Lanadelumab for preventing recurrent attacks of hereditary angioedema

Produced by Aberdeen HTA Group

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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.

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]

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 (11.9%) 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 [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 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.

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.

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.

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.
- 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).
- 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.

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.

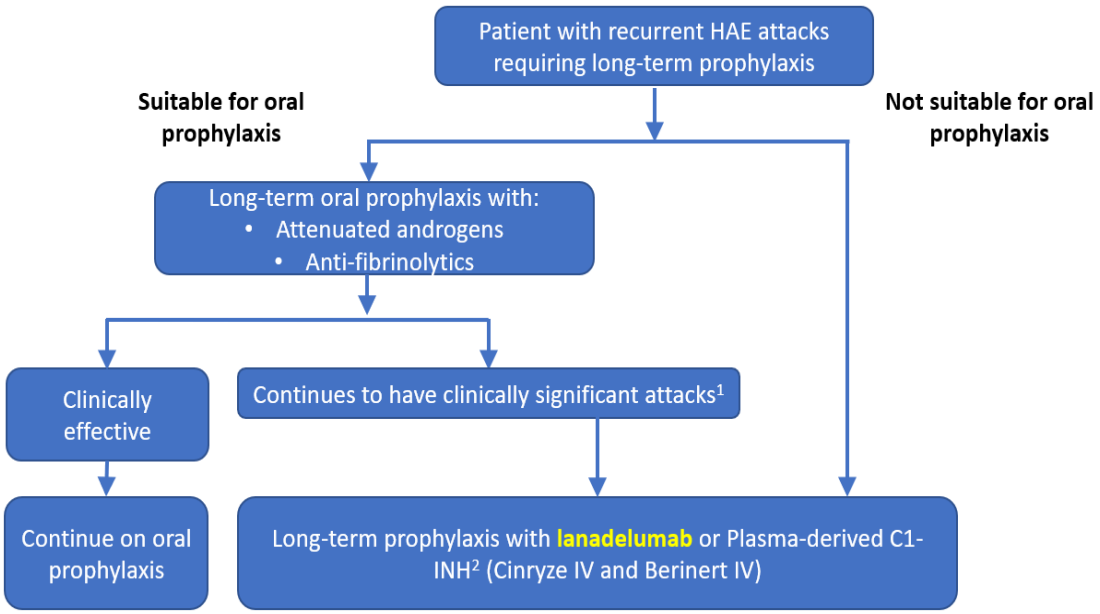


Figure 1 Current clinical pathway for long-term prophylactic management of HAE in the UK and proposed positioning of lanadelumab

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.

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.

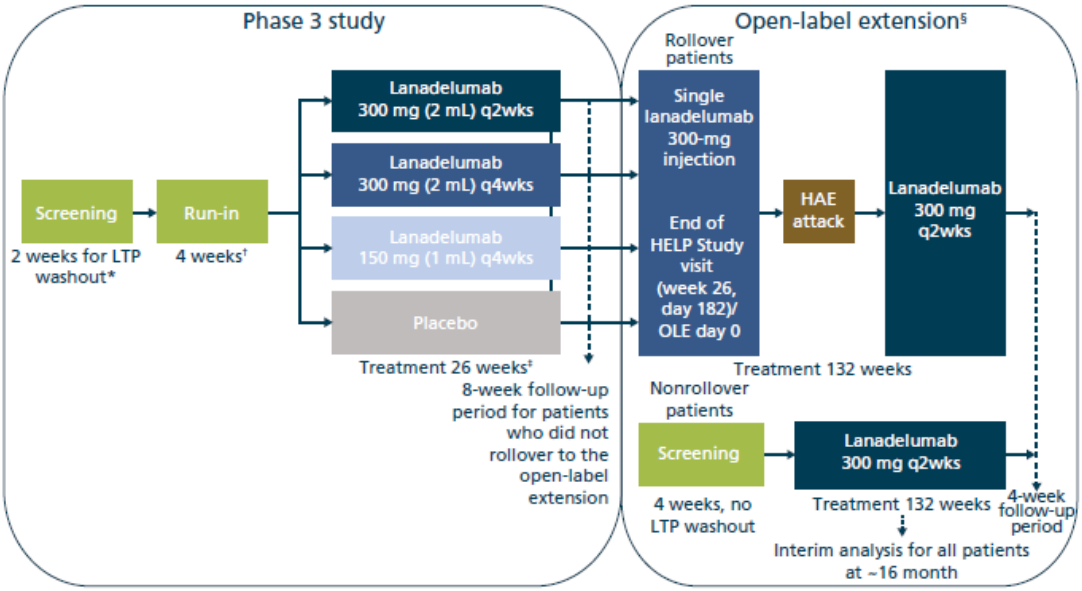
The company presents summaries of the HELP-03 and HELP-04 study design in Tables 4 and 5 and Figure 3 in Document B of the CS and these are reproduced by the ERG as Table 5 and Figure 2 in this report. The company also presents a summary of the DX-2930-02 study design in Table 6, Document B, of the CS 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])

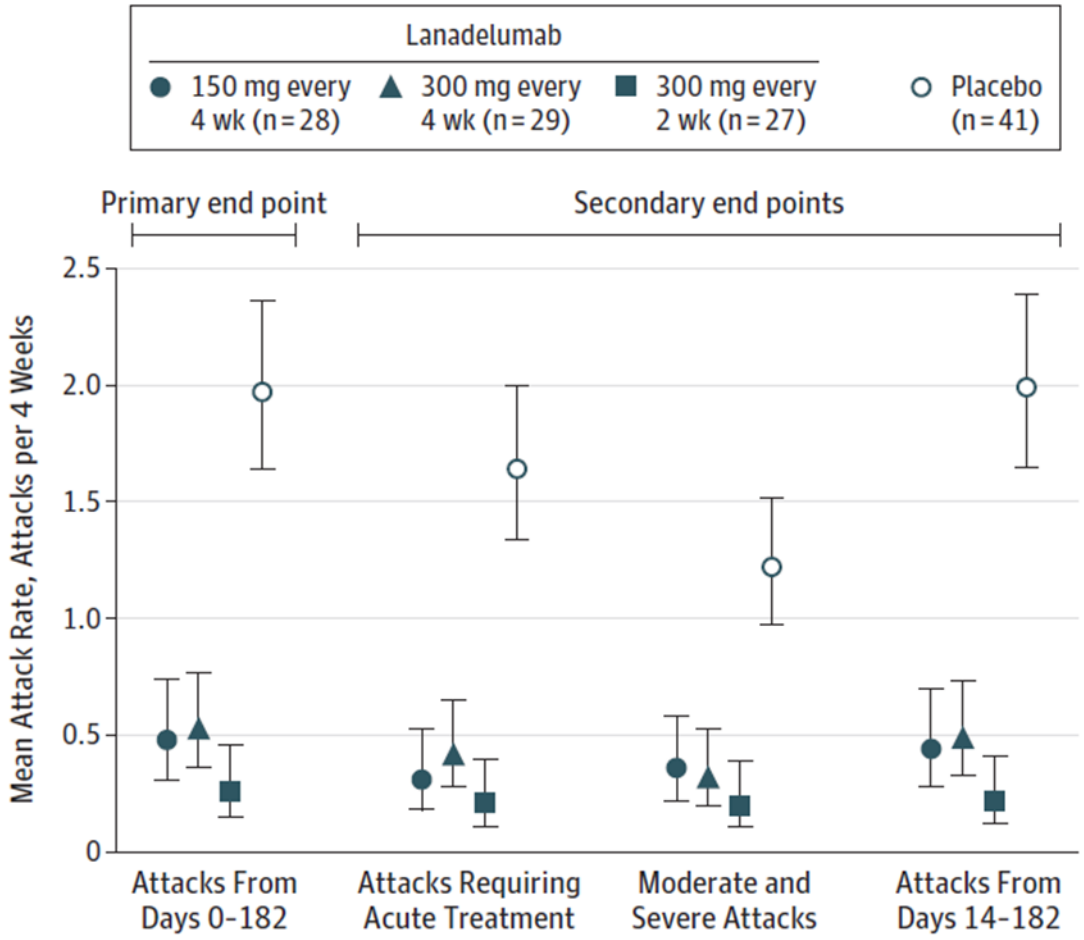
4.2.1 Primary endpoint – investigator-confirmed HAE attacks

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

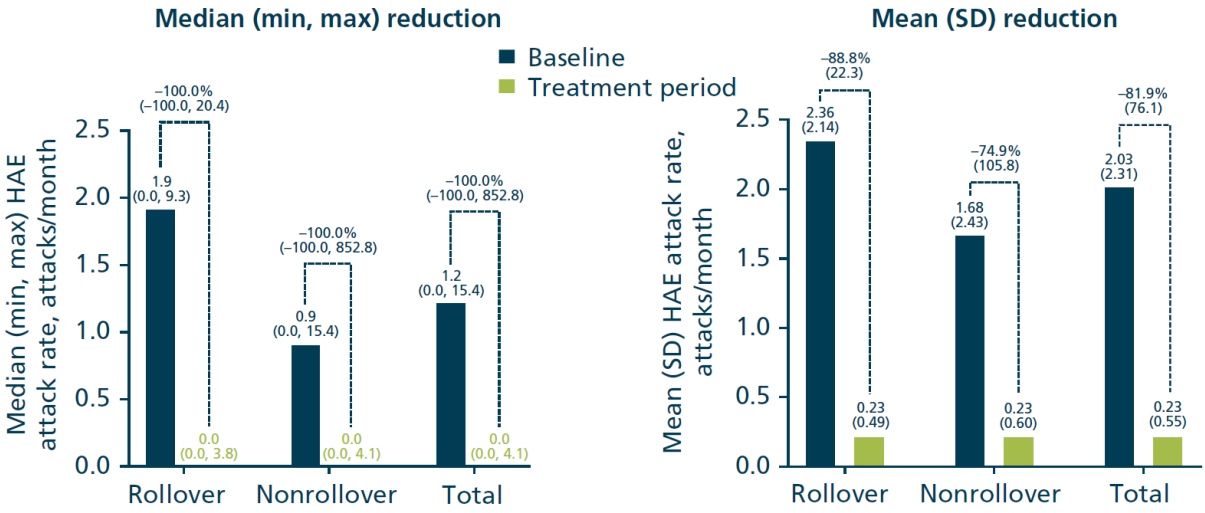
Key: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; LS, least squares; q2w, every 2 weeks; q4w, every 4 weeks; SD, standard deviation.

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.

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 10.50 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])

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)*."

The company presents AEs data in Tables 24-10, 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.

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).

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, 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 AESI (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 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

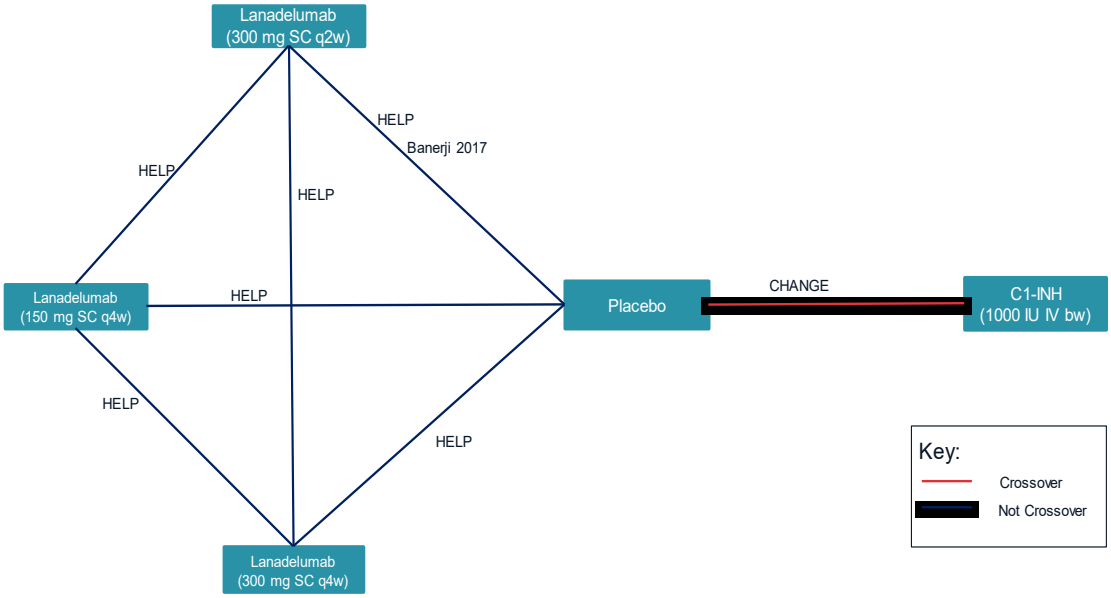
Source	Type of NMA	No of studies in the NMA	Treatment versus placebo	% of reduction
Time to first attack after Day 0				
HELP-03	Fixed effects	2	Lanadelumab 300mg q2w versus placebo [redacted]	[redacted]
HELP-03	Fixed effects	2	Lanadelumab 300mg q4w versus placebo [redacted]	[redacted]
CHANGE	Fixed effects	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)

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 (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.

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)].

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				

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)].

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.

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.

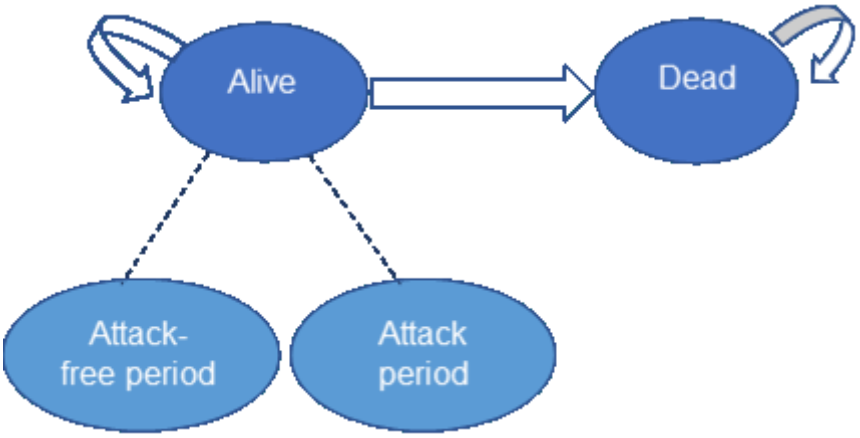
Perspective costs	NHS and Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Mostly covered. However, the company did not include an added mortality risk that could come from certain severe hereditary angioedema attacks such as laryngeal attacks.
Form of economic evaluation	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.

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 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

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
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,

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

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 remaining 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.

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.

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 £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.*

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".

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.

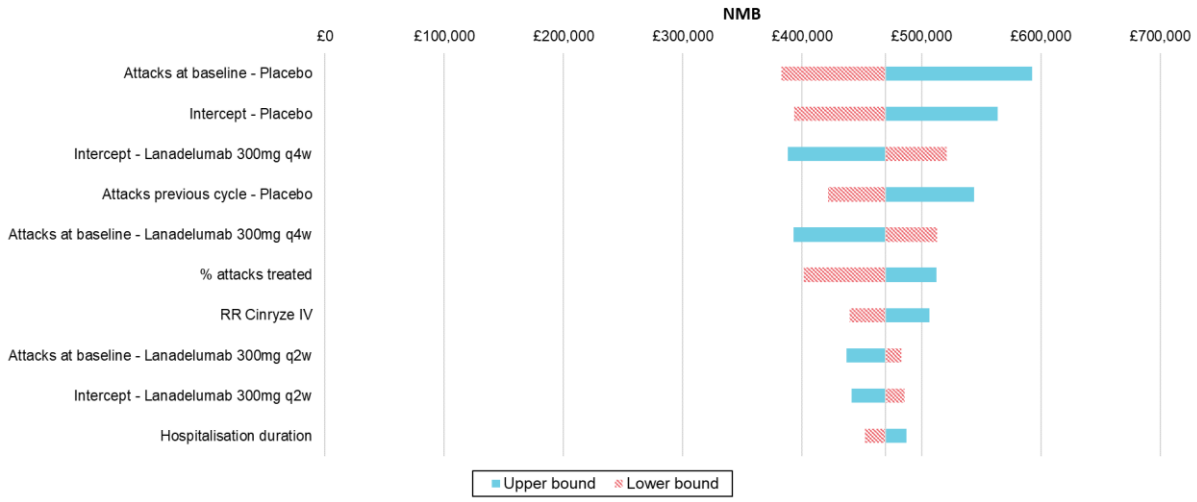
5.2.10 Sensitivity analyses

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.

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.

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.

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).

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 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.

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.

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

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.

7 References

1. Group NECBCR. *Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angiodema (Adult)* 2013. NHS England. Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angiodema (Adult). 2013 [Accessed December 2018]

2. Lumry WR. Overview of epidemiology, pathophysiology, and disease progression in hereditary angioedema. *The American journal of managed care* 2013;**19:**s103-10.

3. Maurer M, Magerl M, Ansotegui I, Aygoren-Pursun E, Betschel S, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. *Allergy* 2018;**73:**1575-96.

4. Caccia S, Suffritti C, Cicardi M. Pathophysiology of Hereditary Angioedema. *Pediatric allergy, immunology, and pulmonology* 2014;**27:**159-63.

5. Zuraw BL. Hereditary angioedema with normal C1 inhibitor: Four types and counting. *Journal of Allergy and Clinical Immunology* 2018;**141:**884-5.

6. Longhurst HJ, Dempster J, Lorenzo L, Buckland M, Grigoriadou S, Symons C, et al. Real-world outcomes in hereditary angioedema: first experience from the Icatibant Outcome Survey in the United Kingdom. *Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology* 2018;**14:**28-.

7. Jolles S, Williams P, Carne E, Mian H, Huissoon A, Wong G, et al. A UK national audit of hereditary and acquired angioedema. *Clinical and experimental immunology* 2014;**175:**59-67.

8. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *The American journal of medicine* 2006;**119:**267-74.

9. Zuraw BL. Current and future therapy for hereditary angioedema. *Clinical Immunology* 2005;**114:**10-6.

10. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *The Journal of allergy and clinical immunology* 2012;**130:**692-7.

11. Allergy NESSCRGfIa. *Clinical commissioning policy: Plasma-derived C1-esterase inhibitor for prophylactic treatment of hereditary angiodedema (HAE) types I and II* 2016. https://www.england.nhs.uk/wp-content/uploads/2018/07/Plasma-derived-C1-esterase-inhibitor-for-prophylactic-treatment-of-hereditary-angioesema-types-I-and-II.pdf [Accessed December 2018]

12. Zanichelli A, Magerl M, Longhurst H, Fabien V, Maurer MJAACI. Hereditary angioedema with C1 inhibitor deficiency: delay in diagnosis in Europe. 2013;**9**.

13. Statistics OfN. *Deaths registered in England and Wales* 2017. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregistrationsummarytables/2017 [Accessed December 2018]

14. Zuraw BL. Hereditary angioedema. *N Engl J Med* 2008;**359;** 1027-1036.

15. Devercelli G, Davis K, Brown M, Hollis K, Hunter S, Long J, et al. Burden of Hereditary Angioedema: Findings From a US Patient Survey. *Journal of Allergy and Clinical Immunology* 2018;**141:**AB57.

16. Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, Wait S, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. 2014;**9:**99.

17. Jindal NL, Harniman E, Prior N, Perez-Fernandez E, Caballero T, Betschel SJA, Asthma, et al. Hereditary angioedema: health-related quality of life in Canadian patients as measured by the SF-36. 2017;**13:**4.

18. Hopman WM, Towheed T, Anastassiades T, Tenenhouse A, Poliquin S, Berger C, et al. Canadian normative data for the SF-36 health survey. 2000;**163:**265-71.

19. Nordenfelt P, Dawson S, Wahlgren CF, Lindfors A, Mallbris L, Bjorkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. *Allergy Asthma Proc* 2014;**35:**185-90.

20. Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, Boysen HB, et al. Estimation of EuroQol 5-Dimensions health status utility values in hereditary angioedema. *Patient preference and adherence* 2016;**10:**1699-707.

21. Weller K, Magerl M, Peveling-Oberhag A, Martus P, Staubach P, Maurer M. The Angioedema Quality of Life Questionnaire (AE-QoL) – assessment of sensitivity to change and minimal clinically important difference. 2016;**71:**1203-9.

22. Prior N, Remor E, Pérez-Fernández E, Caminoa M, Gómez-Traseira C, Gayá F, et al. Psychometric Field Study of Hereditary Angioedema Quality of Life Questionnaire for Adults: HAE-QoL. *The Journal of Allergy and Clinical Immunology: In Practice* 2016;**4:**464-73.e4.

23. Caballero T, Aygoren-Pursun E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, et al. The humanistic burden of hereditary angioedema: results from the Burden of Illness Study in Europe. *Allergy Asthma Proc* 2014;**35:**47-53.

24. Granero-Molina J, Sanchez-Hernandez F, Fernandez-Sola C, Jimenez-Lasserrotte MDM, Antequera-Raynal LH, Hernandez-Padilla JM. The Diagnosis of Hereditary Angioedema: Family Caregivers' Experiences. *Clinical nursing research* 20181054773818780102.

25. Riedl MA, Banerji A, Busse PJ, Johnston DT, Davis-Lorton MA, Patel S, et al. Patient satisfaction and experience with intravenously administered C1-inhibitor concentrates in the United States. *Annals of Allergy, Asthma & Immunology* 2017;**119:**59-64.

26. Jose J, Lehman EB, Craig T. Evaluating satisfaction of patients with hereditary angioedema with their past and present treatments: Implications for future therapies. *Allergy Asthma Proc* 2018;**39:**74-80.

27. Limited SPI. *Cinryze. Summary of product characteristics* 2011. https://www.medicines.org.uk/emc/product/2808/smpc [Accessed February 2019]

28. Banerji A, Riedl MA, Bernstein JA, et al. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: A randomized clinical trial. *JAMA* 2018;**320:**2108-21.

29. Limited SPI. *Lanadelumab. Draft summary of product characteristics* 2018. https://www.ema.europa.eu/documents/product-information/takhzyro-epar-product-information_en.pdf [Accessed February 2019]

30. Newswire G. *The European Medicines Agency (EMA) grants accelerated assessment for Shire's landelumab being evaluated for the prevention of attacks in hereditary angioedema (HAE) patients aged 12 years and older* 2018. https://globenewswire.com/news-release/2018/02/27/1396293/0/en/The-EMA-Grants-Accelerated-Assessment-for-Shire-s-Lanadelumab-Being-Evaluated-for-the-Prevention-of-Attacks-in-HAE-Patients-Aged-12-Years-and-Older.html [Accessed February 2019]

31. Agency EM. *Tahkzyro (lanadelumab) European Public Assessment Report* 2018. https://www.ema.europa.eu/en/medicines/human/EPAR/takhzyro [Accessed February 2019]

32. (CHMP) CfMPfHU. *Summary of opinion (inital authorisation): Takhzyro (lanadelumab)* 2018. https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-takhzyro_en.pdf [Accessed February 2019]

33. (EMA) EMA. *Public summary of opinion on orphan designation Recombinant human IgG1 kappa light chain monoclonal antibody targeting plasma kallikrein for the treatment of hereditary angioedema* 2015. https://www.ema.europa.eu/documents/orphan-designation/eu/3/15/1551-public-summary-opinion-orphan-designation-recombinant-human-igg1-kappa-light-chain-monoclonal_en.pdf [Accessed February 2019]

34. Loke YK PD, Herxheimer A. . *Chapter 14: Adverse effects. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration* 2011. https://handbook-5-1.cochrane.org/chapter_14/14_adverse_effects.htm [Accessed February 2019]

35. Higgins JPT DJe. *Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration* 2011. https://handbook-5-1.cochrane.org/chapter_7/7_selecting_studies_and_collecting_data.htm [Accessed February 2019]

36. NICE. *Developing NICE guidelines: the manual*. London2014. https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview [Accessed Updated October 2018]

37. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. 1998;**52:**377-84.

38. Riedl MA, Bernstein JA, Craig T, Banerji A, Magerl M, Cicardi M, et al. An open-label study to evaluate the long-term safety and efficacy of lanadelumab for prevention of attacks in hereditary angioedema: design of the HELP study extension. 2017;**7:**36.

39. Banerji A, Busse P, Shennak M, Lumry W, Davis-Lorton M, Wedner HJ, et al. Inhibiting Plasma Kallikrein for Hereditary Angioedema Prophylaxis. 2017;**376:**717-28.

40. Clinicaltrials.gov. *Long-term Safety and Efficacy Study of DX-2930 (SHP643) to Prevent Acute Angioedema Attacks in Patients With Type I and Type II HAE.* 2016. https://clinicaltrials.gov/ct2/show/NCT02741596 [Accessed Updated May 2018]

41. Banerji A, Busse P, Shennak M, Lumry W, Davis-Lorton M, Wedner HJ, et al. Inhibiting Plasma Kallikrein for Hereditary Angioedema Prophylaxis. *The New England journal of medicine* 2017;**376:**717-28.

42. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 Inhibitor Concentrate for Treatment of Hereditary Angioedema. 2010;**363:**513-22.

43. Woods BS, Hawkins N, Scott DAJBMRM. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: A tutorial. 2010;**10:**54.

44. Graham C, Machnig T, Knox H, Supina D, Krishnarajah G. P159 Attacks avoided and cost offsets associated with subcutaneous C1-inhibitor (human) long-term prophylaxis of hereditary angioedema. *Annals of Allergy, Asthma & Immunology* 2017;**119:**S40-S1.

45. Javaud N, Bouillet L, Rabetrano H, Bitoun A, Launay D, Lapostolle F, et al. Hereditary angioedema: Clinical presentation and socioeconomic cost of 200 French patients. *The journal of allergy and clinical immunology In practice* 2019;**7:**328-30.

46. Review IfCaE. *Prophylaxis for hereditary angioedema with lanadelumab and C1 inhibitors: Effectiveness and value. Draft evidence report.* 2018. https://icer-review.org/wp-content/uploads/2018/03/ICER_HAE_Draft_Evidence_Report_082318.pdf [Accessed February 2019]

47. van Hout B, Janssen MF, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim Scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L Value Sets. *Value in Health* 2012;**15:**708-15.

48. NICE. *DSU Technical support document 12: The use of health state utility values in decision models*. London: NICE; 2011. http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD12-Utilities-in-modelling-FINAL.pdf [Accessed February 2019]

49. Holko P, aw, Kawalec P, Mossakowska M, gorzata. Quality of life related to oral, subcutaneous, and intravenous biologic treatment of inflammatory bowel disease: a time trade-off study. *European Journal of Gastroenterology & Hepatology* 2018;**30:**174-80.

50. Evans M, Jensen HH, Bogelund M, Gundgaard J, Chubb B, Khunti K. Flexible insulin dosing improves health-related quality-of-life (HRQoL): a time trade-off survey. *J Med Econ* 2013;**16:**1357-65.

51. Riedl MA, Lumry WR, Li HH, Banerji A, Bernstein JA, Ba M, et al. Subcutaneous administration of human C1 inhibitor with recombinant human hyaluronidase in patients with hereditary angioedema. *Allergy and asthma proceedings* 2016;**37:**489-500.

52. Aygoren-Pursun E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, Boysen HB, et al. Estimation of EuroQol 5-Dimensions health status utility values in hereditary angioedema. *Patient Prefer Adherence* 2016;**10:**1699-707.

53. Holko P, Kawalec P, Mossakowska M. Quality of life related to oral, subcutaneous, and intravenous biologic treatment of inflammatory bowel disease: a time trade-off study. *European journal of gastroenterology & hepatology* 2018;**30:**174-80.

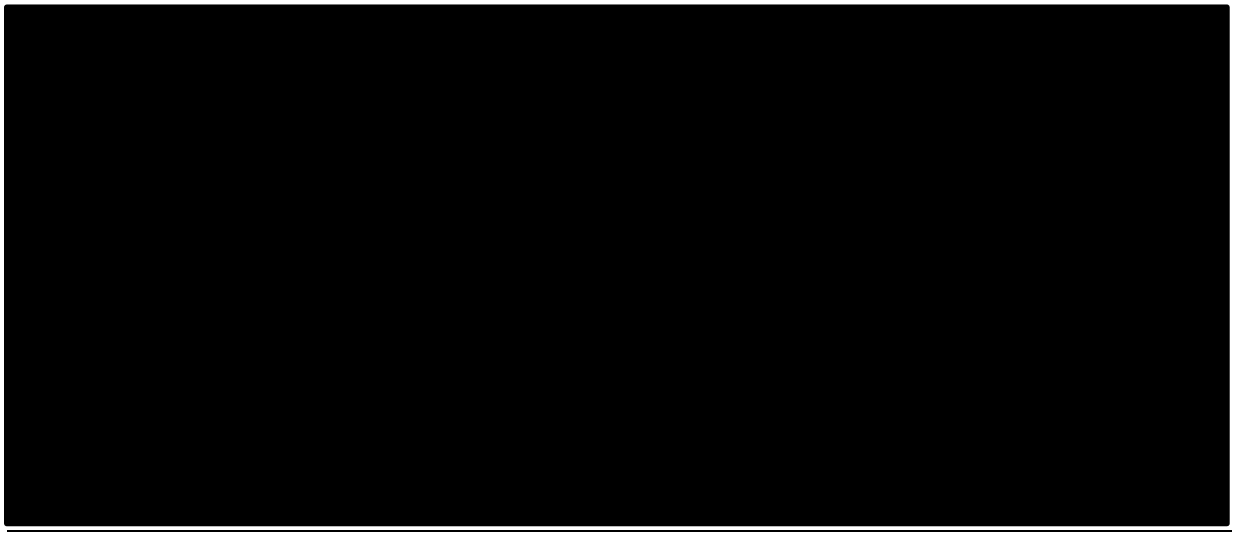
55. Wilson DA, Bork K, Shea EP, Rentz AM, Blaustein MB, Pullman WE. Economic costs associated with acute attacks and long-term management of hereditary angioedema. *Annals of Allergy, Asthma and Immunology* 2010;**104:**314-20.e2.

56. Tappenden P, Chilcott JB. Avoiding and Identifying Errors and Other Threats to the Credibility of Health Economic Models. *PharmacoEconomics* 2014;**32:**967-79.

57. Jørgensen T, Franchi A, Lelli F, Lee XY, Bøgelund M, Alulis S. Preferences for Route of Administration, Frequency and Location - A Time-Trade-Off Study in the Italian General Population. *Value in Health* 2017;**20:**A637.

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

Event, n (%) m	Placebo (n=41)	Lanadelumab		
		300mg q2w (n=27)	300mg q4w (n=29)	Total (n=56)
[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]