the trial included people who were having fewer attacks than the NHS England commissioning policy criteria for long-term prophylactic C1-INH, is the trial generalisable to the proposed positioning of lanadelumab in NHS practice in England?	**I think the data needs to be clear about how each patient suffered with attacks before treatment as well as whilst on treatment, to determine if the overall effects of the drug were the same. I.e. did someone experiencing one attack per month have the same response to the drug as someone experiencing two attacks per week.**
In people for whom long-term oral prophylactic treatment is not controlling the disease, or those for whom it is not suitable, does long-term oral prophylactic treatment ever become suitable again over time?	**How would you determine the failure of current oral prophylactic medication, so to be eligible for lanadelumab?** **Would it prove difficult for the patient if they felt the oral drug wasn't working well enough for them or that side effects meant they didn't like taking it, but their HAE doctor disagreed?** **If lanadelumab was working well for the patient, what would be the reason to cease usage and return to the oral prophylactic medication?**

Issue 2: Comparator	
What is the most appropriate comparator? a. In NHS clinical practice in England, for people for whom long-term prophylactic treatment with C1-INH is an option, what proportion of people have C1-INH and what proportion choose not to have it? b. Given that lanadelumab is given subcutaneously, would it lead people to switch from no long-term prophylactic treatment to treatment with lanadelumab? c. In clinical practice, would lanadelumab be used as an alternative to long-term oral prophylactics, long-term C1-INH or both?	**C1 INH**
What C1-INH treatments are used in clinical practice for long-term prophylaxis? a. What proportion of patients use Berinert? b. What proportion of patients use Cinryze?	
Issue 3: Long-term dose reduction for lanadelumab	
When using long-term prophylactic treatment in clinical practice, when is it appropriate to reduce the dosing frequency? a. Using current treatments (long-term oral therapy and intravenous C1-INH), is the dosing frequency titrated down to the lowest level that achieves control of symptoms?	**In my opinion, as a HAE patient, I would always be keen to use the lowest dose possible of any drug as long as it kept attacks under control. But this should be managed in consultation with the patient and how they felt.**
Are lower dosing frequencies of prophylactic treatment expected to continue in the long-term?	

a. Is it clinically plausible that around 77% of patients continue to have a lower dosing frequency of lanadelumab after 1 year? b. Are any further changes to dosing (for example, increasing the frequency) expected in the long-term? If so, approximately what proportion will need to switch back to a higher dosing frequency, and for how long?	
Issue 4: Subsequent prophylactic treatment and continued treatment effect	
In clinical practice, what long-term prophylactic treatment is used if C1-INH is stopped?	There is no other option
In clinical practice, what long-term prophylactic treatment is likely to be used if lanadelumab is stopped?	C1 INH
Is it clinically plausible that lanadelumab would not lose its effectiveness over time?	

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- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
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your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Royal College of Pathologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Positioning of lanadelumab	
Given that the marketing authorisation is broad, and the trial population differs from the population in the NHS England commissioning policy, is the company's positioning of lanadelumab as a long-term prophylactic treatment after oral therapy appropriate?	
Given that the trial included people who were having fewer attacks than the NHS England commissioning policy criteria for long-term prophylactic C1-INH, is the trial generalisable to the proposed positioning of lanadelumab in NHS practice in England?	**Considering that C1Inhibitor concentrates (Cinryze or Berinert) are the comparators for Lanadelumab, the indications for prophylaxis with Lanadelumab should be the same as those for the C1Inhibitor concentrates which is minimum of 2 attacks per week rather than 2 attacks per month.**
In people for whom long-term oral prophylactic treatment is not controlling the disease, or those for whom it is not suitable, does long-term oral prophylactic treatment ever become suitable again over time?	
Issue 2: Comparator	
What is the most appropriate comparator? a. In NHS clinical practice in England, for people for whom long-term prophylactic treatment with C1-INH is an option, what proportion of people have C1-INH and what proportion choose not to have it?	**When comparing Cinryze or Berinert with Lanadelumab, the risk of thrombotic events when high dose Cinryze is used in neonatal and infant cardiac surgery is mentioned which is not a clinical setting comparable to the use of normal doses in adults having HAE attacks. These drugs have been used for many years with little postmarketing report of thromboembolic events associated with their use in HAE. Whereas, the theoretical risk of reduction in bradykinin production and its potential effects of**

b. Given that lanadelumab is given subcutaneously, would it lead people to switch from no long-term prophylactic treatment to treatment with lanadelumab? c. In clinical practice, would lanadelumab be used as an alternative to long-term oral prophylactics, long-term C1-INH or both?	**vasoconstriction, and cardiovascular risk at the time of an ischemic event for Lanadelumab which has only been tested in human for only 3-4 years is not mentioned.**
What C1-INH treatments are used in clinical practice for long-term prophylaxis? a. What proportion of patients use Berinert? b. What proportion of patients use Cinryze?	
Issue 3: Long-term dose reduction for lanadelumab	
When using long-term prophylactic treatment in clinical practice, when is it appropriate to reduce the dosing frequency? a. Using current treatments (long-term oral therapy and intravenous C1-INH), is the dosing frequency titrated down to the lowest level that achieves control of symptoms?	
Are lower dosing frequencies of prophylactic treatment expected to continue in the long-term? a. Is it clinically plausible that around 77% of patients continue to have a lower dosing frequency of lanadelumab after 1 year? b. Are any further changes to dosing (for example, increasing the frequency) expected in the long-term? If so, approximately what proportion will need to switch back to a higher dosing frequency, and for how long?	

Issue 4: Subsequent prophylactic treatment and continued treatment effect	
In clinical practice, what long-term prophylactic treatment is used if C1-INH is stopped?	
In clinical practice, what long-term prophylactic treatment is likely to be used if lanadelumab is stopped?	
Is it clinically plausible that lanadelumab would not lose its effectiveness over time?	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **Tuesday 30 April 2019** at **5pm**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**UKPIN**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Positioning of lanadelumab	
Given that the marketing authorisation is broad, and the trial population differs from the population in the NHS England commissioning policy, is the company's positioning of lanadelumab as a long-term prophylactic treatment after oral therapy appropriate?	**Yes; although it should be noted that the current commissioning criteria for prophylactic C1-INH only captures those with a very severe attack frequency and there are those patients with lower (but still severe) attack frequency who could benefit from prophylactic treatment, e.g. lanadelumab (when oral treatment failed/not appropriate). See also comments below on next question.**
Given that the trial included people who were having fewer attacks than the NHS England commissioning policy criteria for long-term prophylactic C1-INH, is the trial generalisable to the proposed positioning of lanadelumab in NHS practice in England?	**Yes.** **Although the trial population differs from the NHSE prophylactic C1-INH 'criteria' the studies that are referred to within the NHSE policy have a baseline HAE attack frequency of 1 per week which is the same as the baseline attack rate in the HELP-03 trial. The criteria within the NHSE policy currently only captures patients with a very severe attack frequency (for patients on C1-INH, the criteria is equivalent to the twice weekly dosing of prophylaxis treatment) and the lanadelumab trial population reflects those with a lower but still severe attack frequency, which reflects the overall HAE population seen in clinical practice.**
In people for whom long-term oral prophylactic treatment is not controlling the disease, or those for whom it is not suitable, does long-term oral prophylactic treatment ever become suitable again	**Yes. An example would be in adolescent patients when they become adults or in patients who have to stop oral prophylaxis due to pregnancy.**

over time?	
Issue 2: Comparator	
What is the most appropriate comparator? a. In NHS clinical practice in England, for people for whom long-term prophylactic treatment with C1-INH is an option, what proportion of people have C1-INH and what proportion choose not to have it? b. Given that lanadelumab is given subcutaneously, would it lead people to switch from no long-term prophylactic treatment to treatment with lanadelumab? c. In clinical practice, would lanadelumab be used as an alternative to long-term oral prophylactics, long-term C1-INH or both?	**a. There is no accurate figure for this available. Would propose that the proportion of patients choosing not to receive is low; given that to meet the NHSE criteria patients would need to be treating attacks twice weekly the same as the prophylactic dosing. Although it is accepted that some patients may be treating these attacks with subcutaneous icatibant and not want intravenous treatment.** **b. Yes** **c. Alternative to C1-INH,. Also as an alternative in patients who are unable to receive oral prophylaxis.**
What C1-INH treatments are used in clinical practice for long-term prophylaxis? a. What proportion of patients use Berinert? b. What proportion of patients use Cinryze?	**This will vary between hospitals. Currently no accurate figure available; ongoing HAE network survey will capture this data. CMU figures available but this would not segregate acute and prophylaxis treatment.**
Issue 3: Long-term dose reduction for lanadelumab	
When using long-term prophylactic treatment in clinical practice, when is it appropriate to reduce the dosing frequency? a. Using current treatments (long-term oral therapy and intravenous C1-INH), is the dosing frequency titrated down to the lowest level that achieves control of symptoms?	**Yes. Timescales on dose reductions would vary and be based on individual patient responses.**
Are lower dosing frequencies of prophylactic treatment	**a. Although difficult to determine an accurate figure this is clinically plausible from the**

expected to continue in the long-term? a. Is it clinically plausible that around 77% of patients continue to have a lower dosing frequency of lanadelumab after 1 year? b. Are any further changes to dosing (for example, increasing the frequency) expected in the long-term? If so, approximately what proportion will need to switch back to a higher dosing frequency, and for how long?	**HELP-03 data; the lower dose (300mg 4-weekly) showed a significant improvement from baseline.** **b. Would expect some patients may need to change dose again in the future. The frequency of HAE attacks can be affected, for example, by certain environmental triggers, e.g. emotional stress, and is not static. Therefore it is possible patients may go through a period of increased attack frequency. However, you would then expect patients to be able to lower the dose again in the future.**
Issue 4: Subsequent prophylactic treatment and continued treatment effect	
In clinical practice, what long-term prophylactic treatment is used if C1-INH is stopped?	**If C1-INH treatment stopped and oral prophylaxis not appropriate or effective then there is no alternative.**
In clinical practice, what long-term prophylactic treatment is likely to be used if lanadelumab is stopped?	**C1-INH**
Is it clinically plausible that lanadelumab would not lose its effectiveness over time?	**Yes, although cannot be 100% guaranteed in all patients as has been seen with other biological therapies.**

Lanadelumab for preventing recurrent attacks of hereditary angioedema

ERG critique of the new evidence submitted by the company in response to the technical engagement

Produced by Aberdeen HTA Group

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Date Completed: 22nd May, 2019

Contains [redacted]/[redacted]

This report provides the ERG's brief commentary and critique of additional economic evidence and modelling submitted by the company (Shire, now part of Takeda) on 01/05/2019 and 10/05/2019 in response to the Technical Engagement and in advance of the first AC meeting for this appraisal. The commentary/critique provided below should be read in conjunction with the company's submitted response: ID1268 TE response form 100519 PS updated [ACIC]. This commentary covers the main headings used by NICE, identifying four key issues. It also provides the results of some further analyses conducted by the ERG.

1. Positioning

The ERG has put forward the view that the company's approach is designed to force the cost-effectiveness comparison with C1-esterase inhibitors (C1-INH), which is entirely legitimate but creates two issues:

- The generalisability of evidence from the HELP-03 RCT to the population matching NHS England's commissioning policy in terms of level of attacks at baseline is uncertain, with fewer than [redacted] in the trial potentially matching the criteria at baseline.
- clinical experts (and patients) want lanadelumab to be used more widely and there is little evidence they are 'signed up' to the restriction the company proposes.

The ERG believe there is a risk that if NICE accepts the medicine as an option where a C1-INH would otherwise be used, this will be difficult for commissioners to monitor or enforce. The company's comment on the Technical Engagement seemed to re-state their existing contention that the position was feasible and workable. They re-stated their sensitivity analysis showing that lanadelumab is cost-effective irrespective of number of attacks at baseline. They acknowledge this is based on small numbers of patients for higher frequency of attacks at baseline, and long-term estimated attack rates in this scenario remain based on regression coefficients by treatment arm which were derived from analysis of the wider HELP-03 trial population.

Clinical experts are quoted as saying that baseline attack frequency should not affect the level of reduction seen with lanadelumab, but it is not clear what this view is based on. The company have provided subgroup analysis of HELP-03 by attack frequency at baseline, which showed comparable effects for lanadelumab compared to placebo by categories of attack frequency at baseline, but it can be noted from the economic model that only [redacted] in HELP-03 had a baseline attack rate that would make them potentially eligible for long-term prophylaxis with C1-INH based on NHS England's commissioning policy (≥8 per 28 day cycle).

2. Comparator

The ERG is content that C1-INHs are a comparator. Accepting the logic of the company's positioning, oral prophylactics are not a comparator. However, the ERG has maintained that

lanadelumab could be used in some people who do not use or cannot tolerate the regime associated with C1-INH and who are currently receiving no prophylaxis. This is acknowledged in the comment that the patient group made on this issue that 85% of patients eligible for C1-INH prophylaxis use it, suggesting 15% do not. For these people, the incremental cost per QALY of using lanadelumab compared to treatment on demand for acute attacks would be well above accepted thresholds.

In addition, the ERG estimates that C1-INH prophylaxis has an incremental cost per QALY compared to treatment on demand of a similar order-of-magnitude, suggesting the 'usual care' comparator may not be cost-effective in the first place. The company's economics case is thus that lanadelumab is cost-effective when compared to a treatment that has poor cost-effectiveness in the first place. The company's comment on the Technical Engagement re-states their view that C1-INH are the only alternative.

3. Reduced frequency (dose) after 6 months and 1 year

The company assumed in their economics model that 76.9% of patients will be managed on the 4-weekly lanadelumab treatment regimen from year one onwards. The ERG is concerned that this is by assumption only, such a switch was not observed directly in the clinical study programme. While clinical expert opinion is that some patients can be managed with a less frequent dose, the figure of 76.9% is only derived by assumption from the HELP-03 RCT, with no external supporting or confirming evidence. While 76.9% is plausible, it seems no more or less plausible to the ERG than a range of other possible values, particularly when considering the proposed positioning in a population with much higher baseline attack rate than the HELP-03 trial cohort.

The company's comment on the Technical Engagement mainly re-state the case they have already made. They say the clinical experts on a previous teleconference with NICE supported the 76.9% figure but it could be more accurate to characterise this as support that the figure of 76.9% is covered by the plausible range of values which could, for example, go from 50% to 95% with no particular support for any one figure within this range (in terms of a probability distribution this could be uniform with each value in the range equally likely).

Figures 1 and 2 in the company response to the Technical Engagement are presented as fresh analyses to back up the application of a 76.9% uptake of the four-weekly lanadelumab

regimen independent of baseline attack rate in the model. However, these only say there is no difference in the data that the company bases its assumption upon by baseline frequency of attacks when this is defined as above or equal to/below 3. However, the analyses highlight two things:

- The small number of patients these analyses are actually based on, and
- The lack of patients with baseline frequency to match NHS England guidance and hence use of C1-INHs in England.

4. No waning of treatment effect, and subsequent therapies

The company assumed a constant treatment effect over time, suggesting no waning over time. The ERG view is that a loss of treatment effect due to (for example) the emergence of anti-bodies over time is possible and the company's assumption of 0% loss of effect is optimistic. The company's comment on the Technical Engagement included data on the development of antibodies, but this came from a study with follow-up of less than 1 year. Considering the economic model covers a patient's lifetime, substantial uncertainty remains about the rate at which antibodies may develop in future years. That said, the scenarios provided by the company which assume waning of lanadelumab efficacy with switching to C1-INH show that the results remain relatively robust to more pessimistic assumptions about ongoing lanadelumab efficacy.

Further scenario analysis undertaken by the ERG

In their technical engagement response, the company provided a revised base case analysis that incorporated NICE's preferred assumptions as indicated in the technical engagement report, apart from the application of rate ratios derived from the NMA to the lanadelumab arm of the model. The company continue to use independently fitted Poisson regressions to model attack rates in the lanadelumab arm, while applying the NMA rate ratio for C1-INH to the fitted placebo arm attack rate from HELP-03. The company defend this on the basis that landelumab became more effective relative to placebo over time in HELP-03 as the drug reached steady state. They therefore argue that proportional hazards for lanadelumab versus placebo, assumed by the NMA, do not hold. However, the company do not present any arguments/evidence that proportional hazards do not hold between lanadelumab and C1-INH. Since the NMA gives the best estimates for the effects of lanadelumab relative to C1-INH, the ERG prefer to use these effects in the model. Otherwise the model predicts a proportional reduction in attacks for lanadelumab versus C1-INH which is inconsistent with rate ratios for lanadelumab versus C1-INH derived from the NMA.

When checking the company's revised base case analysis, the ERG was unable to replicate the company's result. The ERG believe this may be because the company forgot to re-estimate the attack rates in the model when applying NICEs preferred assumption of correcting the attack rate of lanadelumab for discontinuation to C1-INH. The ERG have therefore rerun the company's base case with the attack rates updated (Table 1)

In line with NICE's preferred assumptions, the ERG have also incorporated the use of the NMA rate ratios (versus placebo) in both treatment arms in the company's revised model (Table 1). Upon request from NICE, the ERG have also rerun a number of scenarios presented in Table 45 of the original ERG report, around the proportion of the C1-INH cohort on Berinert and the proportion of the lanadelumab cohort on the lower frequency four-weekly treatment regimen (q4w) beyond year 1 (Table 2). The net monetary benefit estimates differ very slightly from Table 45 of the original ERG report, due to some random variation in the simulation process used to re-estimate attack rates in the company revised model. However, the findings remain the same, and with NICEs preferred assumptions, the ICER for lanadelumab versus C1-INH rises above £20,000 per QALY if the proportion of patients on the lower frequency q4w regimen drops to 64%, or when the proportion of the C1-INH arm on Berinert drops to [redacted].

The ERG believe there is further uncertainty in the cost-effectiveness findings which relate to the dosing assumptions applied to Berinert in the company model. Upon advice obtained from six clinicians who were consulted to inform the NICE submission, the company have costed the use of Berinert based on a dose of [redacted]. The company fit a log-normal distribution to patient weight from the HELP-03 trial (mean [redacted]), and then use this to calculate the proportion of patients requiring different numbers of vials to deliver the required weight-based dose. This approach accounts for wastage because partially used vials cannot be shared, [redacted]. Note, a [redacted] patient would receive a [redacted] dose of Berinert (requiring [redacted]), whilst an [redacted] patient on Cinryze would receive 1000 IUs as per the licensed dose for long-term prophylaxis (requiring 2 x 500 IU vials). This is in line with the dose used in the CHANGE clinical trial, which was used to inform the efficacy of C1-INH in the company model. The company acknowledged the [redacted] assumption for Berinert in their original submission, and provided a threshold analysis varying the levels of effectiveness for Berinert (Table 60 of Company submission, document B). However, since Berinert and Cinryze are both plasma derived preparations of C1-INH, the ERG is unsure why different dosing assumptions should necessarily be applied to Berinert when used for long-term prophylaxis. The ERGs clinical expert is of the opinion that the dose of C1-INH generally used for long term prophylaxis is 1000 units twice per week, regardless of whether Berinert or Cinryze is used (although some patient with resistant symptoms may require higher doses). Furthermore, the ERG identified a publication reporting on Berinert Patient Registry data, which used data analysis rules to identify 47 patients from the US and Europe receiving long-term prophylaxis with Berinert (Craig et al. 2017). This publication reported a median dose of 1000 IU (range 500 – 3000) – or 13.77 IU/kg. Whilst dosing practice is clearly variable, and indeed the aforementioned publication points towards a trend for greater efficacy with higher weight based dosing, the ERG believe that a further scenario analysis which assumes a fixed 1000 IU dose of Berinert is justified. This has been provided in Table 2 below, and it clearly illustrates the importance of the Berinert dosing assumptions to the company's economic case.

Table 1 NICE's preferred approach applied in the company's revised model

	Lanadelumab		C1-INH					
Analysis	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. cost**	**Inc. QALY**	**Deterministic ICER**	**Deterministic NMB**
Revised company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£399,269
Revised company base case but assuming the preferred approach by NICE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£346,193

Table 2 ERG's exploratory analyses on NICE's preferred approach

	Lanadelumab		C1-INH					
Analysis	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. cost**	**Inc. QALY**	**Deterministic ICER**	**Deterministic NMB**
NICE's preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£346,193
Proportion of patients switching to the less frequent regimen (q4w)								
80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£427,913

72.4%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£227,566
70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£164,299
60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£186,148	-£99,315
50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£593,866	-£362,930
Proportion on Berinert								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£444,533
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£284,317
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£124,102
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£87,949	-£36,113
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£345,040	-£196,328
Berinert dose								
1000 IU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,463,662	-£893,437

*Numbers differ from the ERG base-case and scenario analyses results (reported in Table 45 of the ERG report) due to random variation in the simulation used to recalculate attack rates.

In their response to the consultation, the company also reran the model for different baseline attack rates in combination with their revised base case assumptions. The ERG replicated this scenario analysis using all of the NICE's preferred assumptions (Table 3). The results show that Lanadelumab remains dominant and the incremental NMB increases with increasing baseline attack rate. However, the absolute value of the incremental NMB is lower at each baseline attack rate compared to the company's revised analysis (reported in Table 5 (Appendix C) of the updated company response to the Technical Engagement consultation).

The analysis utilising a baseline attack risk of ≥8 per 28-day cycle may be more reflective of the population that is eligible for C1-INH according to the NHS England commissioning policy (i.e. individuals who are experiencing 2 or more significant attacks per week over a period of at least 56 days requiring treatment with C1-INH or icatibant). Since the company's proposed positioning of lanadelumab is in those who would otherwise be considered for long-term prophylaxis on C1-INH, the ERG has conducted some further sensitivity analysis around the scenario where the baseline attack rate is ≥8 per 28-day cycle and NICEs preferred assumptions are otherwise applied (Table 4). The results show that when the proportion on the less frequent regimen (q4w) falls to between 60% and 50%, the ICER for lanadelumab rises above £20,000 per QALY. The results also show that when the proportion on Berinert falls to [redacted], lanadelumab is no longer cost-saving but the ICER is below the threshold of £20,000 per QALY gained.

Given uncertainties surrounding the generalisability of the treatment effect of lanadelumab to those eligible for C1-INH prophylaxis according to NHS England commissioning policy (only [redacted] patients in HELP-03 potentially meet the attack rate threshold at baseline), NICE also asked the ERG to explore the impact of reducing the effectiveness of lanadelumab in this scenario. To do this, the ERG have increased the rate ratio for q4w lanadelumab versus placebo in increments from [redacted] (base case) up to [redacted]. Under the most pessimistic rate ratio, lanadelumab remains slightly more effective than C1-INH for preventing attacks (15% reduction in attacks compared to C1-INH), and it remains dominant.

[redacted]

[redacted] and the QALY gains associated with subcutaneous administration. Finally, the ERG replicated the scenario exploring the 1000 IU fixed dosing assumption for Berinert in the

higher baseline attack rate (≥8 per 28 day cycle) group, and found that the ICER still increased well above accepted thresholds of cost-effectiveness with this change.

Overall, the ERG are of the opinion that substantial uncertainties remain in the company's economic case. These relate primarily to:

1. The proportion of patients on long-term C1-INH who are on Berinert
2. The average dose of Berinert used for long-term C1-INH prophylaxis
3. The proportion of patients who can be managed on the lower frequency lanadelumab dosing regimen, particularly in the cohort of patients who currently meet the NHS England commissioning criteria for long-term C1-INH prophylaxis

Table 3 Scenario analysis on NICE's preferred approach (varying the baseline attack rate)

	Lanadelumab		C1-INH					
Analysis	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. cost**	**Inc. QALY**	**Deterministic ICER**	**Deterministic NMB**
NICE's preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£346,193
Baseline attack risk (per 28 day cycle)								
≥ 1 attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£348,351
≥ 2 attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£373,881
≥ 3 attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£403,329
≥ 4 attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£415,128
≥ 5 attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£446,917
≥ 6 attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£501,055
≥ 7 attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£560,878
≥ 8 attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£619,594

Table 4 Scenario analyses on NICE's preferred approach and assuming a baseline attack rate of ≥8 per 28-day cycle

	Lanadelumab		C1-INH					
Analysis	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. cost**	**Inc. QALY**	**Deterministic ICER**	**Deterministic NMB**
Baseline attack risk (per 28 day cycle) ≥8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£619,594
Proportion of patients switching to the less frequent regimen (q4w)								
80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£697,830
72.4%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£506,026
70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£445,456
60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£193,084
50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£99,684	-£59,288
Proportion on Berinert								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£729,202
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£550,628
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£372,054
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£193,480
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,504	£14,906

Rate ratio for Lanadelumab (q4w)								
0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£579,893
0.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£459,235
0.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£338,596
Berinert dose								
Fixed 1000 IU per infusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£799,381	-£620,036

References

Craig T, Shapiro R, Vegh A, Baker JW, Bernstein JA, Busse P, Magerl M, Martinez Saguer I, Riedl MA, Lumry W, Williams-Herman D, Edelman J, Feuersenger H, Machnig T, Rojavin M. Efficacy and safety of an intravenous C1-inhibitor concentrate for long-term prophylaxis in hereditary angioedema. Allergy Rhinol (Providence). 2017 Mar 1;8(1):13-19

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

1. Summary of the technical report

1.1 The technical report should be read with the full supporting documents for this appraisal.

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

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1.2 After technical engagement the technical team has collated the comments received and, if relevant, updated the scientific judgement of the technical team and rationale. Scientific judgements that have been updated after engagement are highlighted in **bold** below.

1.3 In summary, the technical team considered the following:

- **It is unclear whether the current criteria in the NHS commissioning policy for long-term C1-INH reflects a population with severe disease (disease that is not controlled with or not suitable for long-term oral prophylactic treatment and 2 or more clinically significant attacks per week) and should be used to define the company's proposed positioning (see issue 1)**
- The trial evidence for lanadelumab included people who had fewer attacks **(less severe disease)** than those who are **currently** treated with long-term C1-INH in practice, therefore it may not be generalisable to the company's proposed positioning **for people currently eligible for C1-INH** (see issue 1).
- **The most appropriate comparator is C1-INH. The company's proposed positioning of lanadelumab is for people currently eligible for C1-INH in line with the NHS England commissioning policy for long-term C1-INH. Only a small proportion of people eligible for C1-INH choose not to have it and there is no trial evidence, but lanadelumab is unlikely to be cost effective compared with no prophylactic treatment in this group (see issue 2).**
- The company's base case assumption that around [redacted] of people **having C1-INH** have Berinert as a long-term prophylactic treatment, and the remaining people have Cinryze, is clinically plausible (see issue 2).
- **It is unclear whether the company's long-term prophylactic dosing regimen for Berinert (based on weight) reflects current clinical**

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practice. Using a fixed dose of 1000IU is also clinically plausible (see issue 2).

- **Given that attack rates vary over a patient's lifetime, it is clinically plausible to assume that at any given time, the majority of people (77%) having lanadelumab will be on a lower dose frequency after 1 year but it is uncertain whether this can be generalised to severe disease** (see issue 3).
- It is clinically plausible that the effectiveness of lanadelumab will continue in the long-term for people who continue to have it **because only a small proportion are likely to develop non-response. However, this will result in optimistic cost-effectiveness results for lanadelumab because the model does not include non-response** (see issue 4).
- Based on **current clinical practice**, it is appropriate to assume people who stop having lanadelumab will go on to have long-term prophylactic C1-INH, and **people will continue long-term prophylactic C1-INH over a lifetime** (see issue 4).
- **It is reasonable to use discontinuation rates from HELP-03 because the results are similar to longer-term data from HELP-04 (see issue 4).**

1.4 The technical team recognised that the following uncertainties will remain in the analyses and could not be resolved:

- In line with the HELP-03 trial, the company's submission covers people aged 12 years and older with type I or II disease with at least 1 attack every 4 weeks **(less severe disease)**. The company's positioning of lanadelumab for **people currently eligible for C1-INH in the NHS England policy** only covers part of the marketing authorisation (see issue 1).
- There is no comparative data that directly compares lanadelumab with C1-INH, but the company's indirect treatment comparison is acceptable

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for decision-making **because HELP-03 is the best available data source**.

- There is no evidence on the long-term use of the lower frequency dosing schedule for lanadelumab, because the HELP-04 open-label extension study did not use the lower frequency dosing schedule. This cannot be resolved, but clinical expert advice suggests long-term reductions in dosing frequency are clinically plausible (see issue 3).

1.5 The cost-effectiveness results include a commercial arrangement (**simple discount** patient access scheme) for lanadelumab.

1.6 **The technical team's preferred cost-effectiveness analysis (see section 1.3) suggests that lanadelumab is dominant (that is, more effective and less costly) compared with C1-INH for the overall HELP-03 population with less severe disease (at least 1 attack per month) and for the subgroup of patients with at least 8 attacks per month at baseline (severe disease). However, it is noted that the cost-effectiveness estimate for severe disease may not be robust because it was based on small patient numbers. There is also uncertainty around the cost-effectiveness estimate in both populations, because they could be substantially higher if fewer people having C1-INH use Berinert instead of Cinryze or if fewer people have the lower dosing frequency of lanadelumab in the long-term. The dosing used for Berinert has the largest impact on the cost-effectiveness results. The technical team concluded that, despite some uncertainty, lanadelumab could be a cost-effective treatment option compared with C1-INH for people with severe disease but noted that some clinically plausible scenarios showed lanadelumab was not cost-effective compared with C1-INH.**

1.7 Lanadelumab does not meet the end of life criteria specified in NICE's guide to the methods of technology appraisal.

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1.8 The company considers lanadelumab to be innovative because it offers an alternative subcutaneous administration. The technical team considers that all relevant benefits associated with lanadelumab are adequately captured in the model.

1.9 The company states that **the comparator** C1-INH treatment is based on human or animal products that may not be acceptable to some people. The committee will consider this potential equality issue when making its recommendations for lanadelumab.

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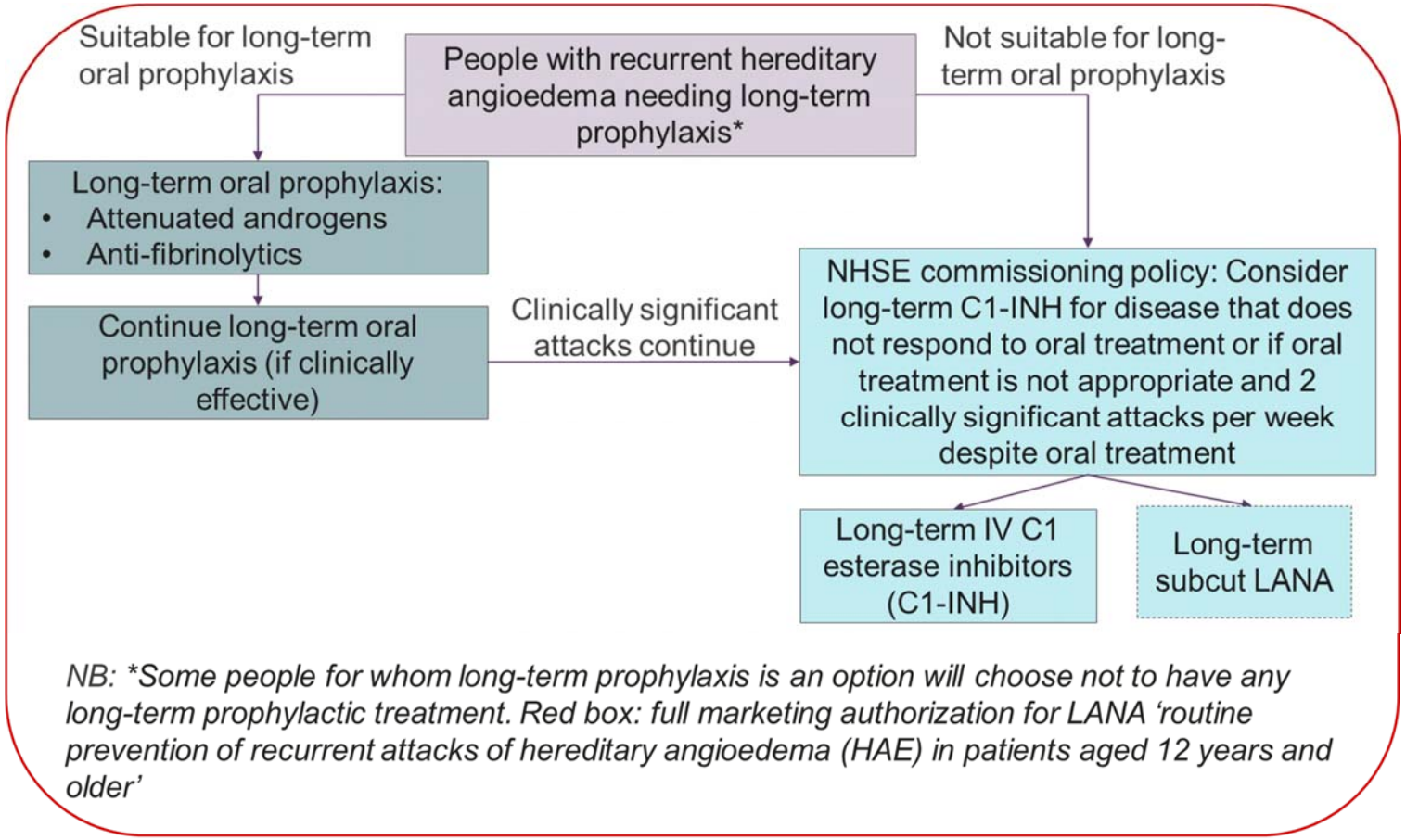
2. Key issues for consideration

Figure 1 Treatment pathway for hereditary angioedema



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Issue 1 – Positioning of lanadelumab

<table>
<tr><td>Questions for engagement</td><td>1. Given that the marketing authorisation is broad, and the trial population differs from the population in the NHS England commissioning policy, is the company's positioning of lanadelumab (see figure 1) as a long-term prophylactic treatment after oral therapy appropriate?
2. Given that the trial included people who were having fewer attacks than the NHS England commissioning policy criteria for long-term prophylactic C1-INH, is the trial generalisable to the proposed positioning of lanadelumab in NHS practice in England?
3. In people for whom long-term oral prophylactic treatment is not controlling the disease, or those for whom it is not suitable, does long-term oral prophylactic treatment ever become suitable again over time?</td></tr>
<tr><td>Background/ description of issue</td><td>The marketing authorisation for lanadelumab is broader than the pivotal trial population (HELP-03). There are differences in the definition of clinically significant attacks in HELP-03 and the NHS England commissioning policy for long-term prophylactic C1-INH. The NHS England policy recommends long-term prophylactic treatment in people with a higher frequency of attacks compared with the trial population (see table 1). In the HELP-03 trial, the average number of attacks of unspecified severity at baseline was 3.9 in the previous 4 weeks, and the inclusion criteria did not specify previous oral therapy or contraindication to oral therapy.
Table 1. Summary of population
<table>
<tr><th></th><th>Marketing authorisation</th><th>HELP-03 trial</th><th>NHS England commissioning policy for long-term prophylactic C1-INH</th></tr>
<tr><td>Population</td><td>Routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.</td><td>Patients with type I and II disease with at least 1 attack in the preceding 4 weeks.</td><td>Recommends long-term prophylactic C1-INH in selected people with disease that is not controlled (2 or more significant angioedema attacks per week over 8 weeks) with oral prophylactic treatment, or if oral treatment is not suitable.</td></tr>
</table>
The company has positioned lanadelumab as an alternative to prophylactic treatment with C1-INH (see figure 1). The company does not consider oral prophylactic treatments (attenuated androgens and anti-fibrinolytics) to be an</td></tr>
</table>

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<table>
<tr><td></td><td>appropriate comparator, because lanadelumab is expected to be used to treat disease that is not controlled by long-term oral prophylactic treatment or if long-term oral prophylactic treatment is not appropriate. The company note there is limited data from HELP-03 to robustly present results for each relevant subgroup specified in the NHS England commissioning policy criteria.

The ERG is concerned that the comparator arm in the company's model differs from the NHS England commissioning policy in terms of:
criteria for starting, stopping or reducing treatment
definition of a clinically significant attack
frequency of attacks before long-term prophylactic treatment is given (NHS England define a population with more frequent attacks compared with the HELP-03 trial)
The clinical experts explained that the ideal position of lanadelumab in the treatment pathway would be in place of current long-term oral prophylactic treatments (such as androgens), before C1-INH is considered. However, they noted that there is no trial evidence for these treatments. The clinical experts agreed that the trial population reflects the overall population of people with hereditary angioedema that is generally seen in clinical practice, explaining that most people have the type I or II disease and the baseline attack rate in the trial reflects a moderate disease burden. They explained that the NHS England clinical commissioning policy for the use of C1-INH is currently followed in clinical practice, and that only a small proportion of people have long-term prophylactic C1-INH.

The technical team is concerned that the evidence for lanadelumab is in people who have 1 attack of unspecified severity over 4 weeks, which reflects less severe hereditary angioedema than the NHS commissioning policy for C1-INH.</td></tr>
<tr><td>Why this issue is important</td><td>The committee will make evidence-based recommendations for lanadelumab, therefore it is important to consider whether the population in HELP-03 is sufficiently similar to the population that would be treated with lanadelumab in NHS clinical practice in England.</td></tr>
<tr><td>Technical team judgement before engagement</td><td>The technical team accepts the company's positioning of lanadelumab for disease that is not controlled with or not suitable for long-term oral prophylactic treatment but notes that this only addresses part of the marketing authorisation for lanadelumab. The technical team is concerned that the trial population may not be generalisable to the population that would receive lanadelumab in NHS clinical practice in England under the proposed positioning (that is, people who currently receive long-term C1-INH).</td></tr>
<tr><td>Summary of comments</td><td><table><tr><th>Stakeholder</th><th>Summary of comments</th></tr><tr><td>Clinical expert</td><td>Lanadelumab should be used earlier in the treatment pathway because although oral treatment is used widely in the UK, it is associated with side-effects and lacks efficacy. The</td></tr></table></td></tr>
</table>

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		trial is generalisable to the company's proposed positioning. In HELP-03 some patients would have >1 attack in last 4 weeks and some people were on long-term prophylactic treatment with C1-INH at baseline (this was stopped for the trial)
	Royal College of Pathologists	If C1-INH is the most appropriate comparator, the indication for long-term prophylaxis with lanadelumab should be the same criteria as used in the NHS England policy
	UKPIN	There are patients with lower (but still severe) attack frequency who could benefit from lanadelumab. Although the trial population differs from the NHS England criteria, the evidence referred to within the policy is similar (most studies have a baseline HAE attack frequency of 1 per week, which is the same as the baseline attack rate in the HELP-03 trial).
	Company	It is appropriate to position lanadelumab for the population who would receive C1-INH because there is a high unmet need in this subgroup and the evidence would still apply if the attack rate criteria were lowered in the future. Efficacy of lanadelumab is not expected to vary by baseline attack rate (this was confirmed by experts at the engagement TC). Subgroup analyses from HELP-03 confirm this, but are based on small patient numbers (see Appendix E of the company submission). Scenario analysis provided in response to clarification also shows lanadelumab is more cost effective as the number of baseline attacks increases **Table 2. Model results by baseline attack risk (revised company base case)**

Baseline attack risk (per 28 day cycle)	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB (£)
≥ 1 attack	[redacted]	[redacted]	Dominant	£400,591
≥ 2 attack	[redacted]	[redacted]	Dominant	£436,794
≥ 3 attack	[redacted]	[redacted]	Dominant	£472,890
≥ 4 attack	[redacted]	[redacted]	Dominant	£460,934
≥ 5 attack	[redacted]	[redacted]	Dominant	£507,322
≥ 6 attack	[redacted]	[redacted]	Dominant	£597,427
≥ 7 attack	[redacted]	[redacted]	Dominant	£716,418
≥ 8 attack	[redacted]	[redacted]	Dominant	£804,778

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<table>
<tr><td></td><td>
<table>
<tr><td></td><td>Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality adjusted life years,</td></tr>
<tr><td>Patient expert</td><td>It is important to consider the variability of this condition; patients often experience more frequent attacks during periods of hormonal or emotional instability</td></tr>
</table>
ERG comments:

Only 7 patients from HELP-03 would be potentially eligible for C1-INH in the NHS England policy.
Company’s subgroup analyses (>8 attacks per month) based on very small patient numbers.
ERG scenario analyses using NICE preferred assumptions and subgroup (>8 attacks per month) show improved cost-effectiveness of lanadelumab compared with full HELP-03 population (see ERG critique).
May be difficult for commissioners to monitor or enforce use of lanadelumab for population currently eligible for C1-INH.

</td></tr>
<tr><td>Technical team scientific judgement after engagement</td><td>

It is unclear whether the current criteria in the NHS commissioning policy for long-term C1-INH (disease that is not controlled with or not suitable for long-term oral prophylactic treatment and 2 or more clinically significant attacks per week) reflects a population with severe disease
HELP-03 is the best available data source, but it is uncertain whether results can be generalised to the company’s proposed positioning for people eligible for C1-INH.
The company’s cost-effectiveness estimate for patients from HELP-03 with severe disease (8 or more attacks per month) also show lanadelumab is dominant. However, it is noted that the cost-effectiveness estimate for severe disease may not be robust because it included small patient numbers and did not include all the technical team’s preferred assumptions.

</td></tr>
</table>

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Issue 2 – Comparator

Questions for engagement	3. What is the most appropriate comparator? a. In NHS clinical practice in England, for people for whom long-term prophylactic treatment with C1-INH is an option, what proportion of people have C1-INH and what proportion choose not to have it? b. Given that lanadelumab is given subcutaneously, would it lead people to switch from no long-term prophylactic treatment to treatment with lanadelumab? c. In clinical practice, would lanadelumab be used as an alternative to long-term oral prophylactics, long-term C1-INH or both? d. Is there any additional evidence (trial or observational) for the use of long-term oral prophylactics? 4. What C1-INH treatments are used in clinical practice for long-term prophylaxis? a. What proportion of patients use Berinert? b. What proportion of patients use Cinryze?
Background/ description of issue	In the HELP-03 trial, around 48% of patients had previously had C1-INH as a long-term prophylactic treatment, and 44% had not had any long-term prophylactic treatment (the reasons for this are not reported). The use of C1-INH treatment with Berinert and Cinryze in the cost-effectiveness model is based on UK prescribing data; however, Berinert is indicated to prevent and treat acute attacks rather than as a long-term prophylactic. **The company** The company does not consider long-term oral prophylactic treatments (attenuated androgens and anti-fibrinolytics, see figure 1) to be an appropriate comparator, because lanadelumab is expected to be used to treat disease that is not controlled by long-term oral prophylactic treatment or if long-term oral prophylactic treatment is not appropriate. The company used hospital dispensing data from July, August and September 2018 to estimate that [redacted] of patients who have C1-INH have Berinert, and [redacted] have Cinryze. Prescribing data across 3 years shows the range is [redacted] for Berinert and [redacted] for Cinryze. In its base case, the company did not consider Ruconest (a non-plasma based C1-INH) a relevant comparator because [redacted]. **The clinical experts** advised that there is variation in clinical practice in the use of C1-INH and, although it is difficult to estimate for all treatment centres, it is plausible that around 50% will use Berinert and 50% will use Cinryze. However, they advised that this is highly uncertain. The experts also noted that some centres are starting to use Ruconest. The experts also explained that many people for whom long-term prophylactic treatment is suitable currently choose not to have treatment, to avoid the side-effects of available options. This may be particularly relevant where the treatment being considered is C1-INH, because these are given intravenously.

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<table>
<tr><td></td><td>
The ERG included exploratory scenario analyses with no long-term prophylaxis as a comparator because some people may choose not to have long-term prophylactic treatment with C1-INH. The ERG was concerned that 3-month dispensing data may not be consistent with long-term prophylactic prescribing.
The technical team is concerned that:

There is a proportion of people for whom C1-INH is an option for long-term prophylactic treatment currently choosing to have no long-term prophylactic treatment, therefore there may be 2 subgroups:

people who currently have long-term prophylactic intravenous treatment
people who do not have long-term prophylactic treatment because it is not acceptable (for example, because of side-effects or the frequency or mode of administration)

It is unclear whether long-term oral prophylactic treatment is a relevant comparator (for people who currently have long-term prophylactic treatment); however, there is no trial evidence for this.
The extent to which each of Berinert, Cinryze and Ruconest accounts for overall C1-INH use as a long-term prophylactic treatment is uncertain, particularly as it is not possible to separate long-term and acute use from the prescribing data.

</td></tr>
<tr><td>Why this issue is important</td><td>
The choice of comparator and the proportion of people having Berinert have a large impact on the cost-effectiveness results, because it is cheaper to use no long-term prophylactic treatment than long-term C1-INH, and when using C1-INH, Berinert is more expensive than Cinryze.
The company's analysis and ERG's preferred analysis estimate that lanadelumab dominates C1-INH (that is, it is cheaper and more effective). Both scenario analyses that compare lanadelumab with no long-term prophylactic treatment and reduce the proportion of people having Berinert when comparing lanadelumab with C1-INH substantially increase the cost effectiveness estimate for lanadelumab (see table 2).
Table 3. Scenario analyses for issue 2
<table>
<tr><th></th><th>Choice of comparator</th><th>Proportion having Berinert</th></tr>
<tr><td>Scenario analysis results</td><td>ERG's exploratory scenario analyses comparing lanadelumab with no long-term prophylaxis: ICER >£2,500,000 per QALY gained</td><td>[redacted] of people in the comparator arm have Berinert when comparing lanadelumab with C1-INH
company's base case: dominant
ERG's preferred analysis: ICER £87,842 per QALY gained</td></tr>
</table>
</td></tr>
</table>

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<table>
<tr><td>Technical team judgement before engagement</td><td>It is plausible that C1-INH is an appropriate comparator for people who have long-term prophylactic treatment. However, no long-term prophylactic treatment could be a clinically plausible comparator for people who do not find current long-term prophylactic treatment acceptable, but would choose to use subcutaneous lanadelumab if available. Therefore, the technical team's judgement is that no long-term treatment may be an appropriate comparator.
In the absence of clinical trial evidence and cost-effectiveness evidence for long-term oral prophylactic treatments, the technical team's judgement is that they are not appropriate comparators (see issue 1 for company's positioning of lanadelumab).
There is variation in clinical practice but the company's base case, which assumes that most people having C1-INH have Berinert instead of Cinryze as a long-term prophylactic treatment, is acceptable for decision-making.
Given the 2 potential subgroups, the technical team consider that:
the company's base case and ERG's preferred analysis both produce ICERs for people who take long-term prophylactic treatment
the ERG's exploratory scenario analysis comparing lanadelumab with no long-term prophylactic treatment produces an ICER for people who find current long-term prophylactic treatments unacceptable.
The technical team could not identify a single preferred ICER because:
the proportion of people who choose to have no long-term prophylactic treatment remains uncertain
it is not clear whether people who find current long-term prophylactic treatments unacceptable would choose to have long-term prophylactic treatment with subcutaneous lanadelumab.</td></tr>
<tr><td>Summary of comments</td><td>
<table>
<tr><th>Stakeholder</th><th>Summary of comments</th></tr>
<tr><td>Clinical expert</td><td>There is variation between hospitals, but Berinert and Cinryze are likely to be used in equal proportions</td></tr>
<tr><td>Royal College of Pathologists</td><td>There is only short-term evidence for lanadelumab, so there is uncertainty in the adverse events associated with long-term treatment</td></tr>
<tr><td>UKPIN</td><td>There is no accurate figure available but the proportion of patients choosing not to receive C1-INH is likely to be low. Proportions using Berinert/Cinryze varies between hospitals, there is no current data but the ongoing HAE network survey will capture this. Lanadelumab would be used as an alternative to C1-INH, and as an alternative in patients who are unable to receive oral prophylaxis.</td></tr>
</table>
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Company

The Company is not aware of any evidence that would allow a robust comparison between lanadelumab and attenuated androgens and does not consider oral therapy to be an appropriate comparator. [redacted]. Table 1 presents the latest results, using revised assumptions from the company's original base-case based on feedback from the ERG and NICE; [redacted].

Table 4: Revised company base-case results

	Total			Incremental			
Technologies	**Costs (£)**	**LYG**	**QALY**	**Costs (£)**	**LYG**	**QALYs**	**ICER (£/QALY)**
C1-INH	[redacted]	21.48	[redacted]	[redacted]	[redacted]	[redacted]	
Lanadelumab	[redacted]	21.48	[redacted]	[redacted]	0.00	[redacted]	Dominant
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Only a small proportion of patients who are eligible for long-term prophylactic treatment with C1-INH will choose not to have (this was confirmed by the clinical experts at the technical engagement teleconference). The company is aware of variation in the proportions using Berinert and Cinryze. The company's base case assumption using 3 month hospital dispensing data is considered to be the most robust. However, scenario analyses using 3 year data from the Hospital Pharmacy Audit ([redacted] for Berinert and [redacted] for Cinryze are included.

Table 5: Scenario analysis for changes in the percentage of patients receiving Cinryze/Berinert IV

Proportions	ICER (£/QALY)	NMB (£)
Base-case ([redacted] Cinryze IV: [redacted] Berinert IV)	Dominant	£424,788
([redacted] Cinryze IV: [redacted] Berinert IV)	Dominant	£346,887
([redacted] Cinryze IV: [redacted] Berinert IV)	Dominant	£715,400

Patient expert

Our patient surveys show the vast majority of those eligible, say, 85% opt for C1-INH; the ones who do not have it usually are unable to carry out the venepuncture and self-administer for

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		some reason (e.g. lack of venous access, needle phobia). The recent shortage/unavailability of Cinryze which had a knock-on effect on Berinert supplies has probably slewed the proportion having each. Lack of, or restriction on supply is a cause of concern.

ERG comments:

- Agree C1-INH is comparator but some people eligible for C1-INH may not use or tolerate it and have no long-term prophylactic treatment. Consultation response from patient expert suggests 15% of those eligible for C1-INH may not use it. ICER for lanadelumab vs. no long-term prophylactic treatment exceeds £2,500,000 per QALY gained.
- ERG identified an additional issue relating to dosing of Berinert that has large impact on ICER, regarding whether long-term treatment with Berinert should be weight-based or a fixed dose of 1000IU. This was not previously covered in the technical report(see ERG critique).

Technical team scientific judgement after engagement	• C1-INH is the most appropriate comparator because it is in line with the company's positioning and there is no trial evidence for either oral therapy or no long-term prophylactic treatment. [redacted]. Only a small proportion of people eligible for long-term prophylactic treatment with C1-INH will choose not to have it, but lanadelumab is unlikely to be cost effective compared with no prophylactic treatment in this group. • There is variation in clinical practice, but the company's revised base case assumption that most people treated with long-term prophylactic C1-INH will have Berinert is clinically plausible. • It is unclear whether the company's long-term prophylactic dosing regimen for Berinert (based on weight) reflects current clinical practice. Using a fixed dose of 1000IU is also clinically plausible.

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Issue 3 – Long-term dose reduction for lanadelumab

<table>
<tr><td>Questions for engagement</td><td>5. When using long-term prophylactic treatment in clinical practice, when is it appropriate to reduce the dosing frequency?
a. Using current treatments (long-term oral therapy and intravenous C1-INH), is the dosing frequency titrated down to the lowest level that achieves control of symptoms?
6. Are lower dosing frequencies of prophylactic treatment expected to continue in the long-term?
a. Is it clinically plausible that around 77% of patients continue to have a lower dosing frequency of lanadelumab after 1 year?
b. Are any further changes to dosing (for example, increasing the frequency) expected in the long-term? If so, approximately what proportion will need to switch back to a higher dosing frequency, and for how long?</td></tr>
<tr><td>Background/ description of issue</td><td>The summary of product characteristics (SmPC) for lanadelumab states that reductions in dosing frequency may be considered, especially in patients with low weight (see table 3). Only 2 of the dosing regimens used in HELP-03 are included in the SmPC (see table 3), but there is no long-term evidence for the lower frequency regimen because it was not used in the open label extension study (HELP-04).
Table 6. Summary of dosing for lanadelumab
<table>
<tr><th></th><th>SmPC</th><th>HELP-03</th><th>HELP-04</th></tr>
<tr><td>Dosing</td><td>The recommended starting dose is 300 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction of 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight.</td><td>Patients were randomly allocated to 1 of 3 doses of lanadelumab:
• 300 mg every 4 weeks (lower frequency)
• 300 mg every 2 weeks (higher frequency)
• 150 mg every 4 weeks (not in SmPC)
Patients on 2-weekly dosing could switch to the less frequent, 4-weekly dosing regimen, in line with the SmPC.</td><td>No patients started on the lower dosing frequency, and all patients who were originally on it were moved to the higher dosing frequency (2-weekly).</td></tr>
</table>
The company assumed in its model that 44% of patients switch to the lower lanadelumab dosing frequency after 6 months. This was based on the proportion of patients in HELP-03 having the higher frequency dose who are attack-free at 6 months, on the assumption that a clinician would seek to reduce the dosing frequency in patients whose</td></tr>
</table>

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<table>
<tr><td></td><td>disease is well controlled. The model also assumes further switching after 1 year, to bring the overall total with lower dosing frequency up to 77%. This is continued for the remaining time horizon. This value was based on the proportion of patients in HELP-03 having the higher dose frequency and who were attack-free between days 70 and 182 (a period of just under 4 months). The company's model assumed that when treatment is switched to a lower dosing frequency, the treatment effect from the once-monthly treatment arm in HELP-03 is applied. The company explained that patients will have increases and decreases in dosing frequency over a lifetime, but this proportion is expected to remain approximately constant because switches will continue to occur in both directions. The dosing regimen for the initial dose of Berinert was based on clinical expert advice and its SmPC for acute attacks. The dosing regimen for Cinryze was 1000IU every 3 to 4 days in line with the SmPC. The dosing frequency for both C1-INH treatments does not increase or decrease in the model.

The clinical experts explained that in current clinical practice, long-term reductions in dosing frequency are achieved with available long-term oral prophylactic treatments in most people, therefore they would expect to be able to achieve this with lanadelumab. They noted that treatment and dosing frequency is always tailored to the needs of the individual.

The technical team is concerned that the proportion of people having a lower lanadelumab dosing frequency after 1 year may be overestimated because there is no long-term data to support it, but notes that it is consistent with clinical expert advice.</td></tr>
<tr><td>Why this issue is important</td><td>The proportion of people taking lanadelumab and switching to the lower dosing frequency in the long-term has a large impact on the cost-effectiveness results because it is associated with lower costs. Scenario analysis of the company's base case show that that if 50% switch to a lower dosing frequency after 1 year, the ICER is £393,947 per QALY gained. If 60% switch, the ICER is £19,064 per QALY gained. The cost-effectiveness results are therefore highly sensitive to this proportion and the ICER would be higher if the dosing frequency was increased in response to attacks becoming more frequent.</td></tr>
<tr><td>Technical team judgement before engagement</td><td>In the absence of long-term evidence, it is clinically plausible that around 77% of people having lanadelumab will switch to a lower dosing frequency and continue this in the long-term.</td></tr>
<tr><td>Summary of comments</td><td>
<table>
<tr><th>Stakeholder</th><th>Summary of comments</th></tr>
<tr><td>Clinical expert</td><td>77% is possible based on some preliminary data from HELP-03 study, but it's impossible to predict accurately at this stage. It is likely that a few patients will require higher frequency of administration at times when HAE is more active.</td></tr>
</table>
</td></tr>
</table>

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	UKPIN	a. Although it's difficult to determine an accurate figure, 77% is clinically plausible from the HELP-03 data. b. Would expect some changes in dose over time as patients may go through a period of increased attack frequency. However, you would expect lower frequency dosing again in the future.
	Company	The SPC of lanadelumab states that the lower dosing frequency may be considered in patients who are stably attack-free on treatment. From the HELP-03 trial data, the proportion of patients expected to be attack-free once lanadelumab has achieved steady-state is 77%. Although the patients who would receive lanadelumab in UK clinical practice would likely be more severe patients based on the UK clinical commissioning policy for C1-INH, the 77% is expected to be representative for these patients based on an analysis of the steady state time to first attack data from HELP-03. Figure 1 and Figure 2 present time for first attack data for the 2-weekly lanadelumab (q2w) and placebo arms from HELP-03 respectively from day 70 onwards (once lanadelumab has achieved steady state), split by patients baseline attack risk (<3 attacks vs >3 attacks). These results demonstrate no differences between the less severe and more severe group in the percentage of patients remaining attack-free in the lanadelumab q2w arm, while differences appear to exist in the placebo group, where the more severe group is less likely to be attack-free. Therefore, these figures provide further evidence that lanadelumab is highly effective in more severe patients and that the results from the ITT population in HELP-03 are broadly generalisable to the population of interest.

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Figure 1: Lanadelumab q2w day 70-182 time to first attack Kaplan-Meier data (by baseline attack risk)

Figure 2: Placebo day 70-182 time to first attack Kaplan-Meier data (by baseline attack risk)

ERG comments:

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	• This proportion receiving the lower dosing frequency is assumed to be associated with attack-free disease and was not directly observed in the clinical trial. Assumption based on short-term data from HELP-03 and there is no other external supporting or confirmatory evidence. • Company submitted figures only show no difference when defining severe disease as < 3 or > 3 attacks per month and highlight small numbers matching NHSE criteria.
Technical team scientific judgement after engagement	• The company's revised base case does not explicitly model changes in dosing frequency over time; however, given that attack rates vary over a patient's lifetime, it is reasonable to assume that at any given time, the majority of people (77%) having lanadelumab will be on a lower dose frequency after 1 year. • However, it is uncertain whether this proportion can be generalised to patients with severe disease, which reflects the company's proposed positioning of lanadelumab.

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Issue 4 – Subsequent prophylactic treatment and continued treatment effect

Questions for engagement	7. In clinical practice, what long-term prophylactic treatment is used if C1-INH is stopped? 8. In clinical practice, what long-term prophylactic treatment is likely to be used if lanadelumab is stopped? 9. Is it clinically plausible that lanadelumab would not lose its effectiveness over time?
Background/description of issue	There is limited follow-up data from the trial, so assumptions about the long-term treatment pathway and effectiveness of lanadelumab need to be made over the model time horizon. Both the ERG and company agree it is plausible that lanadelumab does not lose its effectiveness over time. **The company** base case assumed that people could only stop treatment with lanadelumab or C1-INH in the first 6 months and, after stopping treatment, no further long-term prophylactic treatment was given. The model assumed no difference in the discontinuation rates in the lanadelumab and comparator arm; 9% of patients in discontinue, and the rest receive lifetime treatment thereafter (based on 91% completing treatment in HELP-03). The company suggested that subsequent treatment costs would most likely be equal. The company's model also assumed that the treatment effect of lanadelumab continued over a lifetime. **The ERG** was unclear why the company had not used data from HELP-04 to inform longer term discontinuation rates. The ERG preferred to assume C1-INH is used if lanadelumab is stopped (and apply the same attack rate as C1-INH from the indirect comparison), and that people having C1-INH will continue treatment over a lifetime because this is more likely to reflect the subsequent treatment pathway in clinical practice. **The clinical experts** advised that if long-term treatment with C1-INH is stopped, it is likely that no long-term prophylactic treatment would be used, because at this point other oral prophylactic treatments would have been tried, and there are no alternative treatments available. If lanadelumab was stopped, it is likely that long-term prophylactic C1-INH would be started. The clinical experts also explained that it is plausible that lanadelumab would not lose its effectiveness for most people if they continue treatment. However, like other biological therapies, it is likely there will be a small proportion of people with disease that stops responding to treatment.
Why this issue is important	The combined scenario analysis that assumed the effectiveness of lanadelumab stopped 5 years after starting treatment and no treatment is used after lanadelumab or C1-INH is stopped results in an ICER showing lanadelumab is less costly and less effective, albeit still cost-effective compared with C1-INH.

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<table>
<tr><td>Technical team judgement before engagement</td><td>It is optimistic to assume a continued treatment effect for lanadelumab over time. It is appropriate to assume people have C1-INH treatment after lanadelumab is stopped, and no further long-term prophylactic treatment after C1-INH is stopped.</td></tr>
<tr><td>Summary of comments</td><td>
<table>
<tr><th>Stakeholder</th><th>Summary of comments</th></tr>
<tr><td>Clinical expert</td><td>Yes as with all other biological therapies, some patients will develop secondary non-response. It is difficult to predict what proportion will be affected, but it’s unlikely to be large. There are currently no alternative to C1-INH treatment and C1-INH is likely to be used if lanadelumab is stopped.</td></tr>
<tr><td>UKPIN</td><td>Yes, although cannot be 100% guaranteed in all patients a continued treatment effect has seen with other biological therapies. If C1-INH treatment stopped and oral prophylaxis not appropriate or effective then there is no alternative and C1-INH is likely to be used if lanadelumab is stopped.</td></tr>
<tr><td>Company</td><td>Clinical experts at the technical engagement TC confirmed that C1-INH treatments are rarely stopped because in patients with severe disease, achieving a sub-optimal response is still beneficial and no other option is currently available.
As explained in the Company response to Clarification Questions B6 and B21, in HELP-03 the overall incidence of anti-drug antibodies (ADAs) in treated subjects was just 9.6% (12/125). Furthermore, the development of ADAs did not have an impact on treatment efficacy and did not result in discontinuation. For this reason, we believe assuming that 100% of patients will experience loss of effectiveness after only five years is extremely unlikely and the 5-year scenario should be considered unrealistic.
In response to a request from NICE regarding discontinuation data from the HELP-04 study, interim data (data from 26 May 2016 to 1 September 2017) is provided in Table 3 below, showing that most patients (92.9%) remained in the study. These data are supportive and consistent with the HELP-03 data and in line with the discontinuation rate already used in the model (91.2%).
Table 7: HELP-04 discontinuation data
<table>
<tr><th></th><th>Rollover Subjects</th><th>Non-rollover subjects</th><th>Total</th></tr>
</table>
</td></tr>
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</table>

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		Number of Subjects Treated	109	103	212
		Completed study	0 (0%)	2 (1.9%)	2 (0.9%)
		Ongoing (active study participation)	102 (93.6%)	95 (92.2%)	197 (92.9%)
		Number of subjects who did not complete study	7 (6.4%)	6 (5.8%)	13 (6.1%)

ERG comments:

- Optimistic to assume no one will lose treatment effect over time (for example due to antibodies), but company scenarios show these results are relatively robust to more pessimistic assumptions.

Technical team scientific judgement after engagement	• Only a small proportion of people are likely to develop non-response to lanadelumab, therefore it is acceptable to assume its treatment effect continues over time. However, the model does not account for non-response, therefore this assumption will result in optimistic cost-effectiveness results for lanadelumab. • It is appropriate to assume treatment with C1-INH is continued over a lifetime, and that if lanadelumab is stopped, people will switch to C1-INH. • It is reasonable to use discontinuation rates from HELP-03 because the results are similar to longer-term data from HELP-04.

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3. Issues for information

Tables 8 to 11 are provided to stakeholders for information only and not included in the Technical Report comments table provided.

Table 8: Cost effectiveness results incorporating the technical team's preferred assumptions in full HELP-03 population

The company's revised base case includes the following NICE technical team preferred assumptions:

- People stopping lanadelumab have C1-INH (no utility benefit from subcutaneous administration after lanadelumab is stopped) and C1-INH is continued
- Adjustment to account for higher attack rate for people switching from lanadelumab to C1-INH
- Use lower hospitalisation costs for acute attacks

Table 8 shows the cumulative effect of all NICE technical team preferred assumptions on the cost-effectiveness estimate in the full HELP-03 population and table 9 shows the same cost-effectiveness estimates for a subgroup of the HELP-03 population with ≥8 attacks per month at baseline. Tables 8 and 9 also include clinically plausible scenarios relating to issues 2 and 3 from the technical report.

		Lanadelumab vs. C1-INH	
Alteration	**Technical team rationale**	**ICER**	**Change from revised base case**
Company revised base case	–	**Dominant**	

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1. Clinical effectiveness of lanadelumab vs. placebo using rate ratios from NMA (instead of data from HELP-03)	Technical team agree with ERG amendments (see section 5.2.6 of the ERG report)	Dominant	None
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	**Dominant**	**None**
Clinically plausible scenarios			
2a. Technical team's preferred assumptions and lower the proportion having Berinert to 30% to 50%	Issue 2	Dominant to £345,040	No change to +£345,040
2b. Technical team's preferred assumptions and assume fixed 1000IU dose of Berinert	Issue 2 (see ERG critique)	£1,463,662	+£1,463,662
3. Technical team's preferred assumptions and lower the proportion having long-term lower dose frequency of lanadelumab to 50% to 70%	Issue 3	Dominant to £593,866	No change to +£593,866

Table 9: Cost effectiveness results incorporating the technical team's preferred assumptions in subgroup with ≥8 attacks per month at baseline

		Lanadelumab vs. C1-INH	
Alteration	**Technical team rationale**	**ICER**	**Change from revised base case**
Company scenario ≥8 attacks (per month)	**–**	**Dominant**	

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1. Clinical effectiveness of lanadelumab vs. placebo using rate ratios from NMA (instead of data from HELP-03)	Technical team agree with ERG amendments (see section 5.2.6 of the ERG report)	Dominant	None
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	**Dominant**	**None**
Clinically plausible scenarios			
2a. Technical team's preferred assumptions and lower the proportion having Berinert to 30% to 50%	Issue 2	Dominant to £11,504	No change to +£11,504
2b. Technical team's preferred assumptions and assume fixed 1000IU dose of Berinert	Issue 2 (see ERG critique)	£799,381	+£799,381
3. Technical team's preferred assumptions and lower the proportion having long-term lower dose frequency of lanadelumab to 50% to 70%	Issue 3	Dominant to £99,684	No change to +£99,684

Table 10: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Marketing authorisation	Lanadelumab is intended for 'routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.' The clinical trial only included patients with type I or II disease and at least one angioedema attack in 4 weeks.	Unknown

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	The cost-effectiveness evidence does not cover the full anticipated marketing authorisation.	
Lack of direct comparative data	There is no comparative data that directly compares lanadelumab with C1-INH. The clinical effectiveness is uncertain because an indirect comparison was needed.	The cost-effectiveness results may be more uncertain because it was informed by indirect evidence, and this uncertainty has not been addressed because the company used a fixed effects model.
Lack of long-term data on lower lanadelumab dosing frequency	There is no evidence on the long-term use of a lower lanadelumab dosing frequency because the HELP-04 open-label extension study did not use this dosing regimen. The cost-effectiveness results are uncertain because the proportion using lower frequency dosing may be over-estimated in the model.	The cost-effectiveness results may be optimistic.

Table 11: Other issues for information

Issue	Comments
Ongoing studies	The open-label extension study (HELP-04) is currently ongoing. The technical team considers that further data from HELP-04 will not sufficiently address the uncertainties in the cost-effectiveness analyses because the lower lanadelumab dosing frequency was not used.
Innovation	The company considers lanadelumab to be innovative. However, the technical team considers that all relevant benefits associated with lanadelumab are adequately captured in the model.
Equality considerations	The company state that C1-INH treatment is based on human or animal products that may not be acceptable to some people. No other equality issues were anticipated by the company, consultees and their nominated clinical and patient experts. The committee will consider this issue when making its recommendations

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NICE National Institute for Health and Care Excellence

Slides for public – all confidential data redacted

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

Lead team presentation

Lead team: Derek Ward, Ugochinyere Nwulu & Paul Tappenden

ERG: Aberdeen

Technical team: Stephen O'Brien, Jamie Elvidge, Abi Senthinathan, Frances Sutcliffe

Company: Shire (now part of Takeda)

6th June 2019

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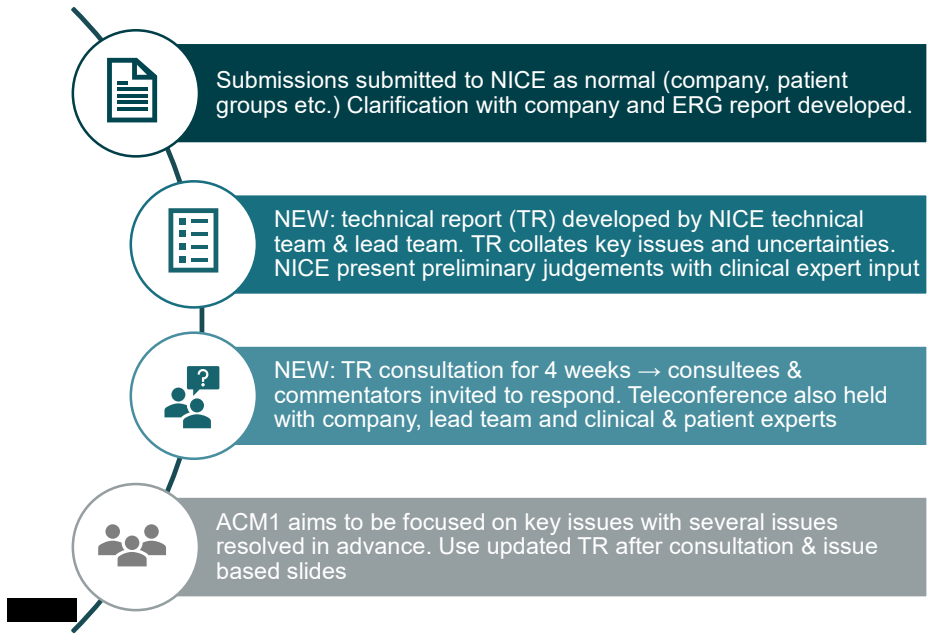
New STA process



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Key issues

Model driver

Issue 1: Positioning of lanadelumab [LANA] (generalisability)

- Should current C1-INH NHSE criteria for selected people only be used to define company's proposed lanadelumab positioning (severe disease)?
- Can results from HELP-03 be generalised to company's proposed positioning?
- Should subgroup results (≥8 attacks per month) be used for LANA cost-effectiveness?

Issue 2: Comparator (C1-INH treatment)

- Is it plausible to assume [redacted] have Berinert and [redacted] have Cinryze?
- Should a weighted dose or fixed dose (1000IU) be assumed for Berinert?

Issue 3: Long-term dose reduction for lanadelumab

- Is it plausible to assume 77% are on a lower dosing frequency after 1 year?
- Does this also apply to company's proposed positioning (severe disease)?

Issue 4: Subsequent prophylactic treatment & continued treatment effect

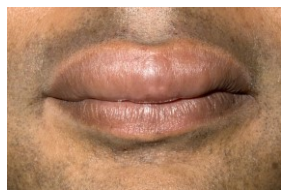
- Is it appropriate to assume a continued treatment effect over time for LANA?
- Is it appropriate to assume all people having C1-INH will continue for a lifetime, and if LANA is stopped people will switch to C1-INH?
- Is it acceptable to use discontinuation rates from HELP-03?
- A stopping rule is used in current C1-INH NHSE criteria, does this need to be considered?

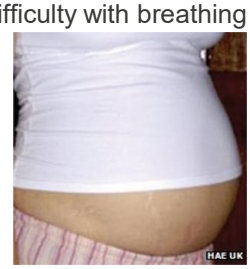
[redacted]

3

Hereditary angioedema (HAE)

- HAE is a rare genetic disorder, associated with the deficiency of the protein C1-esterase inhibitor, which is a regulator of inflammatory pathways.
- It is estimated that HAE affects between 1 per 50,000 to 1 per 100,000 of the population.
- Most cases develop in childhood and some cases develop in early adulthood. HAE usually occurs during the first 10 to 20 years of life.
- In patients with HAE, at times of physiological or psychological stress, the function of the C1-esterase inhibitor is insufficient, resulting in the accumulation of excessive fluid (oedema) and localised oedematous swellings
- The swellings usually occur in the mouth, the gut (affecting the submucosal tissues) and the airway, causing difficulty with breathing (with potential asphyxia) and severe pain in the stomach





Lanadelumab (Takhzyro, Shire)

Cross-reference

Marketing authorisation	Routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older
Administration	Subcutaneous injection
Dosing	The recommended starting dose is 300 mg lanadelumab **every 2 weeks**. In patients who are stably attack free on treatment, a dose reduction to 300 mg lanadelumab **every 4 weeks** may be considered, especially in patients with low weight.
Price	List price of £12,420 per 300 mg vial has been approved by the Department of Health and Social Care. PAS (simple discount) approved

	Marketing authorisation	HELP-03 trial	NHS England commissioning policy for long-term prophylactic C1-INH
Population	Routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.	Patients with type I and II disease with **at least 1 attack in the preceding 4 weeks**.	Recommends long-term prophylactic C1-INH in selected people with disease that is not controlled (**2 or more significant angioedema attacks per week over 8 weeks**) with oral prophylactic treatment, or if oral treatment is not suitable.

Differences in population is covered in Issue 1 of the technical report (see slide 18)

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Background

Comparators Issue 2	**Company**: C1-INH only (position after oral therapy for those eligible for C1-INH) **Technical team**: acceptable because: • LANA is positioned after oral therapy or where oral therapy is not suitable • No trial evidence for no long-term prophylactic & unlikely to be cost-effective
Clinical trial	HELP-03 RCT (N=125) • compares LANA vs. placebo in people ≥ 12 years with type I or II HAE and at least 1 attack in last month • 3 doses: 300 mg 4-weekly (low frequency, n=29), 300 mg 2-weekly (high frequency, n=27), 150 mg 4-weekly (not included in SmPC, n=28)
Key results	Investigator-confirmed monthly attack rates: LANA 300 mg 2-weekly: **0.257** (0.145 to 0.458); LANA 300 mg 4-weekly: **0.526** (0.358 to 0.771); placebo: **1.970** (1.640 to 2.358)
LANA vs. C1-INH	Network meta-analysis using HELP-03 and CHANGE (cross-over trial)
Key result	HAE attack rate ratio (fixed effects model): LANA 300 mg 2-weekly vs. C1-INH: [redacted] LANA 300 mg 4-weekly vs C1-INH: [redacted]
Model	Cohort model. 2 health states: 'Alive with HAE' & 'Dead'.
Preferred ICER	**Company**: LANA dominant (compared with C1-INH) **Tech team**: Agree, but uncertain for company's positioning (severe disease)
ICER uncertainties	*ICERs for severe disease (≥ 8 attacks per month) not robust → small sample.* *All ICERs substantially higher if ↓ people use Berinert or ↓ have LANA low dose frequency. Berinert dosing has largest impact.*

Patient and carer perspectives

- HAE is characterised by unpredictable and sporadic attacks of subcutaneous swelling which can occur anywhere and varies from mild to life-threatening if it affects airways
- There are no confirmed triggers for attacks, but some common triggers appear to include hormonal changes, stress and anxiety invasive procedures such as dentistry, minor surgery, infections
- Swellings reach a very large size in a short time – around 30 to 40 minutes – and then take 2 or more days to resolve
- Current treatments may be effective, but can be problematic (long-term prophylactic C1-INH requires venepuncture twice weekly, which can lead to reduced venous access as veins become damaged, and doesn't prevent breakthrough attacks [attacks despite long-term prophylaxis])

[redacted]

Patient and carer perspectives

- Unpredictable HAE attacks can affect every area of life. This uncertainty requires people with the condition to carry medications for emergencies and to plan carefully when travelling
- Whilst most live normal lives, people with the condition are more likely to suffer from anxiety and depression due to fear of future attacks. Daily activities can be hampered due to fear of attacks.
- Families with children with HAE have to develop a number of strategies – school life, sports, trips away as well as avoidance of certain triggers.
- Self-administration of long term prophylactic treatment would be in addition to the practical measures patients already have in place to try to manage their condition.

"C1-INH is good treatment but the inconvenience it caused by having to have it administered in hospital was huge and it started to impact on my work and social life…Being able to self-administer C1-INH at home is a huge life-changer…means I can carry on my life as normal"

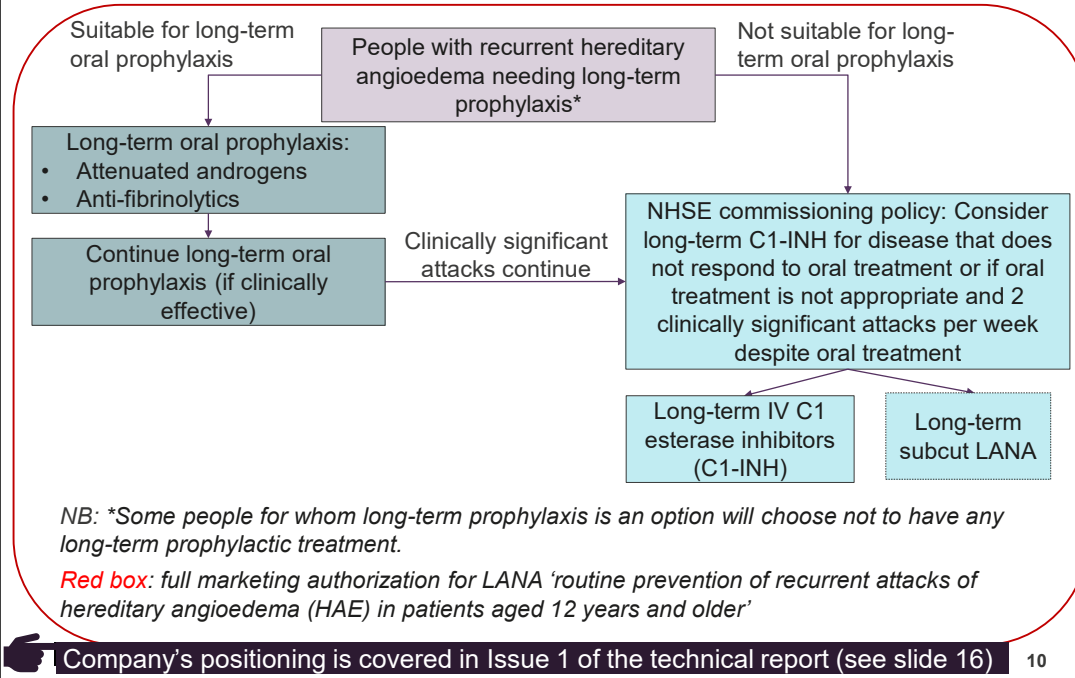
[redacted]

Clinical expert perspective

- Treatment is individualised with the aim to reduce attacks and, ideally, become attack-free.
- Acute attacks are exacerbated by stress, some predictable (for example exams, surgery and dental treatment) and some unpredictable (for example “good stress” life events, such as weddings and holidays).
- People who have regular swelling and those at risk of severe swelling would be considered to benefit from long-term prophylactic treatment
  - In clinical practice, many patients have oral prophylactic treatment, such as attenuated androgens, but this is associated with side effects and limited effectiveness
  - C1-INH is used in line with the NHSE commissioning policy. It is primarily used as short-term prophylaxis (for example before surgery). Only a minority of patients take C1-INH as a long-term prophylactic treatment
- Changes to dosing frequency are made iteratively, but long-term reductions are currently achieved with oral prophylactic treatments in most people

[redacted]

Treatment pathway



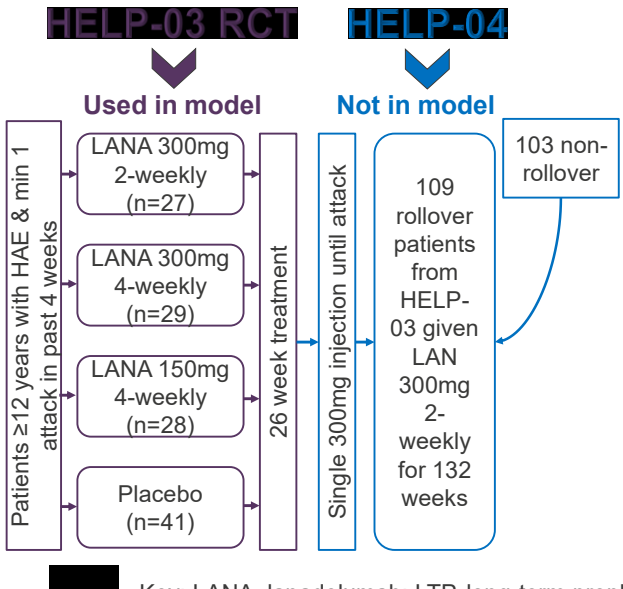
*NB: *Some people for whom long-term prophylaxis is an option will choose not to have any long-term prophylactic treatment.*

Red box: full marketing authorization for LANA 'routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older'

Company's positioning is covered in Issue 1 of the technical report (see slide 16)

Clinical evidence summary (1)

Direct clinical trial evidence



Key: LANA, lanadelumab; LTP, long-term prophylactic

HELP-03 RCT

- 125 patients aged 12 years and older with types I or II HAE and **at least 1 attack (any severity)** in 4 week run-in period
- 4 treatment arms (3 LANA doses), no switches to alternative doses
- At baseline 90% type I HAE, mean 3.9 attacks in last month, 48% had previous C1-INH, 44% no previous LTP, 3% oral LTP and 52% have 3+ attacks in 4 week run-in
- Only 8% of attacks classed 'severe'

HELP-04

- On-going open-label extension from HELP-03 but also includes some new patients (non-rollover)
- Only used 2-weekly LANA dose (no lower dosing frequency arm)

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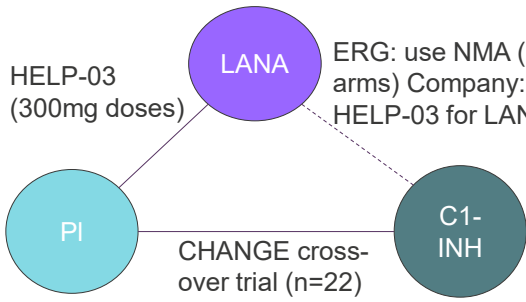
Clinical evidence summary (2)

Indirect network meta-analysis (NMA)



- NMA diagram based on figure 13 in company submission (150mg dose not in SmPC)
- Company used Bayesian NMA of attack rate in fixed effects model (random effects not robust given small sample size). Use Woods (2010) adjustment to allow both HRs and count data in single analysis
- ERG not able to validate company's hazard ratios or standard errors for NMA, but broadly agree with approach

	Monthly attack rate	
	HELP-03 (% change mean attack rate)	NMA (95% credible interval)
LANA 2-weekly vs. placebo	-86.9% (-92.8% to -76.1%)	[redacted]
LANA 4-weekly vs. placebo	-73.3% (-82.4% to -59.5%)	[redacted]
LANA 2-weekly vs. C1-INH	N/A	[redacted]
LANA 4-weekly vs. C1-INH	N/A	[redacted]

[redacted] Key: LANA, lanadelumab; PI, placebo

Note: Slide has been amended after Appraisal Committee Meeting

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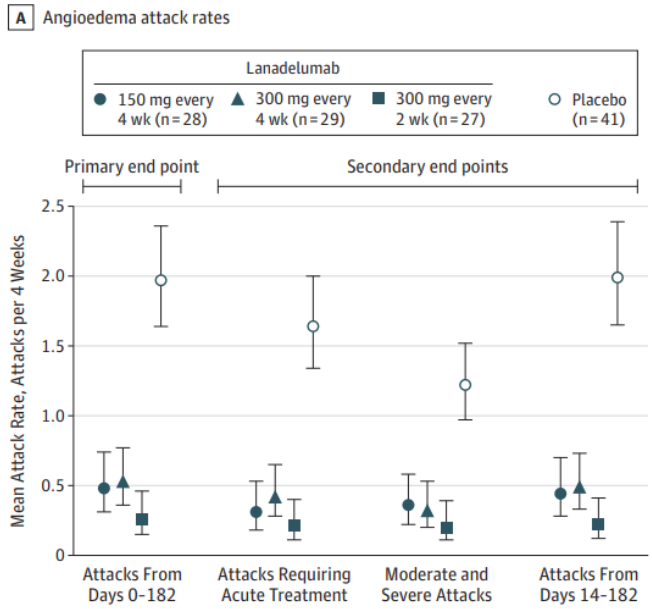
Clinical evidence summary (3)



- Figure 3 in ERG report: primary and secondary endpoints in ITT population
- Attack rates are model-based mean attacks per month (error bar = 95%CI)
- Both 300mg doses of LANA met primary endpoint and showed statistically significant and clinically meaningful (>50%) reductions in number of HAE attacks during the treatment period compared with placebo

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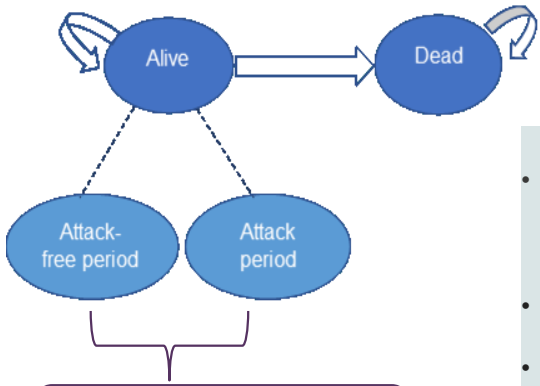
Cost effectiveness summary (1)



1. Tech team prefer attack rates from NMA for both arms. Company use HELP-03

2. Company adjust attack rate ↑ if stop & switch treatment (instead of treatment specific rates for all)

[redacted]

Company model

- Cohort approach with 2 heath states. Only attack frequency used (location of attack does not have important impact on quality of life)
- Attack disutility is based on average attack rate and severity (not location)
- After clarification, model allows subsequent treatment with C1-INH (if LANA is stopped)
- Model uses lifetime horizon (41 years at start from HELP-03 and run for 60 years)
- Discount rate 3.5%

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Cost effectiveness summary (2)

	Company revised base case	Tech team
Pop	LANA vs. C1-INH only	Agree
Treatment	• C1-INH: Cinryze [redacted], Berinert [redacted] • 91% continue treatment for life (HELP-03) • C1-INH stay on treatment. If LANA stopped, switch to C1-INH (no utility benefit for subcut admin)	Company assumption clinically plausible
Dose	**LANA lower dose frequency**: 44% after 6 months & 77% after 1 year. **C1-INH**: no dose changes	Company assumption clinically plausible
Utility	Nordenfelt (2014) with added benefit for subcut admin. EQ-5D from HELP-03 is limited	Agree
Cost	• Resource use from clinical experts. • Correct acute attack costs if switching from LAN to C1-INH • £455 hospitalisation cost (for acute attack) • Acute icatibant costs excluded.	Accept revised base case

The only difference between company's revised base case & tech team preferred analysis is LANA treatment effect

⇩

Company: use HELP-03 data
ERG: concerned company apply rate ratio for C1-INH vs. placebo to estimate attack rate in C1-INH arm but use regression based attack rates from HELP-03 to estimate attack rate in LANA arm. Creates inconsistency in percentage reduction of attacks for LANA vs. C1-INH (company base case: [redacted] vs. [redacted] reduction in NMA). ERG prefer to use NMA for best estimate of treatment effect for LANA vs. C1-INH

⇩

Tech team: use NMA for both arms (attack rate adjusted for discontinuation/switching in LANA arm)

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Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	In updated base case?
2	**Comparator (positioning)** **Company:** position LANA after oral therapy therefore only consider C1-INH a comparator. **Clinical experts:** LANA could be used earlier in treatment pathway as an alternative to oral therapy **NICE tech team:** Is no long-term prophylactic (LTP) an appropriate comparator?	***Oral therapy*** **Company:** submitted new evidence showing cost-effectiveness [redacted] ***No LTP*** **Clinical experts:** although many patients may prefer no LTP to oral therapy, only small % eligible for C1-INH would choose not to have it **Patient expert:** majority (85%) will choose to have long-term C1-INH	***Oral therapy*** No trial evidence for oral LTP. Accept company's positioning after oral therapy ***No LTP*** Only small % choose not to have C1-INH, no trial evidence for no LTP & not cost-effective (see slide 24)	Company **x** ERG **x** Company **x** ERG **x**

⚠ NICE accept most relevant comparator is C1-INH → oral or no LTP not included in technical team's preferred assumptions for company's proposed positioning (severe disease)

[redacted] Proportion using Berinert vs Cinryze covered in issue 2, slide 23

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Outstanding issues after technical engagement

- **Issue 1:** Positioning of LANA (generalisability)
- **Issue 2:** Comparator (C1-INH treatment) 
- **Issue 3:** Long-term dose reduction for LANA 
- **Issue 4:** Subsequent prophylactic treatment & continued treatment effect

Issue 1: Positioning of LANA (generalisability)

Background

- Company position LANA after oral therapy (those currently eligible for C1-INH in the NHS England commissioning policy) but the full MA for LANA is wider (covered in slide 10)
- NHSE commissioning policy only recommends C1-INH in a severe disease group (≥2 attacks per week over 8 weeks). This definition differs compared with HELP-03 (at least 1 attack in last 4 weeks)
- HELP-03 did not specify previous treatment

See next slide for baseline characteristics in HELP-03

Stakeholder comments

- **Clinical experts:** Criteria for C1-INH in NHSE policy is well defined and followed in clinical practice. In HELP-03 some patients would have >1 attack in last 4 weeks and some people at baseline were having long-term prophylactic C1-INH at baseline (stopped for trial)
- **Royal College of Pathologists (RCPth):** should use same criteria as NHSE
- **UKPIN:** studies used to support NHSE policy had similar attack frequency to HELP-03

[redacted]

Note: Slide has been amended after Appraisal Committee Meeting

Issue 1: Positioning of LANA (generalisability)

- In the HELP-03 trial, the average number of attacks of unspecified severity at baseline was 3.9 in the previous 4 weeks
- Inclusion criteria did not specify previous oral therapy or contraindication to oral therapy.

Baseline characteristic		Lanadelumab			
HELP-03	**Placebo**	**300mg q2w**	**300mg q4w**	**All LANA***	**Total***
Mean (SD) attacks in last 4 wks	4.15 (3.98)	2.96 (2.79)	3.76 (3.51)	3.79 (4.31)	3.90 (4.19)
1 to <2 run-in attack rate/month	12 (29.3%)	7 (25.9%)	9 (31.0%)	26 (31.0%)	38 (30.4%)
2 to <3 run-in attack rate/month	8 (19.5%)	6 (22.2%)	5 (17.2%)	14 (16.7%)	22 (17.6%)
≥ 3 run-in attack rate/month	21 (51.2%)	14 (51.9%)	15 (51.7%)	44 (52.4%)	65 (52.0%)
Prior long term C1-INH only (%)	22 (53.7%)	9 (32.1%)	18 (62.1%)	38 (45.2%)	60 (48.0%)
Oral therapy	1 (2.4%)	0	1 (3.4%)	3 (3.6%)	4 (3.2%)
C1-INH and oral therapy	1 (2.4%)	3 (11.1%)	1 (3.4%)	5 (6.0%)	6 (4.8%)
No LTP use	17 (41.5%)	16 (57.1%)	9 (31.0%)	38 (45.2%)	55 (44%)
* Includes 150mg q4w arm (not in MA and not considered relevant)					

[redacted]

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Issue 1: Positioning of LANA (generalisability)

Company

- Appropriate to position LANA for same population who would receive C1-INH (high unmet need). If NHSE criteria becomes less stringent over time, NICE rec and LANA data still relevant
- Efficacy not expected to vary by baseline attack rate (confirmed by clinical experts). Subgroup analyses from HELP-03 confirm this, but small patient numbers (not presented here).
- Scenario analysis using company's revised base case shows LANA is more cost-effective as baseline attacks increases

Baseline attack rate (per 28 day cycle)	Incremental costs	Incremental QALYs	ICER (£/QALY)
≥ 8 attack	[redacted]	[redacted]	Dominant

[redacted]

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Issue 1: Positioning of LANA (generalisability)

ERG comments

Subgroup analyses

- [redacted] from HELP-03 would be potentially eligible for C1-INH in the NHS England policy.
- Company's subgroup analyses (≥8 attacks per month) based on very small patient numbers

Scenario analyses

- ERG scenario analyses using NICE preferred assumptions and subgroup (≥8 attacks per month) show improved cost-effectiveness of LANA compared with full HELP-03 population
-  (see slides 35 and 36 for ICERs)

Implementation issues

- May be difficult for commissioners to monitor or enforce use of LANA for population currently eligible for C1-INH

[redacted]

Note: Slide has been amended after Appraisal Committee Meeting

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Key issue for cttee

Issue 1: Positioning of LANA (generalisability)

Technical report

- Unclear whether NHSE criteria for long-term C1-INH reflects severe disease
- HELP-03 is the best available data source but uncertain whether results can be generalised to company's proposed positioning for those currently eligible for C1-INH
- The company's ICER for severe disease (8+ attacks per month) show LANA is dominant but may not be robust because of small patient numbers & did not include all tech team preferred assumptions

NHSE criteria for long-term prophylactic C1-INH

a) Individuals who fail, or are intolerant of oral prophylaxis and who experience **2 or more clinically significant attacks per week**, despite oral prophylaxis over a period of at least 56 days requiring treatment with c1 esterase inhibitor or icatibant.

b) Individuals in whom oral prophylaxis is contraindicated for example pregnant women, recognising that there are currently no other prophylactic treatment options during pregnancy and that there is increased risk of rapid deterioration in condition and additional risks to women during pregnancy.

Should current C1-INH NHSE criteria for selected people only be used to define company's proposed lanadelumab positioning (severe disease)?
Can results from HELP-03 be generalised to people with severe disease?
Should subgroup results (≥8 attacks per month) be used for LANA cost-effectiveness?

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Issue 2: Comparator (C1-INH treatment)

Background
- Company assumes [redacted] have Berinert and [redacted] have Cinryze using hospital dispensing data from Jul-Sep 2018
- NICE technical team: based on short-term data but clinically plausible

Stakeholder comments
- **UKPIN:** varies between hospitals, no data but ongoing HAE network survey will capture this
- **Clinical experts**: varies, but likely to be used in approximately equal proportions

Company
- Aware of variation, base case assumptions using 3-month hospital dispensing data considered most robust but also report scenario analyses using 3-year data from the Hospital Pharmacy Audit ([redacted] for Berinert and [redacted] for Cinryze)

Proportions	Revised base case ICER (£/QALY)
Base-case ([redacted] Cinryze IV: [redacted] Berinert IV)	Dominant
([redacted] Cinryze IV: [redacted] Berinert IV)	Dominant
([redacted] Cinryze IV: [redacted] Berinert IV)	Dominant

In ERG model, when assume [redacted] have Berinert, ICER switches from being dominant to over £30,000 per QALY gained

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Issue 2: Comparator (C1-INH treatment)

ERG:

- Agree C1-INH is comparator but some people eligible for C1-INH may not use or tolerate it and have no long-term prophylactic treatment. Consultation response from patient expert suggests 15% of those eligible for C1-INH may not use it
  - ICER for LANA vs. no long-term prophylactic treatment: >£2,500,000 per QALY gained

ERG identified additional issue relating to dosing of Berinert that has large impact on ICER (not covered in technical report at consultation stage, but covered in final technical report)

Company	ERG
Berinert cost is based on dose [redacted] compared with 1000IU Cinryze (2 x 500IU vials)	• CHANGE trial used 1000IU dose of Cinryze → used to inform efficacy data for C1-INH • Question whether same fixed dose (1000IU) would be used for Berinert & Cinryze long-term prophylaxis as they are both C1-INH • Clinical expert to ERG: use 1000IU regardless of Berinert/Cinryze for long-term prophylaxis. Resistant symptoms may need higher dose • Identified publication reporting Berinert Patient Registry data which identified 47 patients from USA and Europe having long-term prophylaxis with Berinert: median dose 1000IU (range 500 to 3000IU) or 13.77IU/kg • ERG scenario analyses using 1000IU fixed dose & NICE preferred assumptions is £1,463,662 per QALY gained

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Issue 2: Comparator (C1-INH treatment)

Additional clinical expert input (after technical engagement)

- In clinical practice have used 1000IU dose for long-term prophylaxis with Berinert. When considering weight based dosing, would take into account vial sizes – would under-dose rather than use only part of a vial
- C1-INH prescribed in secondary care only (not prescribed or dispensed in primary care). Estimate around 15-25 people eligible for C1-INH in England.

Other potential data sources

- Prescribing data – company use HPAI data (prescribing in secondary care)
- NHS England – does NHSE collect any data around C1-INH use to monitor the commissioning policy?
- HAE network survey – raised as potential data source at technical engagement by UKPIN but no published data or details about this

Technical report

- There is variation in clinical practice but the company's base case (assumes that most people having C1-INH have Berinert instead of Cinryze as a long-term prophylactic treatment) is clinically plausible.
- It is unclear whether the company's long-term prophylactic dosing regimen for Berinert (based on weight) reflects current clinical practice. Using a fixed dose 1000IU is also clinically plausible

Is it plausible to assume [redacted] have Berinert and [redacted] have Cinryze?
Should Berinert be dosed by weight or as a fixed 1000IU dose?

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Issue 3: Long-term dose reduction for lanadelumab

Background

- Company assumes 77% have lower frequency dosing (q4w) of LANA after 1 year using short-term freedom from attack data from HELP-03
- SmPC "lower dosing frequency may be considered in patients who are stably attack-free on treatment…especially in patients with low weight"

Stakeholder comments

- **Clinical experts, UKPIN:** can't predict accurately, but 77% is plausible.
- HAE attack rates vary over a patient's lifetime and dose frequency may need to be ↑ if HAE becomes more active, but would expect to lower again in future

Company

- 77% likely to be representative of more severe disease (NHSE criteria), based on new HELP-03 analysis of time to 1st attack after steady state with LANA is achieved (day 70 onwards) split by baseline attack risk (< 3 attacks vs. >3 attacks)
- Provides evidence that LANA is effective to treat more severe disease (also addresses Issue 1: generalisability of LANA evidence)

[redacted]

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Issue 3: Long-term dose reduction for lanadelumab

For LANA → no diff between less severe (blue) and more severe group (green) in % staying attack-free

For placebo → more severe group (green) less likely to stay attack-free

[redacted]

Issue 3: Long-term dose reduction for lanadelumab

ERG:

- This proportion is an assumption and was not directly observed in the clinical trial. Assumption based on short-term data from HELP-03 and there is no other external supporting or confirmatory evidence
- Company submitted figures only show no difference when defining severe disease as < 3 or > 3 attacks per month and highlight small numbers matching NHSE criteria

Technical report

- Company base case does not explicitly model changes in dosing frequency over time, but given that attack rates vary over a patients lifetime, it's reasonable to assume that at any given time, the majority of people having LANA with be on the lower frequency after 1 year
- Uncertain whether this can be generalised to patients with severe disease, which reflects the company's proposed positioning of LANA

Is it plausible to assume 77% having LANA are on a lower dosing frequency after 1 year? Does this also apply to company's proposed positioning (severe disease)?

[redacted]

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Issue 4: Subsequent prophylactic treatment & continued treatment effect

Background

- Company assume LANA won't lose effectiveness over time. ERG, tech team & experts agree this is plausible for most people → optimistic CE results
- Company's revised base case:
  - If stop LANA, switch to C1-INH
  - Continue C1-INH in comparator arm
- Company assume 91% continue treatment over lifetime. ERG unclear why HELP-04 not used to inform discontinuation rates

Stakeholder comments

- **Clinical experts, UKPIN:** only small proportion develop non-response over time (5-10%).
- Agree no alternatives after C1-INH but if LANA is stopped C1-INH would be used

Company

- C1-INH rarely stopped because achieving a sub-optimal response still beneficial for patients with severe disease and no other treatment options (confirmed by experts)
- Discontinuation rates were based on HELP-03 but new evidence from longer-term HELP-04 show most people stayed on treatment

[redacted]

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Issue 4: Subsequent prophylactic treatment & continued treatment effect

HELP-04 discontinuation (interim data: May 2016 to Sept 2017)

HELP-04	Rollover	Non-rollover	Total
Number treated	109	103	212
Completed study	0 (0%)	2 (1.9%)	2 (0.9%)
Ongoing (active study participation)	102 (93.6%)	95 (92.2%)	197 (92.9%)
Discontinued	7 (6.4%)	6 (5.8%)	13 (6.1%)

ERG comments

Continued treatment effect

- Optimistic to assume no one will lose treatment effect over time (for example due to antibodies) but company scenarios show results relatively robust to more pessimistic assumptions (see table 18 in company response to clarification, all ICERs dominant)

Subsequent treatment

- No change in ERG preferred assumptions

Discontinuation

- No change in ERG preferred assumptions

[redacted]

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Issue 4: Subsequent prophylactic treatment & continued treatment effect

Technical report

- Only a small proportion are likely to develop non-response to lanadelumab, therefore it is acceptable to assume a continued treatment effect for lanadelumab over time. However, the model does not account for this non-response, therefore this assumption will result in optimistic cost-effectiveness results for LANA
- It is appropriate to assume C1-INH is continued over a lifetime
- If lanadelumab is stopped, it is acceptable to assume people will switch to C1-INH
- It is reasonable to use discontinuation rates from HELP-03 because the results are similar to longer-term data from HELP-04

[redacted]

Issue 4: Subsequent prophylactic treatment & continued treatment effect

NHSE criteria for long-term prophylactic C1-INH

- After the first 6 months of treatment, the time between dosing should be gradually increased. If, at a dosing interval of one treatment per week, the symptoms remain below two or more clinically significant attacks per week a trial of treatment discontinuation should be commenced. If breakthrough attacks present above this level, the time between dosing should be reduced to regain adequate symptom control.
- If treatment is ineffective after two months (defined as a lack of reduction in attack frequency despite optimised treatment) then treatment with prophylactic C1-inhibitor should be discontinued and alternative therapy options considered.

1) Is it appropriate to assume a continued treatment effect over time for LANA?
2) Is it appropriate to assume all people having C1-INH will continue for a lifetime and if LANA is stopped, people will switch to C1-INH?
3) Is it acceptable to use discontinuation rates from HELP-03?
4) A stopping rule is used in NHSE criteria for using C1-INH, does this need to be considered for LANA (not included in model)?

Outstanding uncertainties in evidence base

From table 10 in technical report → these are areas of uncertainty that cannot be resolved. Committee should be aware of these when making its recommendations.

Issue	Why issue is important	Impact on ICER
Lack of direct comparative data	• no comparative data that directly compares LANA with C1-INH. • The clinical effectiveness is uncertain because an indirect comparison was needed.	Results may be more uncertain→ the company used a fixed effects model due to small sample size, but random effects models show wider credible intervals. This uncertainty is not accounted for in the model.
Lack of long-term data on lower LANA dosing frequency	• no evidence on the long-term use of a lower lanadelumab dosing frequency because the HELP-04 open-label extension study did not use this dosing regimen.	The cost-effectiveness results may be optimistic.

[redacted]

Technical report summary of cost-effectiveness (section 1.6)

- **Technical team's preferred cost-effectiveness analysis**
  - LANA is dominant compared with C1-INH for the overall HELP-03 population with less severe disease (at least 1 attack per month).
  - ICERs for severe disease (8+ attacks per month) show improved cost-effectiveness for LANA but this is based on very few patient numbers so unlikely to be robust.
- **Uncertainty around ICER**
  - ICER for severe disease (8+ attacks per month) is similar to current C1-INH NHSE criteria but includes small patient numbers and may not be robust
  - The ICER for the overall HELP-03 population could be substantially higher if Berinert is given as a fixed 1000IU dose, if fewer people use Berinert, or if fewer people having LANA use lower dosing frequency
- **Overall conclusion**
  - Despite some uncertainty LANA could be cost-effective compared with C1-INH but some clinically plausible scenarios show ICERs substantially >£30,000 per QALY gained

[redacted]

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Cost effectiveness results (with PAS) LANA vs. C1-INH

Full HELP-03 population

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company revised base case (ERG run)	[redacted]	[redacted]	Dominant
Use rate ratios for LANA vs. placebo from NMA including adjusted attack rate (not HELP-03)			
Technical team's preferred assumptions	[redacted]	[redacted]	Dominant
Clinically plausible scenario issue 2 (comparator: [redacted] have Berinert)			
a) ERG scenario: [redacted] have Berinert	[redacted]	[redacted]	Dominant
b) ERG scenario: [redacted] have Berinert	[redacted]	[redacted]	£87,949
c) ERG scenario: [redacted] have Berinert	[redacted]	[redacted]	£345,040
d) Fixed 1000IU per Berinert infusion	[redacted]	[redacted]	£1,463,662
Clinically plausible scenario issue 3 (long-term dose reduction for LANA: 77%)			
a) ERG scenario: 70%	[redacted]	[redacted]	Dominant
b) ERG scenario: 60%	[redacted]	[redacted]	£186,148
c) ERG scenario: 50%	[redacted]	[redacted]	£593,866

*Company report incremental costs [redacted] and incremental QALYs [redacted] in revised base case but ERG could not replicate this

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Cost effectiveness results (with PAS) LANA vs. C1-INH

Subgroup with ≥8 attacks per month at baseline

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company scenario ≥8 attacks (per month)	[redacted]	[redacted]	Dominant
Use rate ratios for LANA vs. placebo from NMA including adjusted attack rate (not HELP-03)			
Technical team's preferred assumptions			
a) ≥8 attacks (per month) at baseline	[redacted]	[redacted]	Dominant
Clinically plausible scenario issue 2 (comparator: [redacted] have Berinert)			
a) ERG scenario: [redacted] have Berinert	[redacted]	[redacted]	Dominant
b) ERG scenario: [redacted] have Berinert	[redacted]	[redacted]	Dominant
c) ERG scenario: [redacted] have Berinert	[redacted]	[redacted]	£11,504
d) Fixed 1000IU per Berinert infusion	[redacted]	[redacted]	£799,381
Clinically plausible scenario issue 3 (long-term dose reduction for LANA: 77%)			
a) ERG scenario: 70%	[redacted]	[redacted]	Dominant
b) ERG scenario: 60%	[redacted]	[redacted]	Dominant
c) ERG scenario: 50%	[redacted]	[redacted]	£99,684

Innovation and Equality

Technical report

- The company considers lanadelumab to be innovative.
  - The technical team considers that all relevant benefits associated with lanadelumab are adequately captured in the model.
- The company states that C1-INH treatment is based on human or animal products that may not be acceptable to some people. No other equality issues were anticipated by the company, consultees and their nominated clinical and patient experts.
  - The committee will consider this issue when making its recommendations

[redacted]

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Key issues

Model driver

Issue 1: Positioning of lanadelumab [LANA] (generalisability)

- Should current C1-INH NHSE criteria for selected people only be used to define company's proposed lanadelumab positioning (severe disease)?
- Can results from HELP-03 be generalised to company's proposed positioning?
- Should subgroup results (≥8 attacks per month) be used for LANA cost-effectiveness?

Issue 2: Comparator (C1-INH treatment)

- Is it plausible to assume [redacted] have Berinert and [redacted] have Cinryze?
- Should a weighted dose or fixed dose (1000IU) be assumed for Berinert?

Issue 3: Long-term dose reduction for lanadelumab

- Is it plausible to assume 77% are on a lower dosing frequency after 1 year?
- Does this also apply to company's proposed positioning (severe disease)?

Issue 4: Subsequent prophylactic treatment & continued treatment effect

- Is it appropriate to assume a continued treatment effect over time for LANA?
- Is it appropriate to assume all people having C1-INH will continue for a lifetime, and if LANA is stopped people will switch to C1-INH?
- Is it acceptable to use discontinuation rates from HELP-03?
- A stopping rule is used in current C1-INH NHSE criteria, does this need to be considered?

[redacted]

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