NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

Contents:

The following documents are made available to consultees and commentators:

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

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

Committee Papers

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

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1	Consultee	Shire, now part of Takeda	Executive Summary Shire, now part of Takeda, is disappointed to see a provisional negative recommendation for lanadelumab and hopes the additional evidence and analyses provided as part of this consultation will support a final positive recommendation for lanadelumab. The company recognises the lack of long-term data inherent in the evidence base for rare conditions and related to the accelerated regulatory timelines, leading to uncertainty in some parameters and assumptions. The appraisal consultation document (ACD) identifies three elements for which uncertainty remains in the evaluation of the cost-effectiveness of lanadelumab: (i) the Berinert dosing used in clinical practice, (ii) the actual proportion of patients who would switch to the 4-weekly (Q4W) administration of lanadelumab, and (iii) the comparator cost to use in the model. With our responses and additional evidence submitted, we aim to reduce the uncertainty the committee may have on the outstanding issues. Any outstanding uncertainty should be considered against the conservative assumptions in the cost-effectiveness model, which were incorporated to ensure a conservative approach in the presence of limitations of data: • no survival benefits due to the prevention of potentially fatal laryngeal attacks; this was raised as an important issue at the first appraisal committee meeting • no impact of lanadelumab on the severity of attacks, while trial data showed a significant reduction in severe attacks with lanadelumab • no benefits in terms of caregiver quality of life (QoL), which at the first appraisal committee meeting was described by the patient experts as a significant aspect • the selection of the shortest duration of attacks ([redacted]) vs longer	Thank you, your comments have been noted. The appraisal committee considered the new evidence at the second committee meeting and concluded that given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the cost-effectiveness results. Therefore, the final appraisal decision (FAD) recommends lanadelumab only if: • they are eligible for preventive C1-esterase inhibitor (C1-INH) treatment in line with NHS England's commissioning policy, that is, they are having 2 or more clinically significant attacks (as defined in the policy) per week over 8 weeks despite oral preventive therapy, or oral therapy is contraindicated or not tolerated • the lowest dosing frequency of lanadelumab is used in line with the summary of product

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			estimates from other arms of the HELP-03 trial or from the CHANGE trial, also considering the testimony of the patient representatives at the committee meeting (over 2 days of duration, as reported in section 3.1 of the ACD) • Cinryze is used in the model at its licensed dose, [redacted] While no data source is perfect, the company believes the revised base case provided as part of the ACD consultation is based on the most robust data available. Furthermore, the company has increased the discount level through a simple patient access scheme (PAS), which should help minimise the uncertainty over the cost-effectiveness of lanadelumab.	characteristics, that is, when the condition is in a stable, attack-free phase '(see section 2) and • the company provides lanadelumab according to the commercial arrangement (see section 2).
2	Consultee	Shire, now part of Takeda	<u>Dosing of Berinert</u> Further to the issues raised at the first committee meeting, the company has revised the base-case analysis in line with the information reported below. The results of this analysis show that lanadelumab is cost-effective using both the overall HELP-03 population and the more severe population (i.e. at least 8 attacks per month). On page 4 of the ACD it is reported that "*it is unclear what dose of Berinert (a C1-INH) is used in clinical practice*" while point 3.13 concludes that "*there is substantial uncertainty around the dosing schedule for Berinert but that a rounded fixed dose of 1,000 IU is the mostly likely to reflect NHS practice.*" The latter statement in particular contradicts the general opinion of clinicians practicing in England and Wales: • At the first committee meeting, the clinical expert explained that a pragmatic approach is adopted and as a result some rounding occurs when calculating the required and actual dose used for Berinert. The company believes the example reported in the ACD is only illustrative of one specific case (i.e. the example of a patient requiring 1,100IU) and it would be incorrect to assume every rounding leads to an actual 1,000IU dose. Based on the weight-based dosing, most patients in actual practice require a dose higher than 1,000IU.	Thank you, your comments have been noted. The appraisal committee considered the new evidence at the second committee meeting and concluded there is substantial uncertainty around the dosing schedule for Berinert (see section 3.14 of the final appraisal determination [FAD]). The committee concluded that although all cost-effectiveness estimates for lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers an acceptable use of NHS resources. Given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the

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			• In addition to clinical expert interviews conducted by the company to inform the original submission[1] that confirmed Berinert is used on a weight-based dosing, the company recently conducted two virtual advisory panel meetings and eight individual calls involving 22 clinicians during which they were asked about Berinert dosing in practice with specific focus on the rounding of dose.[2] The detailed report has been added to Appendix A of the company's ACD comments. The feedback received represents 72% of specialist centres for HAE in England and Wales treating [redacted] patients on long term prophylaxis with C1-INH of which [redacted] were treated with Berinert. The clinical experts stated that [redacted] of Berinert treated patients were receiving a dose [redacted] with Berinert most commonly dosed according to weight [redacted]. The clinical experts also confirmed that [redacted]. Dependent on the weight-based estimate of the required dose, the actual dose is [redacted] due to Berinert being available in 500IU vials. [redacted]. Experts also indicated that [redacted]. • Additional information from clinical experts is that [redacted]. This is conservatively not included in the model base case. In the company's revised cost-effectiveness model, the pragmatic approach of rounding Berinert dosing is applied based on the advice received by the clinical	cost-effectiveness results.

[1] Shire. Discussion Guide – KOL advisory discussions to inform NICE and SMC submissions for lanadelumab for the treatment of hereditary angioedema, 2018.
[2] Takeda. ACD Panel Research Report, 2019.

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			expert at the NICE committee meeting [redacted]. This rounding approach uses the midpoint between the closest multiples of 500IU as the threshold for rounding up or down. In an alternative scenario analysis, the specific dosing regimens for Berinert reported by the experts participating in the Advisory Boards and interviews were used as a weighted average to inform this parameter in the model. The results of both the revised base case and scenario analysis show that lanadelumab is cost-effective using both the overall HELP-03 population and the severe subgroup with at least 8 attacks per month. The ERG referenced a registry publication[3] as evidence supporting the use of Berinert in a fixed dose of 1,000IU. The company has reviewed this publication and noted the following limitations, which makes this source unrepresentative of current practice in the UK: - The registry includes no UK data, with the majority of centres being in the USA (30); the rest in 7 European sites (Germany, 5; Denmark, 1; Switzerland, 1) - Data were collected between 2010 and 2014 and is outdated considering that disease management has changed in the interim - The study only reports the median dose of 1000IU while the average dose across the patient population is more representative for the purpose of calculation in the model. As the range reported is between 500 and 3,000IU, this demonstrates that the data is skewed and therefore that the median is not representative of the mean, which is likely to be greater than the median. For these reasons, using this publication to inform current practice data would be inappropriate. Finally, the ACD notes that the randomised control trial (RCT) informing the indirect treatment comparison (ITC) used in the model is on the 1,000IU dose of C1-esterase inhibitors (C1-INH). However, it fails to mention that the original company's submission provided a scenario analysis where the effectiveness of Berinert was increased to reflect the potentially average higher dose compared	

[3] Craig T, Shapiro R, Vegh A, et al. Efficacy and safety of an intravenous C1-inhibitor concentrate for long-term prophylaxis in hereditary angioedema. *Allergy Rhinol (Providence)*. 2017; 8: 13-9.

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			to the dose for which clinical effectiveness data are available. The same analysis is presented in the updated model results submitted as part of the ACD consultation. The results of this analysis show that lanadelumab remains dominant at any value or the rate ratio of Berinert vs placebo explored in the analysis (range 0.1 to 1.0), both in the full HELP-03 population and in the more severe population (i.e. with at least 8 attacks per month).	
3	Consultee	Shire, now part of Takeda	<u>Proportion of patients on lanadelumab switching to the Q4W dosing in the long-term</u> The proportion of patients who would be receiving the Q4W dosing frequency was one of the issues highlighted at technical engagement stage. In response to the technical engagement questions asked by NICE, clinical experts and patient representatives confirmed willingness on both sides to reduce dosing frequency when patients are attack-free, supporting the plausibility of the company's approach to estimating the proportion of patients on lanadelumab that would switch to the Q4W dosing frequency. This is also noted in point 3.14 of the ACD: "*The clinical experts explained that it was clinically plausible that 77% of people would have their dosing frequency reduced, though noted that this is difficult to predict.*" The committee argued that some patients who are attack-free would choose not to reduce their dosing schedule; however, this seems to be in conflict with the patient experts' view heard at the committee meeting suggesting a willingness and desire to move to a more infrequent administration and expressed as part of the technical engagement consultation. Noting the committee's uncertainty around this estimate, the company has sought further clinical opinion on this issue through two virtual advisory board panels and eight individual calls involving 22 clinical experts including 13 consultant immunologists and 9 specialist nurses, representing 72% (n=16) of the specialist centres for HAE across England and Wales. The clinical experts [redacted]; in fact, 44.8% of patients in the Q4W arm of the	Thank you, your comments have been noted. The appraisal committee considered the new evidence at the second committee meeting and concluded there is substantial uncertainty around the proportion of people that would have the lower dosing frequency of lanadelumab, but accepted the company's scenario analysis value of 61% for its decision-making (see section 3.15 of the FAD). The committee concluded that although all cost-effectiveness estimates for lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers an acceptable use of NHS resources**.** **G**iven the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS**.** The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the cost-effectiveness results.

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			HELP-03 trial were completely attack free at steady state. Four clinicians felt confident to suggest a proportion that may be managed on a four-weekly dosing schedule and gave a range of [redacted]. Data on the proportion of patients who are stably attack-free on Q2W are available from the HELP-03 trial; showing that 77% of patients in the Q2W arm were stably attack-free once lanadelumab achieved steady state (day 70). In practice, [redacted],[4] it is possible that the number of patients who are "stably" attack-free may exceed the 77% estimate. Recognising that the committee may still have some uncertainty over this estimate, the company has conducted a scenario analysis whereby the proportion of attack-free patients is based on a mid-point between the attack-free patients from both the Q2W arm and the Q4W arms of the HELP-03 trial (61%). This lower figure represents a pragmatic approach to model the proportion of patients who will be switched as stably attack-free based on clinical opinion but also allows for not all patients who were attack free on Q2W moving to Q4W. The results of this analysis show that the ICER for lanadelumab vs C1-INH in the overall HELP-03 population is £31,061 per QALY, while lanadelumab is dominant vs C1-INH in the subgroup with at least 8 attacks per month.	
4	Consultee	Shire, now part of Takeda	<u>Tender prices</u> Section 1 of the ACD states that "*discounted price of C1-INH treatments paid by the NHS is not currently included in the cost-effectiveness results. Therefore, all estimates of cost effectiveness for lanadelumab compared with C1-INH are highly uncertain*." While it is true that the NHS procures C1-INH through a tender process, and the NHS likely pay lower than list prices, it is important to note that a tender is a procurement process with the tender price applied for a limited period of time and subject to fluctuation. This may be particularly relevant for plasma-derived C1-INHs where supply constraints may have an impact on pricing. The company highlights that there will be a new C1-INH tender in place for the start	Thank you, your comments have been noted. The appraisal committee considered the new evidence at the second committee meeting and concluded that cost-effectiveness results including the current discounted prices for C1-INH treatments were preferred (see section 3.13 of the FAD). In particular, the committee acknowledged that price discounts may change over time but considered that cost-effectiveness analyses should include prices that are currently used in the NHS.

[4] Takeda. ACD Panel Research Report, 2019.

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			of 2020 and that current C1-INH prices are likely to be updated. Tender prices for C1-INH therefore should be considered unreliable to inform long-term cost-effectiveness analyses. Moreover, as company is not aware of the tender prices for the overall C1-INH comparator due to confidentiality, it could not incorporate these in any scenario analyses.	
5	Consultee	Shire, now part of Takeda	ITC vs Poisson regression As stated in point 3.6 of the ACD, the committee "*concluded that using the indirect treatment comparison to inform attack rates for both lanadelumab and C1-INH is the more consistent and robust approach*". The company disagrees with the conclusion that this is a more robust approach because – as noted in section B.2.6, page 66, of the original company's submission – lanadelumab reaches its steady state after day 70 and therefore it is important to capture the change in lanadelumab's clinical efficacy over time, which the ITC estimate fails to do. The Poisson regression, on the other hand, estimates more precisely the number of attacks with lanadelumab at each cycle and outputs an attack frequency that matches more closely the observed data in the trial compared to the ITC estimate. Additionally, as patient-level data over multiple time points is available from HELP-03 it is appropriate to make use of this data, whereas similar data is not available for C1-INH and therefore requires the use of the ITC. While the company believes that using the Poisson regression to model the clinical effectiveness of lanadelumab remains the correct approach, it is willing to accept the committee's preference in order to present a more conservative approach. Therefore, the ITC informs both arms of the revised base case model. A scenario analysis where the Poisson regression is informing the clinical effectiveness of lanadelumab is presented in the revised analysis document. This shows lanadelumab is dominant in both scenarios. .	Thank you, your comments have been noted. The appraisal committee considered this issue at the first committee meeting and concluded that the indirect treatment comparison should be used to estimate the treatment effect for lanadelumab and C1-INH (see section 3.6 of the FAD).
6	Consultee	Shire, now part of Takeda	**New base case and results** Upon consideration of the committee preferred analysis noted within section 3.18 of the ACD, the company has adjusted the base-case settings of the cost-effectiveness analysis as follows:	Thank you, your comments have been noted. The appraisal committee considered the new evidence at the second committee meeting and concluded that although all cost-

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			- New PAS based on the recent update in the confidential discount - Use of ITC to inform both arms as per point 5 above - Results presented for the full HELP-03 population and the subgroup of people with at least 8 attacks in the previous 4 weeks - assuming C1-INH is a subsequent treatment if lanadelumab is stopped, and C1-INH that is continued over a lifetime - Using a rounding approach for Berinert dosing as per point 2 above together with the most common dose ([redacted] twice weekly) The new base-case is fully detailed in the separate document. The new base-case generates [redacted] incremental QALYs and savings of [redacted] in the full HELP-03 population, and [redacted] incremental QALYs and savings of [redacted] in the more severe subgroup, for lanadelumab versus C1-INH, showing lanadelumab is dominant compared to C1-INH.	effectiveness estimates for lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers an acceptable use of NHS resources. Given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the cost-effectiveness results.
7	Consultee	Shire, now part of Takeda	**Factual accuracy check** The following points within the ACD have been noted as factually inaccurate or not fully reflective of the evidence base. We would request that for future documents the text is corrected. • On page 9 it is reported that "*At the appraisal committee meeting, the company advised that 3 ongoing studies (1 in the USA, 1 in Europe and 1 in France) were collecting data on the lower frequency dosing schedule*". It would be more accurate to state that "*At the appraisal committee meeting, the company advised that 3 ongoing studies (1 in the USA, 1 in Europe and 1 in France) were collecting data on the real-world use of lanadelumab including both licenced dosing schedules"*. Section 3.2 reports that "After technical engagement, the company positioned lanadelumab for the population currently eligible for long-term prophylactic C1-INH in the NHS England commissioning policy." This is not correct as the company had already clarified the positioning while responding to the ERG clarification questions in January 2019.	Thank you for your comments. Sections 3.5 and 3.2 of the FAD have been amended.
8	Consultee	Patient expert (HAE UK)	This medication will be a life changer for many patients, especially those suffering severe attacks who cannot self-infuse medication due to poor vein access.	Thank you, your comments have been noted. The appraisal committee considered the impact on a person's quality of life. The committee concluded that although all cost-effectiveness

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				estimates for lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers an acceptable use of NHS resources. Given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the cost-effectiveness results.
9	Consultee	Patient expert (HAE UK)	Even patients who have prophylactic medication have breakthrough attacks and have to either self-administer an acute attack medication or visit A&E for emergency treatment.	Thank you, your comments have been noted. The rate and cost of breakthrough attacks were included in the model in line with use in the HELP-03 trial. The committee concluded that although all cost-effectiveness estimates for lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers an acceptable use of NHS resources. Given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the cost-effectiveness results.
10	Consultee	Patient expert (HAE UK)	HAE has a big impact on mental health too. Stress is one of the main triggers for attacks and the fear of an attack and the unpredictability can cause a lot of stress, not only when an attacks is presenting, but every day. Having a	Thank you, your comments have been noted. The appraisal committee considered impact on a person's quality

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			treatment that will stop attacks will be hugely life changing, patients will feel more relaxed and have the confidence to live a normal life.	of life. The committee concluded that although all cost-effectiveness estimates for lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers an acceptable use of NHS resources. Given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the cost-effectiveness results.
11	Consultee	Patient expert (HAE UK)	This medication will be much easier to administer, being a sub-cut medication. I myself have very good veins but having to treat twice weekly for a number f year has caused much scaring on my veins and it becomes much more difficult being able to self-treat effectively without problems. Having this medication will also save time for administration – my current medication takes time to prepare as well as time to infuse. It also needs to be administered in a sterile environment which is not always possible at short notice when an attacks presents.	Thank for your comment. The benefit of subcutaneous administration of lanadelumab has been included in the model, see section 3.16 of the FAD for more details.
12	Consultee	Clinical expert (Immunology and Allergy CRG)	UK Primary immunodeficiency network has recently completed a survey looking at the usage of plasma derived C1 concentrates for long-term prophylaxis in patients with HAE. The findings of this survey suggest higher usage then what was originally considered when compared to cost effectiveness of lanadelumab. I hope that this new information can be taken into account.	Thank for your comment. At the second committee meeting, the committee considered the evidence submitted by the UK Primary immunodeficiency network on C1-INH dosing. Please see section 3.14 of the FAD for more details.
13	Consultee	Clinical expert (Immunology and Allergy CRG)	I would like to express my support here for the additional comments made by the UKPIN regarding the likely significant reduction in cost of on-demand therapy if lanadelumab is introduced into routine clinical practice. Furthermore, it is worthwhile highlighting innovative nature of this treatment, which has a potential to truly transform how we look after the patients with HAE	Thank for your comment. At the second committee meeting, the committee considered the evidence submitted by the UK Primary immunodeficiency network. Please see section 3.14 of the FAD for more details. The committee also considered innovation but agreed that all benefits from lanadelumab were

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				captured in the model (see section 3.20 of the FAD).
14	Consultee	NHS England	[redacted] Data is commercial in confidence and is not reported here	Thank you for your comments. At the second committee meeting, the committee considered the evidence submitted by NHS England on the use of prophylactic C1-INH. Please see section 3.12 of the FAD for more details.
15	Consultee	British Association of Dermatologists Therapy & Guidelines sub-committee	Hereditary angioedema (HAE) is due to C1 esterase inhibitor deficiency (Types 1 or 2) but also occurs in patients with normal C1 esterase inhibitor. HAE with normal inhibitor has been linked with mutations in genes for Factor XII, plasminogen and angiopoeitin but the underlying mutation in other patients is unknown. The HELP-03 study population was drawn from patients with Type 1 or Type 2 HAE so the analysis and implementation of the technology appraisal should be confined to HAE types 1 and 2 and clearly stated as such. HAE presents with angioedema without weals. Angioedema without weals may also be a presentation of chronic spontaneous urticaria (CSU). CSU is considerably more common than HAE but angioedema probably never results in asphyxiation and can be expected to remit naturally whereas HAE may cause death from asphyxiation in a few individuals1 and is potentially life long. The aim of treatment of HAE should be complete disease control to prevent a risk of asphyxiation and improve quality of life. The only licensed treatment for long-term prophylaxis of patients 6 years and older with HAE types 1 and 2 in the UK is Cinryze (C1 esterase inhibitor) by intravenous administration. Berinert (C1 esterase inhibitor) is licensed for treatment and pre-procedure prevention of acute attacks of HAE but not for long-term prophylaxis even though it is commonly used off licence for this. The correct financial comparator for lanadelumab should therefore be Cinryze rather than Berinert, despite estimated lower NHS usage (section 3.12). Self-administration by subcutaneous injection is much easier for patients than	Thank you for your comments. Although Berinert is not licensed for prophylactic use, it is currently used in clinical practice in the NHS therefore this is included in the model. See section 3.12 of the FAD for more details. The benefit of subcutaneous administration of lanadelumab has also been included in the model, see section 3.16 of the FAD for more details. The costs of acute treatment were also included in the model in line with use in the HELP-03 trial (see section 3.13 of the FAD for more details).

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			repeated intravenous cannulation and safer in the context of poor peripheral access requiring long-term central lines. The subcutaneous route is likely to be an increasing advantage over a lifetime as venous access becomes more difficult and the ability of patients to self-cannulate becomes less with age. As a further confounder, in the calculation of cost, it should not be forgotten that acute breakthrough episodes still require emergency treatment with C1 inhibitor (Berinert, Cinryze or Ruconest) or icatibant +/- supportive medical care so the total costs to the NHS of lanadelumab will not be limited to prophylactic administration. Furthermore, the need for high frequency administration may be reduced by co-administration of oral prophylaxis (danazol or tranexamic) where tolerated and appropriate. The HELP-03 study provides no data to estimate any advantage of concurrent oral treatment in terms of attack frequency, severity or optimal treatment frequency. Concentrated C1 esterase inhibitor (Haegarda™) by subcutaneous injection has recently been approved by the FDA for long-term prophylaxis based presumably on data from the COMPACT trial2. Guidance on using lanadelumab in the NHS in England should be revisited if EMA approval for its use in Europe is granted or pending. 1. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol 2012;130:692-7. 2. Longhurst H, Cicardi M, Craig T, Bork K, Grattan C, Baker J et al. Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. N Engl J Med. 2017;376:1131-1140.	
16	Consultee	HAE UK	The comparator of C1 Esterase Inhibitor treatment is difficult to quantify because even patients receiving prophylactic C1-INH under the NHS England Commissioning report having breakthrough attacks of Hereditary Angioedema and so are not attack free. They then have to use more C1-INH to treat an attack or in order to remain attack free they shorten the interval between doses but in either case use more C1-INH that is calculated on merely assessing the numbers of patients receiving C1-INH prophylaxis. There is also the issue that patients receiving Berinert are dosed on an iu/kg weight basis and so the dose may be higher than that specified in the NHS England document which only deals with Cinryze using a fixed dose. I therefore think that the cost comparision is underestimating the cost of C1-INH per patient.	Thank you for your comments. The costs of acute treatment were also included in the model in line with use in the HELP-03 trial (see section 3.13 of the FAD for more details). In addition the appraisal committee considered the new evidence at the second committee meeting and concluded there is substantial uncertainty around the dosing schedule for Berinert (see section 3.14 of the FAD).
17	Consultee	HAE UK	This product is a subcutaneous injection, which even used every fortnight is	Thank for your comment. The benefit of subcutaneous administration of

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			very quick and easy to administer. This has the double effect of making the product available to patients who are unable to administer C1-INH because of physical or practical issues such as poor venous access, and also means this is an much easier product for patients patient established on treatment. leading a less structured lifestyle, for example students or travellers. Use of intravenous C1-INH, whilst effective and many patients are able to successfully self-treat, requires a suitable environment for administration, and considerable time is taken to reconstitute the product, carry out the venepuncture and infuse the product. It is then recommended that the patient rests for at least 30 minutes after infusing. This all results in a considerable amount of time being devoted to this twice a week instead of a short time once a fortnight, or even monthly once	lanadelumab has been included in the model, see section 3.16 of the FAD for more details.
18	Consultee	HAE UK	The psychological effect of patients living with the fear of attacks and also the ever present fear of a shortage of C1-INH (which happens all too frequently, despite the best efforts of the supplier companies) means that patients live in a state of constant anxiety. This in turn exacerbates their attacks. The most beneficial effect for them is to have treatment in which they have confidence and which they know will be available without the arbitrary supply issues which affect plasma derived products.	Thank you for your comment. The impact of lanadelumab on health-related quality of life was included in the model and this included an additional benefit for subcutaneous administration (see section 3.16 of the FAD).
19	Consultee	HAE UK	The clinical data shows that many patients respond well to Lanadelumab and it is of considerable benefit to these patients. It is now widely used in Europe and the US and to deny access to patients in England is putting us at a considerable disadvantage to these other countries.	Thank you, your comments have been noted. The committee concluded that although all cost-effectiveness estimates for lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers an acceptable use of NHS resources. Given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the cost-effectiveness results.
20	Consultee	Royal college of	We would like to point out that there are promising oral Kallikrein inhibitors in	Thank you, your comments have been

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		Pathologists	Phase 2 and phase 3 trials for prophylaxis and acute attacks that will probably be entering the market within the next 5 years. The impact of these medications on management of HAE has not been taken into account.	noted. However, the appraisal committee is only able to consider treatments that are currently used in NHS clinical practice.
21	Consultee	Royal college of Pathologists	The long half-life (weeks) of Lanadelumab which is probably one of the contributing factors to its efficacy, results in long term inhibition of plasma Kallikrein and reduction in bradykinin (BK) production. The long term effect of reduction in BK production is not known as the use of Lanadelumab in human is limited to a maximum of 3-4 years. The effect of Kallikrein inhibition on cardiovascular events is not known and could only be established after long term post-marketing surveillance. Lanadelumab has been considered as an orphan drug in a disease in which for majority of patients there are many effective treatments such as C1Inhibitor replacement therapy which would supplement the physiological deficit of C1Inhibitor. Lanadelumab would effectively create a second knock out in this disease resulting in absence of C1Inhibitor function in addition to reduction in Kallikrein activity. Until a reasonable post-marketing period, we believe that the use of Lanadelumab should be limited to very severe and/or frequent disease for which alternative medications do not exist.	Thank you, your comments have been noted. The committee concluded that although all cost-effectiveness estimates for lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers an acceptable use of NHS resources. Given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the cost-effectiveness results.
22	Consultee	Royal college of Pathologists	HAE is a rare disease and most clinical centres have a small number of patients with HAE. Initiation of C1-Inh prophylaxis, based on the department of health commissioning policy, requires a multidisciplinary decision and approval from two consultant immunologist from different. Patients who are considered to be appropriate for Lanadelumab, should be reviewed (virtually or in person) by designated national centres with large cohorts of HAE patients where alternative treatments may be considered before embarking on treatment with Lanadelumab.	Thank you for your comments. The committee considered the population currently eligible for C1-INH treatment in the NHS England commissioning policy (see sections 3.2 and 3.4 in the FAD).
23	Consultee	United Kingdom Primary Immunodeficiency Network (UKPIN)	We are concerned that this recommendation does not take into account the actual amount of Berinert and Cinryze used in clinical practice for prophylaxis. UKPIN has completed a snap survey of immunology centres to determine this. 82% (28 out of 34) of immunology centres responded in time, contributing data from 66 patients on prophylaxis with C1 inhibitor. Patients on Berinert (n=33) were using an average of 2781 units per week for prophylaxis and patients on Cinryze (n=31) were using an average of 2343 units per week for prophylaxis.	Thank you for submitting this data. At the second committee meeting, the committee considered the evidence submitted by the UK Primary immunodeficiency network on C1-INH dosing. Please see section 3.14 of the FAD for more details.

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			Two patients on Ruconest were on 8400 units per week prophylaxis. The average usage per week for prophylaxis is higher than the licensed dose of Cinryze and the assumed fixed dose of 1000 units of Berinert twice per week. We would like to know what the cost-effectiveness data looks like with these figures. This data also indicates that the actual usage of Berinert for prophylaxis is higher than the fixed dose used in the model.	
24	Consultee	United Kingdom Primary Immunodeficiency Network (UKPIN)	We are concerned the model does not seem to take into account the additional costs associated with treatment of breakthrough attacks for patients on prophylaxis (i.e. medication, additional hospital visits etc). We would expect there to be a greater reduction in breakthrough attacks in patients treated with lanadelumab rather than iv C1 inhibitor. The average number of breakthrough attacks in HAE patients in the UKPIN snap survey was 2.4 per month (data on breakthrough attacks available for 27 patients), which is a lot higher than the number of breakthrough attacks for patients in the HELP study. We would be like to see the additional costs associated with this included in the cost-effectiveness analysis.	Thank you for your comments. The costs of acute treatment were also included in the model in line with use in the HELP-03 trial (see section 3.13 of the FAD for more details).
25	Consultee	United Kingdom Primary Immunodeficiency Network (UKPIN)	We would also like to stress that lanadelumab is a genuinely innovative prophylactic treatment for patients with HAE, and has the potential to reduce both burden of treatment (significantly less injections) and burden of illness (less attacks compared to iv C1 inhibitor prophylaxis). The reduced burden of treatment and burden of illness means less days off work/school (reduced economic impact) and reduced anxiety for patients – these are factors which would not necessarily be accounted for in the model used.	Thank you for your comments. The committee considered innovation but agreed that all benefits from lanadelumab were captured in the model (see section 3.20 of the FAD). The burden of treatment and illness are expected to be captured by and reflected in the health-related quality of life measures.
26	Web comment		I am the President and CEO of Hereditary Angioedema International, the umbrella organization that represents the world's HAE patient groups. The critiques associated with using QALYs as the basis for healthcare utilization decisions are well known so I won't recount those arguments here. What I will present, however, is an alternative perspective on the value of a highly effective subcutaneous prophylaxis treatment based on a pharmaco-economic study performed by one of our member organizations--the United States Hereditary Angioedema Association. 737 HAE patients with HAE types I and II responded to a survey that asked questions on quality of life (using the validated Angioedema Quality of Life questionnaire) and a variety of other topics including direct and socioeconomic costs associated with HAE. The American Academy of Asthma, Allergy, and Immunology accepted the study for a poster presentation at their February 2019 annual meeting in San Francisco, California. A manuscript containing the study findings has been prepared and will be submitted to a medical journal later this month. Below we	Thank you for your comments. The impact of lanadelumab on health-related quality of life was included in the model and this included an additional benefit for subcutaneous administration (see section 3.16 of the FAD). The methods used were in line with the NICE reference case which prefers EQ-5D to measure health-related quality of life (see section 5.3 of the NICE Guide to the Methods of technology Appraisal). The economic study carried out by the United States Hereditary Angioedema Association may not be directly relevant to NHS clinical practice in England.

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			present the principle findings from the study, ""A Comprehensive Approach to Assessing the Value of Treating an Ultra Rare Disease: Hereditary Angioedema."" Two internationally recognized, well published HAE expert physician/scientists are co-authors. Study Overview and Highlights --Recent clinical trials evaluating new, subcutaneous (SC) prophylaxis therapies reveal significant reductions in the number of HAE attacks and improvement in QoL. Moreover, SC prophylaxis treatments, for the first time, offer HAE patients an opportunity for a normal, attack-free life. Despite the clear advantages to patients, questions have been raised regarding the value of new SC prophylaxis therapies when compared to an on-demand only treatment model. --Our study assessed the value of the new SC prophylaxis therapies compared to on-demand only treatment using real world patient data to quantify QoL, pharmacoeconomic, and socioeconomic impact. --Members of the US HAE Association were invited to complete an anonymous online survey designed to obtain a comprehensive profile of education, employment, attack frequency, treatments, comorbidities, caregiver economic costs, and actual billed costs for attack-related hospitalizations, physician office visits or emergency room admissions. In addition, QoL was measured by the validated Angioedema Quality of Life (AE-QoL) questionnaire (where 0 = no impact and 100 = severe impact). QoL -Use of prophylaxis therapy led to significant reductions in median QoL impairment score when compared to either on-demand treatment alone (42.6 vs 50.0, p<.01) and periods of time when prophylaxis was not available (42.6 vs 73.5, p<.01). --Fewer HAE attacks led to a clinically relevant and statistically significant reduction in QoL impairment. -- Patients using the newest SC prophylaxis therapy who (1) were attack free in the last 3 months and (2) reported a period without access to prophylaxis showed a 83.3% reduction in median QoL impairment score (11.8 vs. 70.6; p<.01). Economic Analysis	

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			--A comprehensive health economics analysis of patients using on-demand only treatment revealed costs of $417,100 per patient per year as follows: --Direct costs - including on-demand only treatment (assuming only 7 out of 10 attacks are treated); ER visits, hospital stays, and HAE-linked co-morbidities totaled $364,500. -- Indirect socioeconomic costs, calculated using the cost of missed work due to sick days, reduced wages, and under employment, totalled $52,600. Conclusions --The survey of 737 patient members of the US HAEA community is the largest ever sample of HAE Type I and II patients. --Recent data indicate that the population of patients achieving zero attack status increases with sustained exposure to a SC prophylaxis therapy. --a post hoc analysis performed as part of the lanadelumab clinical trial indicated that treatment efficacy increases over time and that a substantial majority of patients on the new therapies will be attack free. --The value of a SC prophylactic HAE treatment should be assessed in the context that: -- a substantial majority of patients using the newest SC prophylaxis therapies are likely to become attack free, -- there is potential for remarkable improvements in health outcomes, quality of life and potential socioeconomic gain, --the on-demand only treatment model is associated with high direct and indirect costs. Why should HAE patients be left to suffer from a dramatically reduced quality of life from attacks when there is an easy to use and highly effective medicine available to prevent the physical and mental anguish associated with this painful, disfiguring, and potentially fatal ultra rare disease? Moreover, as the US pharmaco-economic study shows, when looked at from a comprehensive perspective (direct and socioeconomic costs), on-demand only therapy is quite expensive.	
27	Web comment		**Response 1: New treatment option** This sounds like it will be life changing especially for us who cannot treat at home plus save valuable time being treated in A&E **Response 2: Proposed date for review of guidance** 3 years will feel like a lifetime with us but will still be life changing treatment	Thank you, your comments have been noted. The appraisal committee considered the potential benefits of lanadelumab to people with HAE. The committee concluded that although all cost-effectiveness estimates for

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				lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers an acceptable use of NHS resources. Given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the cost-effectiveness results.
28	Web comment		**Response 1:** Question: Has all of the relevant evidence been taken into account? I have HAE and was on the clinical trial for this medication and have subsequently been on it open label for the last 2 1/2 years. This medication has made an enormous difference in my life. I was in the process of being considered for the C1-INH when I joined the trial. My sister (who lives in another country) has been on C1-INH before, so I have some awareness of what is involved. Since been on Lanadelumab, the number of attacks I have has reduced dramatically and the attacks I have had were much milder. What's more, my mental health has improved because I'm not worried or anxious now about when my next attack is coming or what that will mean to my colleagues at work and the ability to do my job and keep social commitments. Finally, my overall health has improved. When I'm not constantly about to have an attack, having an attack or recovering from an attack, I can eat better and exercise more and enjoy an overall much-higher quality of life. Thanks to this medication, I am working to my full potential and living with joy. I could not stress enough what a difference this medication has made to me and the ripple-effects of this difference to my family, friends, colleagues and beyond. I cannot speak to whether or not I would have had the same results with C1-INH, but I do know that a sub-cutaneous injection every two weeks is much less daunting to me than finding a vein and self-injecting every few days with a medication that is also somewhat complex and time-consuming to prepare and does carry with it the risk of an infection like hepatitis.	Thank you, your comments have been noted. The appraisal committee considered the potential benefits of lanadelumab to people with HAE. The committee concluded that although all cost-effectiveness estimates for lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers an acceptable use of NHS resources. Given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the cost-effectiveness results. The impact of lanadelumab on health-related quality of life was included in the

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			Response 2: Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? I think it is difficult to know the true cost-effectiveness of a whole group of people being well who formerly were not. The difference in cost isn't just between the price of different medical treatments. If one treatment does significantly increase quality of life, then the benefits to well-being of someone as a whole, society as a whole, the NHS as a whole, the economic system as a whole are difficult to quantify. That being said, £12,420 per 300 mg vial is very high, and though I support100% the medication being widely available to HAE patients with moderate to severe levels of attacks, I would also support NICE in further price negotiations. **Response 3:** Question: Are the recommendations sound and a suitable basis for guidance to the NHS? I would like to see a positive recommendation to the NHS from NICE. It is a valuable product which significantly enhances wellness and quality of life for patients suffering with HAE. **Response 4:** Question: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? None that I am aware of.	model and this included an additional benefit for subcutaneous administration (see section 3.16 of the FAD). The NICE reference case considers all direct health effects for patients and other people but does not normally consider wider benefits to society (see section 5.1 of the NICE Guide to the methods of technology appraisal)
29	Web comment		I suffers with Hereditary Angioedema which predisposes me to get sporadic swelling of the peripheries (hands, feet, arms, legs, torso or genitals) which can be painful and limit the ability to use my hands or feet when they get swollen. In addition, I get sporadic abdominal swellings with abdominal distension, pain, vomiting or diarrhoea. I also get life threatening swellings involving the face in particular the airways. These swellings need to be treated promptly. I have been trained to self-inject Icatibant for peripheral or abdominal swellings but on quite a few occasions I	Thank you, your comments have been noted. The appraisal committee considered the potential benefits of lanadelumab to people with HAE. The committee concluded that although all cost-effectiveness estimates for lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers

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			have need to go to the nearest emergency department for un-resolving swellings, in particular for swellings of my face to be given intravenous Berinert to replenish the depleted C1 esterase inhibitor. Even though I have been trained to self-inject Icatibant subcutaneously, at times I am unable to given the injection if my hands are particularly swollen or my abdomen is swollen too much. Under these circumstances I have to get help from my sister in injecting the drug (she has also been trained to inject Icatibant into me). At other times when my feet or legs are swollen I will have difficulty in mobilising, walking, using stairs, going to the toilet, etc. If my hands are swollen I find it difficult to feed myself, take other medication, operate doors, use my mobile phone as my dexterity is severely compromised. The frequency of these episodes are variable, and my attacks can last anywhere from 2-5 days or so. I believe this medication will enable provision of a more comfortable life taking into account the condition and the limitations it puts on my mobility and functionality.	an acceptable use of NHS resources. Given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the cost-effectiveness results.
30	Web comment		This new medication would be amazing, been hoping for something for so long to bring a quality of life back. I have 2 to 3 attacks a week and sometimes can end up having 5 injections a week to treat attacks as it stands. I am a single mum with a little girl who has the same condition who is experiences swells early. Every day is a struggle. I am finding it impossible to administer I.V C1 to myself despite attempting training so this could be a life changer for me and my little girl.	Thank you, your comments have been noted. The appraisal committee considered the potential benefits of lanadelumab to people with HAE. The committee concluded that although all cost-effectiveness estimates for lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers an acceptable use of NHS resources. Given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the cost-effectiveness results.

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31	Web comment		**Response 1** Question: Are the recommendations sound and a suitable basis for guidance to the NHS? I have been closely involved with the medical care of hereditary angioedema (HAE) patients for many years and was an investigator in the lanadelumab trial. Patients with HAE still cry when they are told that their child has HAE. This is because almost everyone continues to have some breakthrough swellings, which are greatly feared, despite currently available prophylaxis. In the trial, lanadelumab prevented attacks to a much greater extent that I have seen with any other agent, with resulting transformation in the lives of those participants, who were some of my most severely affected patients. For example, one lady, was able to go on holiday for the first time and to do her job without the special provisions for unexpected absence that needed previously to be in place. Her relatives with HAE are unable to work because of frequent attacks and are semi-reclusive as a result. It is imperative that we gain access to this medication for the widest possible range of HAE patients. **Response 2** Question: Are the recommendations sound and a suitable basis for guidance to the NHS? I have been closely involved with the medical care of hereditary angioedema (HAE) patients for many years and was an investigator in the lanadelumab trial. Patients with HAE still cry when they are told that their child has HAE. This is because almost everyone continues to have some breakthrough swellings, which are greatly feared, despite currently available prophylaxis. In the trial, lanadelumab prevented attacks to a much greater extent that I have seen with any other agent, with resulting transformation in the lives of those participants, who were some of my most severely affected patients. For example, one lady, was able to go on holiday for the first time and to do her job without the special provisions for unexpected absence that needed previously to be in place. Her relatives with HAE are unable to work because of frequent attacks and are semi-reclusive as a result. It is imperative that we gain access to this medication for the widest possible range of HAE patients. **Response 3** Question: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of	Thank you, your comments have been noted. The appraisal committee considered the potential benefits of lanadelumab to people with HAE. The committee concluded that although all cost-effectiveness estimates for lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers an acceptable use of NHS resources. Given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the cost-effectiveness results. The committee considered potential equality issues but agreed there are no equality issues relevant to the recommendation (see section 3.21 of the FAD). The recommendation in the FAD applies to all people aged 12 years or older eligible for routine prevention of recurrent attacks of hereditary angioedema, regardless of race or disability.

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			people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? In my experience, access to effective medical care for HAE is much more likely for those not disadvantaged by social circumstances (who may be overrepresented in racial minorities or the disabled community). In fact those most disabled by HAE often do not get the treatment required, because of the difficulties they have engaging with medical care because of unpredictable disabling/disfiguring attacks and the psychological consequences of these. Current prophylaxis is too complex (or ineffective) for them to cope with.	
32	Web comment		I experience Type 1 HAE. For many years I had to go to A&E to be treated every time I had an attack. It had an impact on both my work and my social life. I can remember going to London for the day, buying a theatre ticket, having a coke and realising I had a fast moving attack coming, and having to forget the theatre, catch a train home, camped out in the toilet. My brother who also experiences HAE has had a similar experience, passing out on a platform and people just stepping over him, assuming he was drunk. He was also airlifted once from Hever Castle due to an attack in his larynx. I had another fast moving attack and had to drive 30 minutes to hospital. By the time I reached the car park I couldn't walk, colapsed on the floor, vomited, my limbs locked, my vision went completely (I believe due to hyperventilation tetany as part of an acute attack) Thankfully someone ran to get help and hospital staff were able to get me in and to recognise me as I was so regular there, and treat me. This is a really stressful and dangerous way to live. I currently have 1-2 attacks a week. I take tranexamic acid and treat attacks with Berinert. I am now able to treat at home (or indeed out and about, which I've had to do on many occasions) Without this safety net, I had to constantly be thinking about how far away I was from hospital and whether I could get to treatment in time. Being able to treat attacks myself is so much better. It has made a huge difference in my quality of life. I suspect that with my attacks as regular as they currently are, if I had to go to hospital every time for treatment, I'd struggle to remain working (I'm a counsellor so this would mean lots of last minute cancellations, a damage to the therapeutic relationship, and ultimately impacting whether I am safe to practice) I don't have enough attacks to proactively treat with Berinert, but I would love to be in a position to be able to treat proactively, and be less concerned about when my next attack will come and how I might find time and appropriate space to be able to treat. I am aware through HAE UK that treatments that for some are really effective, for others are much less so or have difficult side effects. To have an increase in options available would be	Thank you for your comment. The appraisal committee recognised that there is an unmet need for more effective treatment options (see section 3.1 of the FAD). The committee concluded that although all cost-effectiveness estimates for lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers an acceptable use of NHS resources. Given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the cost-effectiveness results.

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			extremely benefitial in managing what is a very difficult condition.	
33	Web comment		This drug is a life changer for the likes of myself who suffer from HAE. I have been able to live my life and forget that I have hae. I've been able to plan days out with my family. I've also been abroad on holidays. This drug has just not changed my life but it's changed the lives of my family to. Time away from work due to hae attacks is a thing of the past due to this drug. I cannot shout this out enough and say how brilliant it is. But it's simply fantastic.	Thank you, your comments have been noted. The committee concluded that although all cost-effectiveness estimates for lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers an acceptable use of NHS resources. Given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the cost-effectiveness results.
34	Web comment		I have very severe HAE and am on C1 injections in my veins every day. My veins are not good and they are getting painful. This new medication would change my life as I am now 67 and can't go on this way. My mental health has deteriorated and my husband is 71 with a heart condition an d the stress on both of us is immense. We would be able to do so much more with0ut the restrictions of daily infusions. My anxiety and depression would definitely improve. We know people in other countries that have told us the difference in their lives this news medication has made. One person said they were on the brink of suicide and now have a happy and fulfilled family life. Please, please consider the life changing effect this would make to people as seriously affected as I am. No other treatment works so please give us hope for the future.	Thank you for your comment. The appraisal committee recognised that there is an unmet need for more effective treatment options (see section 3.1 of the FAD). The committee concluded that although all cost-effectiveness estimates for lanadelumab compared with C1-INH are highly uncertain, most estimates are within the range NICE normally considers an acceptable use of NHS resources. Given the company's proposed positioning, lanadelumab is only recommended for people who are currently eligible for long-term prophylactic C1-INH treatment in the NHS. The committee also considered that the lowest dosing frequency of lanadelumab should be used in line with the summary of product characteristics because this has a large impact on the

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				cost-effectiveness results. The impact of lanadelumab on health-related quality of life was included in the model and this included an additional benefit for subcutaneous administration (see section 3.16 of the FAD).

NICE National Institute for Health and Care Excellence

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 19 July 2019 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Shire, now part of Takeda
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
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Comment number	**Comments** Insert each comment in a new row.

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NICE National Institute for Health and Care Excellence

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Executive Summary Shire, now part of Takeda, is disappointed to see a provisional negative recommendation for lanadelumab and hopes the additional evidence and analyses provided as part of this consultation will support a final positive recommendation for lanadelumab. The company recognises the lack of long-term data inherent in the evidence base for rare conditions and related to the accelerated regulatory timelines, leading to uncertainty in some parameters and assumptions. The appraisal consultation document (ACD) identifies three elements for which uncertainty remains in the evaluation of the cost-effectiveness of lanadelumab: (i) the Berinert dosing used in clinical practice, (ii) the actual proportion of patients who would switch to the 4-weekly (Q4W) administration of lanadelumab, and (iii) the comparator cost to use in the model. With our responses and additional evidence submitted, we aim to reduce the uncertainty the committee may have on the outstanding issues. Any outstanding uncertainty should be considered against the conservative assumptions in the cost-effectiveness model, which were incorporated to ensure a conservative approach in the presence of limitations of data: • no survival benefits due to the prevention of potentially fatal laryngeal attacks; this was raised as an important issue at the first appraisal committee meeting • no impact of lanadelumab on the severity of attacks, while trial data showed a significant reduction in severe attacks with lanadelumab • no benefits in terms of caregiver quality of life (QoL), which at the first appraisal committee meeting was described by the patient experts as a significant aspect • the selection of the shortest duration of attacks ([redacted]) vs longer estimates from other arms of the HELP-03 trial or from the CHANGE trial, also considering the testimony of the patient representatives at the committee meeting (over 2 days of duration, as reported in section 3.1 of the ACD) • Cinryze is used in the model at its licensed dose, [redacted] While no data source is perfect, the company believes the revised base case provided as part of the ACD consultation is based on the most robust data available. Furthermore, the company has increased the discount level through a simple patient access scheme (PAS), which should help minimise the uncertainty over the cost-effectiveness of lanadelumab.
2	Dosing of Berinert Further to the issues raised at the first committee meeting, the company has revised the base-case analysis in line with the information reported below. The results of this analysis show that lanadelumab is cost-effective using both the overall HELP-03 population and the more severe population (i.e. at least 8 attacks per month). On page 4 of the ACD it is reported that "*it is unclear what dose of Berinert (a C1-INH) is used in clinical practice*" while point 3.13 concludes that "*there is substantial uncertainty around the dosing*

schedule for Berinert but that a rounded fixed dose of 1,000 IU is the mostly likely to reflect NHS practice."

The latter statement in particular contradicts the general opinion of clinicians practicing in England and Wales:

- At the first committee meeting, the clinical expert explained that a pragmatic approach is adopted and as a result some rounding occurs when calculating the required and actual dose used for Berinert.

  The company believes the example reported in the ACD is only illustrative of one specific case (i.e. the example of a patient requiring 1,100IU) and it would be incorrect to assume every rounding leads to an actual 1,000IU dose. Based on the weight-based dosing, most patients in actual practice require a dose higher than 1,000IU.

- In addition to clinical expert interviews conducted by the company to inform the original submission[1] that confirmed Berinert is used on a weight-based dosing, the company recently conducted two virtual advisory panel meetings and eight individual calls involving 22 clinicians during which they were asked about Berinert dosing in practice with specific focus on the rounding of dose.[2] The detailed report has been added to Appendix A of the company's ACD comments.

  The feedback received represents 72% of specialist centres for HAE in England and Wales treating [redacted] patients on long term prophylaxis with C1-INH of which [redacted] were treated with Berinert. The clinical experts stated that [redacted] of Berinert treated patients were receiving a dose [redacted] with Berinert most commonly dosed according to weight [redacted]

  The clinical experts also confirmed that [redacted]. Dependent on the weight-based estimate of the required dose, the actual dose is [redacted] due to Berinert being available in 500IU vials. [redacted]

  Experts also indicated that [redacted]

- Additional information from clinical experts is that [redacted]. This is conservatively not included in the model base case.

In the company's revised cost-effectiveness model, the pragmatic approach of rounding Berinert dosing is applied based on the advice received by the clinical expert at the NICE committee meeting [redacted] This rounding approach uses the midpoint between the closest multiples of 500IU as the threshold for rounding up or down.

In an alternative scenario analysis, the specific dosing regimens for Berinert reported by the experts participating in the Advisory Boards and interviews were used as a weighted average to inform this parameter in the model.

[1] Shire. Discussion Guide – KOL advisory discussions to inform NICE and SMC submissions for lanadelumab for the treatment of hereditary angioedema, 2018.
[2] Takeda. ACD Panel Research Report, 2019.

	The results of both the revised base case and scenario analysis show that lanadelumab is cost-effective using both the overall HELP-03 population and the severe subgroup with at least 8 attacks per month. The ERG referenced a registry publication[3] as evidence supporting the use of Berinert in a fixed dose of 1,000IU. The company has reviewed this publication and noted the following limitations, which makes this source unrepresentative of current practice in the UK: - The registry includes no UK data, with the majority of centres being in the USA (30); the rest in 7 European sites (Germany, 5; Denmark, 1; Switzerland, 1) - Data were collected between 2010 and 2014 and is outdated considering that disease management has changed in the interim - The study only reports the median dose of 1000IU while the average dose across the patient population is more representative for the purpose of calculation in the model. As the range reported is between 500 and 3,000IU, this demonstrates that the data is skewed and therefore that the median is not representative of the mean, which is likely to be greater than the median. For these reasons, using this publication to inform current practice data would be inappropriate. Finally, the ACD notes that the randomised control trial (RCT) informing the indirect treatment comparison (ITC) used in the model is on the 1,000IU dose of C1-esterase inhibitors (C1-INH). However, it fails to mention that the original company's submission provided a scenario analysis where the effectiveness of Berinert was increased to reflect the potentially average higher dose compared to the dose for which clinical effectiveness data are available. The same analysis is presented in the updated model results submitted as part of the ACD consultation. The results of this analysis show that lanadelumab remains dominant at any value or the rate ratio of Berinert vs placebo explored in the analysis (range 0.1 to 1.0), both in the full HELP-03 population and in the more severe population (i.e. with at least 8 attacks per month).
3	<u>Proportion of patients on lanadelumab switching to the Q4W dosing in the long-term</u> The proportion of patients who would be receiving the Q4W dosing frequency was one of the issues highlighted at technical engagement stage. In response to the technical engagement questions asked by NICE, clinical experts and patient representatives confirmed willingness on both sides to reduce dosing frequency when patients are attack-free, supporting the plausibility of the company's approach to estimating the proportion of patients on lanadelumab that would switch to the Q4W dosing frequency. This is also noted in point 3.14 of the ACD: "*The clinical experts explained that it was clinically plausible that 77% of people would have their dosing frequency reduced, though noted that this is difficult to predict.*" The committee argued that some patients who are attack-free would choose not to reduce their dosing schedule; however, this seems to be in conflict with the patient experts' view heard at the committee meeting suggesting a willingness and desire to move to a more infrequent administration and expressed as part of the technical engagement consultation. Noting the committee's uncertainty around this estimate, the company has sought further clinical opinion on this issue through two virtual advisory board panels and eight individual calls involving 22

[3] Craig T, Shapiro R, Vegh A, et al. Efficacy and safety of an intravenous C1-inhibitor concentrate for long-term prophylaxis in hereditary angioedema. *Allergy Rhinol (Providence)*. 2017; 8: 13-9.

	clinical experts including 13 consultant immunologists and 9 specialist nurses, representing 72% (n=16) of the specialist centres for HAE across England and Wales. The clinical experts [redacted]; in fact, 44.8% of patients in the Q4W arm of the HELP-03 trial were completely attack free at steady state. Four clinicians felt confident to suggest a proportion that may be managed on a four-weekly dosing schedule and gave a range of [redacted]. Data on the proportion of patients who are stably attack-free on Q2W are available from the HELP-03 trial; showing that 77% of patients in the Q2W arm were stably attack-free once lanadelumab achieved steady state (day 70). In practice, [redacted],[4] it is possible that the number of patients who are "stably" attack-free may exceed the 77% estimate. Recognising that the committee may still have some uncertainty over this estimate, the company has conducted a scenario analysis whereby the proportion of attack-free patients is based on a mid-point between the attack-free patients from both the Q2W arm and the Q4W arms of the HELP-03 trial (61%). This lower figure represents a pragmatic approach to model the proportion of patients who will be switched as stably attack-free based on clinical opinion but also allows for not all patients who were attack free on Q2W moving to Q4W. The results of this analysis show that the ICER for lanadelumab vs C1-INH in the overall HELP-03 population is £31,061 per QALY, while lanadelumab is dominant vs C1-INH in the subgroup with at least 8 attacks per month.
4	<u>Tender prices</u> Section 1 of the ACD states that "*discounted price of C1-INH treatments paid by the NHS is not currently included in the cost-effectiveness results. Therefore, all estimates of cost effectiveness for lanadelumab compared with C1-INH are highly uncertain*." While it is true that the NHS procures C1-INH through a tender process, and the NHS likely pay lower than list prices, it is important to note that a tender is a procurement process with the tender price applied for a limited period of time and subject to fluctuation. This may be particularly relevant for plasma-derived C1-INHs where supply constraints may have an impact on pricing. The company highlights that there will be a new C1-INH tender in place for the start of 2020 and that current C1-INH prices are likely to be updated. Tender prices for C1-INH therefore should be considered unreliable to inform long-term cost-effectiveness analyses. Moreover, as company is not aware of the tender prices for the overall C1-INH comparator due to confidentiality, it could not incorporate these in any scenario analyses.
5	<u>ITC vs Poisson regression</u> As stated in point 3.6 of the ACD, the committee "*concluded that using the indirect treatment comparison to inform attack rates for both lanadelumab and C1-INH is the more consistent and robust approach*".

[4] Takeda. ACD Panel Research Report, 2019.

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	The company disagrees with the conclusion that this is a more robust approach because – as noted in section B.2.6, page 66, of the original company's submission – lanadelumab reaches its steady state after day 70 and therefore it is important to capture the change in lanadelumab's clinical efficacy over time, which the ITC estimate fails to do. The Poisson regression, on the other hand, estimates more precisely the number of attacks with lanadelumab at each cycle and outputs an attack frequency that matches more closely the observed data in the trial compared to the ITC estimate. Additionally, as patient-level data over multiple time points is available from HELP-03 it is appropriate to make use of this data, whereas similar data is not available for C1-INH and therefore requires the use of the ITC. While the company believes that using the Poisson regression to model the clinical effectiveness of lanadelumab remains the correct approach, it is willing to accept the committee's preference in order to present a more conservative approach. Therefore, the ITC informs both arms of the revised base case model. A scenario analysis where the Poisson regression is informing the clinical effectiveness of lanadelumab is presented in the revised analysis document. This shows lanadelumab is dominant in both scenarios. .
6	**New base case and results** Upon consideration of the committee preferred analysis noted within section 3.18 of the ACD, the company has adjusted the base-case settings of the cost-effectiveness analysis as follows: - New PAS based on the recent update in the confidential discount - Use of ITC to inform both arms as per point 5 above - Results presented for the full HELP-03 population and the subgroup of people with at least 8 attacks in the previous 4 weeks - assuming C1-INH is a subsequent treatment if lanadelumab is stopped, and C1-INH that is continued over a lifetime - Using a rounding approach for Berinert dosing as per point 2 above together with the most common dose ([redacted] twice weekly) The new base-case is fully detailed in the separate document. The new base-case generates [redacted] incremental QALYs and savings of [redacted] in the full HELP-03 population, and [redacted] incremental QALYs and savings of [redacted] in the more severe subgroup, for lanadelumab versus C1-INH, showing lanadelumab is dominant compared to C1-INH.
7	**Factual accuracy check** The following points within the ACD have been noted as factually inaccurate or not fully reflective of the evidence base. We would request that for future documents the text is corrected. • On page 9 it is reported that "*At the appraisal committee meeting, the company advised that 3 ongoing studies (1 in the USA, 1 in Europe and 1 in France) were collecting data on the lower frequency dosing schedule*". It would be more accurate to state that "*At the appraisal committee meeting, the company advised that 3 ongoing studies (1 in the USA, 1 in Europe and 1 in France) were collecting data on the real-world use of lanadelumab including both licenced dosing schedules"*.

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	• Section 3.2 reports that "After technical engagement, the company positioned lanadelumab for the population currently eligible for long-term prophylactic C1-INH in the NHS England commissioning policy." This is not correct as the company had already clarified the positioning while responding to the ERG clarification questions in January 2019.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Initiate.

Lanadelumab▼ NICE ACD Advisory Panel

[redacted]

Initiate.

Table of Contents

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Abbreviations

ACD	Appraisal Consultation Document
C1-INH	C1-Esterase inhibitor
HAE	Hereditary angioedema
IV	intravenous
NICE	National Institute for Health and Care Excellence

Cinryze®▼ (C1 inhibitor (human)) is a registered trademark of Shire Pharmaceuticals Limited, which is now part of Takeda

Berinert® is a registered trademark of CSL Behring GmbH.

Initiate.

Executive Summary:

In response to the Appraisal Consultation Document (ACD) issued by National Institute for Health and Care Excellence (NICE) for lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268], Takeda have commissioned research to inform their commentary to this ACD.

In order to fully respond to the points raised by the ACD, this research sought to explore C1-esterase usage and dosing in the UK setting and clarify the clinical plausibility of 4 weekly dosing of lanadelumab.

22 respondents have participated in this research, covering 16 HAE treatment centres in England and Wales.

The proportion of patients who receive Cinryze®▼ (C1 inhibitor (human)) and the proportion who receive Berinert® is described below in Table 1. These patients all meet the NHS England clinical commissioning policy criteria for long term C1 esterase inhibitor prophylaxis.

Table 1: Summary of HAE Prophylaxis Use

Use of HAE Prophylaxis	Total number of patients	%
HAE Patients on prophylaxis	[redacted]	[redacted]
HAE Patients on Berinert® for prophylaxis	[redacted]	[redacted]
HAE Patients on Cinryze®▼for prophylaxis	[redacted]	[redacted]

Clinicians report that [redacted] of patients receive Berinert® and [redacted] receive Cinryze®▼.

1000 IU of Cinryze®▼ every 3 or 4 days is the recommended starting dose for routine prevention (prophylaxis) against angioedema attacks; the dosing interval may need to be adjusted according to individual response (Cinryze SPC, 2019).

For patients who receive Berinert® as a prophylactic treatment, there is variation of weight-based dosing [redacted] and dosing based on individual needs, as described in Table 2 (Berinert SPC, 2019).

Table 2: Berinert® Dosing

Berinert® Dosing	Total number of patients	%
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

The most commonly used dosing regimen is [redacted]. The assumption of the NICE committee which defined utilisation of a fixed dose of 1000 units of Berinert® twice weekly, is not representative of clinical practice for [redacted] of the patients discussed in this research.

In calculating the weighted average weekly dose, we can see from the [redacted] cases, that an average weekly consumption is [redacted] units.

When considering lanadelumab, [redacted]. Stably attack free was defined by the majority of clinicians as after approximately [redacted]. At this point clinicians [redacted]. Clinicians did state that they would individualise frequency depending on a patient's circumstances.

[redacted].

[redacted].

Clinicians who felt confident to suggest a proportion that may be managed on a 4 weekly dosing schedule gave a range of [redacted].

Initiate.

Background and Objectives

Lanadelumab is currently in the National Institute for Health and Care Excellence (NICE) appraisal process (lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]). NICE have raised a number of questions around the hereditary angioedema (HAE) market and have issued an Appraisal Consultation Document (ACD).

Following NICE's preliminary decision not to recommend lanadelumab for use in the NHS this research sought to respond to these points and test the clinical plausibility of modelling data. Advisory panel meetings and/or one-to-one consultations were held to seek opinion.

This research was designed to explore C1-Esterase usage and dosing in the UK setting and clarify the clinical plausibility of 4 weekly dosing of lanadelumab.

Research Methodology

61 Consultant Immunologists and 48 Specialist Immunology nurses from 28 centres with a known interest and expertise in HAE were invited to participate in the advisory panel.

There were 22 respondents:

- 9 Specialist Nurses
- 13 Consultant Immunologists

Covering 16 specialist centres across England and Wales, this represents 72% of specialist centres for HAE.

Two virtual advisory board panels were conducted on 10th July 2019 (10 participants) and 15th July 2019 (4 participants), with an approximate duration of one hour for each session. In addition, eight individual calls were conducted with clinicians, all sessions shared the same agenda and discussion points.

All participants received an honoraria payment for their participation in line with fair market values.

The discussion guide concentrated on seeking individual opinion on C1-Esterase (C1-INH), its usage and dosing in the UK setting to gain a representative picture of utilisation in the UK to inform the ACD process. The second focus of the discussion was to consider lanadelumab dosing and the potential to move from 2 weekly to 4 weekly dosing.

The key discussion areas of the research were:

C1 Esterase Inhibitor

- The number of patients who receive C1 esterase inhibitors, Cinryze®▼ or Berinert® in line with the NHS England clinical commissioning policy criteria for prophylaxis
- Berinert® as a prophylactic treatment and its dosing
- How would you choose the number of vials to use?

- How frequently do patients administer their treatment?
- Changes to the dose (in terms of units and frequency) over time

Lanadelumab dosing

- When would you consider a patient 'Stably Attack Free'?
- How important would a reduction in dosing be to a patient and their quality of life?
- What proportion of patients would you consider being able to maintain this status on 4 weekly dosing?

Initiate.

C1-Esterase Inhibitor utilisation in prophylaxis

Quantitative findings

The proportion of patients who receive Cinryze®▼ (C1 inhibitor (human)) and the proportion who receive Berinert® (clinical commissioning policy criteria) is described below in Table 3.

Table 3: Summary of HAE Prophylaxis Use

Use of HAE Prophylaxis	Total number of patients	%
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Clinicians report that [redacted] of patients receive Berinert® and [redacted] receive Cinryze®▼.

For patients who receive Berinert® as a prophylactic treatment, there is variation of weight based dosing [redacted], as described in Table 4.

Table 4: Berinert® Dosing

Berinert® Dosing	Total number of patients	%
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

The most commonly used dosing regimen is [redacted].

The assumption of the NICE committee which defined utilisation of a fixed dose of 1000 units of Berinert® twice weekly for prophylaxis is not representative of clinical practice for [redacted] of the patients discussed in this research.

When we consider the dose of Berinert® used in current clinical practice we can simulate an average weekly, unit consumption. In order to do this, we have discounted the 3 patients for whom dosing was classed as an 'other' as we simply do not have enough information to include these cases. These cases were all described as utilising [redacted] but insufficient clarity was given for inclusion in an average calculation.

The average patient weight used in this calculation is [redacted], calculated as a weighted average of the average weight of females and males, and the ratio of females to males

(70.4% versus 29.6%) as reported in the HELP-03 trial (Clinical Study Report, SHIRE PHARMACEUTICALS, 2017).

In calculating the average weekly dose, we can see from the [redacted] cases, that an average weekly consumption is [redacted] units.

Table 5: Berinert® Dosing weekly average consumption

Berinert Dosing	Total number of patients	Infusion weekly total (units)	Sum total weekly units (units, all patients)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]

Qualitative findings

The key discussion points of the research are presented below together with a summary of the findings and respondent quotes.

Berinert® as a prophylactic treatment

Fixed based dosing of Berinert® is not demonstrated by clinical practice which was either weight-based dosing of [redacted].

[redacted]

Respondent 16

Most respondents reported patients on [redacted]

[redacted]

Respondent 3

[redacted]

Respondent 23

[redacted]

Respondent 5

[redacted]

Respondent 10

How would you choose the number of vials to use?

[redacted]

Respondent 9

[redacted]

Respondent 5

How frequently do patients administer their treatment?

Treatment is individualised to the patient, so [redacted]

Respondent 6

[redacted]

Respondent 17

[redacted]

[redacted]

Respondent 18

How would you change the dose (in terms of units and frequency) over time?
Dosage is individualised to the patient and their needs and reflects their number of break through attacks, tolerance of intravenous (IV) and current risk of attacks

[redacted]

Respondent 8

[redacted]

Respondent 15

Lanadelumab dosing

When would you consider a patient 'Stably Attack Free'?

The definition of being 'stably attack free' resulted in a discussion over whether being [redacted].

Clinicians found it hard to define a percentage of patients they would be able to reduce the dose with, as there is limited data and experience in this area and the individual patient's circumstances would need to be considered. [redacted]

Stably attack free was defined by the majority of clinicians as [redacted] Clinicians did state that they would individualise frequency depending on a patient's circumstances.

[redacted]

Respondent 22

[redacted]

Respondent 14

[redacted]

Respondent 13

[redacted]

Respondent 1

When do you expect you would reduce lanadelumab dose?

[redacted]

[redacted]

Respondent 5

[redacted]

Respondent 3

[redacted]

[redacted]

Respondent 22

[redacted]

Respondent 2

[redacted]

[redacted]

Respondent 16

Considering the 4-weekly dosing, how important would a reduction in dosing be to a patient and their quality of life?

[redacted]

[redacted]

Respondent 6

[redacted]

Respondent 15

[redacted]

Respondent 13

What proportion of patients would you consider being able to maintain this status on 4 weekly dosing?

Respondents found this question difficult to answer as there is limited experience of lanadelumab in the clinical community. The group have asserted that confidence will come with use and experience of the product.

[redacted]

One clinician discussed his experience of patients on lanadelumab post open label extension phase of a trial where [redacted]

Clinicians who felt confident to suggest a proportion that may be managed on a 4 weekly dosing schedule gave a range [redacted]

References:

Berinert SPC. (2019). Berinert 500 IU Powder and solvent for solution for injection / infusion.

Cinryze SPC. (2019). Summary of Product Characteristics, Cinryze 500 IU powder and solvent for solution for injection.

Clinical Study Report, SHIRE PHARMACEUTICALS. (2017). 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).

Revised cost-effectiveness analyses in response to:

National Institute for Health and Care Excellence

Appraisal Consultation Document – Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

Takeda UK Ltd

19 July 2019

Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for the ongoing single technology appraisal (STA) for lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268].

We are disappointed that the committee have given a provisional 'not recommended' decision and we wish to present some further evidence and analyses reflecting the committee's preference and conclusions from the ACD. In addition, the company has also revised the patient access scheme related to this appraisal.

Some of the issues highlighted in the ACD are discussed in our response document, however additional detail is provided here alongside the revised base-case economic analysis.

We hope that this additional evidence plus the new analysis will ensure that a positive recommendation is now achievable.

Yours sincerely,

Shire, now part of Takeda

1. Berinert dosing

Clinical expert interviews conducted by the company to inform the original submission suggested that Berinert is used on a weight-based dosing[1], therefore this approach was used in the original submission.

Further to the concerns raised by the committee at the committee meeting on 6 June 2019, the company has sought further clinical opinion about the Berinert dosing used in clinical practice; conducting two online Advisory Board meetings and series of individual consultation interviews. As a result, 22 clinical experts were asked about Berinert dosing in practice, with specific focus on the rounding of dose units.

There was agreement from the clinical advisors that Berinert is dosed [redacted].

The participating clinical experts explained that [redacted]. In the company's revised base case cost-effectiveness model, the pragmatic approach of rounding Berinert dosing is applied based on the advice received by the clinical expert at the NICE committee meeting [redacted].

In an alternative scenario analysis, the specific dosing regimens for Berinert reported by the clinical experts were used as a weighted average to inform this parameter in the model. The dosing details are reported in Table 1 below and results are reported in Section 4.
The results of both the revised base-case and scenario analysis show that lanadelumab is cost-effective using data from both the overall HELP-03[2] population and the severe population subgroup with at least 8 attacks per month.

[1] Shire. Discussion Guide – KOL advisory discussions to inform NICE and SMC submissions for lanadelumab for the treatment of hereditary angioedema, 2018.
[2] Banerji A RM, Bernstein JA, Cicardi M, Longhurst HJ, Zuraw BL, Busse PJ, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks A Randomized Clinical Trial. JAMA. 2018; 320: 2108-21

Table 1 - Berinert dosing as reported by clinical experts*

Berinert Dosing	Total number of patients	Infusion weekly total (units)	Sum total weekly units (units, all patients)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]			[redacted]

* Attendees at two Advisory Board and consultation interview participants

Since the randomised control trial (RCT) informing the indirect treatment comparison (ITC) used in the model is based on the 1,000IU dose of C1-esterase inhibitors (C1-INH), the company's original submission provided a scenario analysis, where the effectiveness of Berinert was increased to reflect a potentially higher average dose compared to the dose for which clinical effectiveness data are available. This same analysis is presented in Section 4 and shows that lanadelumab remains dominant at any value of rate ratio of Berinert vs. placebo explored in the analysis (range 0.1 to 1.0), both in the full HELP-03 population and in the more severe population (i.e. with at least 8 attacks per month).

2. Proportion of patients switching to Q4W in the long term

Noting the committee's uncertainty around this estimate, the company has sought further clinical opinion on this issue through two online Advisory Board and a series of individual consultation interview involving 22 clinical experts including 13 consultant immunologists and 9 specialist nurses, covering 16 specialist centres for HAE across England and Wales.

[redacted] Clinicians who felt confident to suggest a proportion that may be managed on a four-weekly dosing schedule gave a range of [redacted].

Data on the proportion of patients who are stably attack-free on Q2W are available from the HELP-03 trial; showing that 77% of patients in the Q2W arm were stably attack-free once lanadelumab achieved steady state (day 70). In practice, [redacted],[3] it is possible that the number of patients who are "stably" attack-free may exceed the 77% estimate.

Recognising that the committee may still have some uncertainty over this estimate, the company have conducted a scenario analysis whereby the proportion of attack-free patients is based on a mid-point between the attack-free patients from both the Q2W arm and the Q4W arms of the HELP-03 trial (61%).

[3] Takeda. ACD Panel Research Report, 2019.

This lower figure represents a pragmatic approach to model the proportion of patients who will be switched as stably attack-free, as it is based on clinical opinion but also considers not all patients who were attack-free on Q2W moving to Q4W.
The results of this analysis are presented in Section 4 and show that the ICER for lanadelumab vs. C1-INH in the overall HELP-03 population is £31,061 per QALY, while lanadelumab is dominant vs. C1-INH in the severe subgroup with at least 8 attacks per month.

3. Revised base case analysis

Upon consideration of the committee-preferred analysis noted within Section 3.18 of the ACD, and points agreed on at previous stages in the appraisal, the company has made a number of adjustments to the original base-case settings of the cost-effectiveness analysis; these are detailed in Table 2 below.

Table 2 - Company's base-case revisions at ACD stage

Assumption	Original base-case	Revised base-case
Lanadelumab price	Simple PAS discount of [redacted] on list price	Simple PAS discount of [redacted] on list price
Discontinuation	A percentage of patients are assumed to discontinue both lanadelumab and C1-INH	A percentage of patients are assumed to discontinue lanadelumab while all patients receiving C1-INH are assumed to remain on treatment given the lack of alternative treatment options
Population	Full HELP-03 population	Full HELP-03 population and severe subgroup from HELP-03 with at least 8 attacks over 4 weeks
Adjustments for discontinuation	No adjustments to costs, efficacy and utility estimates are made for treatment discontinuation	The following are adjusted for treatment discontinuation: Lanadelumab attack rate Subcutaneous treatment utility benefit Acute attack treatment costs
Subsequent treatment	No subsequent treatment costs are captured	Patients who discontinue lanadelumab are assumed to receive C1-INH
Hospitalisation cost	A daily hospitalisation cost of £2,961 is applied for the proportion of patients who have an inpatient stay due to experiencing an attack	A revised cost of £455 is applied
Berinert dosing	All patients are assumed to receive a dose of [redacted] with vial wastage applied	All patients have a target dose of [redacted] with pragmatic dose rounding applied to ensure there is no vial wastage
Lanadelumab attack rate method	The attack rate of lanadelumab is estimated through a Poisson regression utilising patient-level data from HELP-03	The attack rate is estimated by applying rate ratios estimated from an ITC to the placebo arm attack rate estimates from HELP-03

The results of the new base-case analysis are presented in Table 3 and Table 4 below and show that lanadelumab is more effective and less costly than treatment with C1-INH.

Table 3: Revised base-case results (HELP-03 population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NMB (£)
C1-INH	[redacted]	21.48	[redacted]	[redacted]	[redacted]	Dominant	£379,506
Lanadelumab	[redacted]	21.48	[redacted]				
Key: C1-INH, C1 esterase inhibitor; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Table 4: Revised base-case results (≥8 attack population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NMB (£)
C1-INH	[redacted]	21.48	[redacted]	[redacted]	[redacted]	Dominant	£654,306
Lanadelumab	[redacted]	21.48	[redacted]				
Key: C1-INH, C1 esterase inhibitor; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

4. Scenario analyses

A series of scenario analyses were conducted as part of the ACD comments; these include:

- Using a lower proportion of patients switching to Q4W (Table 5 and Table 6)
- Applying the Poisson regression to model lanadelumab effectiveness (Table 7 and Table 8)
- Analysis exploring the impact of changing Berinert effectiveness on the cost-effectiveness results (Table 9)
- Using the dosing of Berinert described by clinicians participating in the recent Advisory Boards and interviews (Table 10 and Table 11)

The results of these scenario analyses show that lanadelumab is a cost-effective treatment for patients with HAE who are eligible for long-term prophylactic treatment with C1-INH.

Table 5: 60.9% switching to Q4W (HELP-03 population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NMB (£)
C1-INH	[redacted]	21.48	[redacted]	[redacted]	[redacted]	£31,061	-£674
Lanadelumab	[redacted]	21.48	[redacted]				
Key: C1-INH, C1 esterase inhibitor; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Table 6: 60.9% switching to Q4W (≥8 attack population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NMB (£)
C1-INH	[redacted]	21.48	[redacted]	[redacted]	[redacted]	Dominant	£292,249
Lanadelumab	[redacted]	21.48	[redacted]				
Key: C1-INH, C1 esterase inhibitor; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Table 7: Applying Poisson regression (HELP-03 population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NMB (£)
C1-INH	[redacted]	21.48	[redacted]	[redacted]	[redacted]	Dominant	£432,600
Lanadelumab	[redacted]	21.48	[redacted]				
Key: C1-INH, C1 esterase inhibitor; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Table 8: Applying Poisson regression (≥8 attack population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NMB (£)
C1-INH	[redacted]	21.48	[redacted]	[redacted]	[redacted]	Dominant	£837,664
Lanadelumab	[redacted]	21.48	[redacted]				
Key: C1-INH, C1 esterase inhibitor; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Table 9: Threshold analysis – rate ratio of Berinert IV [redacted]

Rate ratio vs placebo	HELP-03		≥ 8 attacks	
	ICER	NMB	ICER	NMB
Base case (0.492)	Dominant	£379,506	Dominant	£654,306
0.1	Dominant	£172,081	Dominant	£203,369
0.2	Dominant	£226,763	Dominant	£320,241
0.3	Dominant	£279,869	Dominant	£435,521
0.4	Dominant	£332,096	Dominant	£549,908
0.5	Dominant	£383,780	Dominant	£663,738
0.6	Dominant	£435,106	Dominant	£777,196
0.7	Dominant	£486,183	Dominant	£890,391
0.8	Dominant	£537,079	Dominant	£1,003,392
0.9	Dominant	£587,839	Dominant	£1,116,243
1.0	Dominant	£638,495	Dominant	£1,228,976
Key: ICER, incremental cost-effectiveness ratio, NMB, net monetary benefit.				

Table 10: Berinert clinical practice dosing (HELP-03 population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NMB (£)
C1-INH	[redacted]	21.48	[redacted]	[redacted]	[redacted]	Dominant	£166,024
Lanadelumab	[redacted]	21.48	[redacted]				
Key: C1-INH, C1 esterase inhibitor; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Table 11: Berinert clinical practice dosing (≥8 attack population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NMB (£)
C1-INH	[redacted]	21.48	[redacted]	[redacted]	[redacted]	Dominant	£444,840
Lanadelumab	[redacted]	21.48	[redacted]				
Key: C1-INH, C1 esterase inhibitor; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Taking all factors into account, Takeda is optimistic that the steps we have taken in this ACD response can reduce the clinical uncertainty felt by the Committee and allow the Committee to conclude on the most plausible cost-effectiveness range and recommend lanadelumab for use within the NHS in England and Wales.

Such an outcome would allow patients and the NHS to benefit from timely access to lanadelumab as a treatment option for preventing recurrent attacks of HAE. With that objective in mind, Takeda remains committed and willing to working constructively with NICE, and if necessary other stakeholders, to secure a positive outcome from this appraisal.

NICE National Institute for Health and Care Excellence

Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 19 July 2019 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	HAE UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The comparator of C1 Esterase Inhibitor treatment is difficult to quantify because even patients receiving prophylactic C1-INH under the NHS England Commissioning report having breakthrough attacks of Hereditary Angioedema and so are not attack free. They then have to use more C1-INH to treat an attack or in order to remain attack free they shorten the interval between doses but in either case use more C1-INH that is calculated on merely assessing the numbers of patients receiving C1-INH prophylaxis. There is also the issue that patients receiving Berinert are dosed on an iu/kg weight basis and so the dose may be higher than that specified in the NHS England document which only deals with Cinryze using a fixed dose. I therefore think that the cost comparision is underestimating the cost of C1-INH per patient.
2	This product is a subcutaneous injection, which even used every fortnight is very quick and easy to administer. This has the double effect of making the product available to patients who are unable to administer C1-INH because of physical or practical issues such as poor venous access, and also means this is an much easier product for patients leading a less structured lifestyle, for example students or travellers. Use of intravenous C1-INH, whilst effective and many patients are able to successfully self-treat, requires a suitable environment for administration, and considerable time is taken to reconstitute the product, carry out the venepuncture and infuse the product. It is then recommended that the patient rests for at least 30 minutes after infusing. This all results in a considerable amount of time being devoted to this twice a week instead of a short time once a fortnight, or even monthly once patient established on treatment.
3	The psychological effect of patients living with the fear of attacks and also the ever present fear of a shortage of C1-INH (which happens all too frequently, despite the best efforts of the supplier companies) means that patients live in a state of constant anxiety. This in turn exacerbates their attacks. The most beneficial effect for them is to have treatment in which they have confidence and which they know will be available without the arbitrary supply issues which affect plasma derived products.
4	The clinical data shows that many patients respond well to Lanadelumab and it is of considerable benefit to these patients. It is now widely used in Europe and the US and to deny access to patients in England is putting us at a considerable disadvantage to these other countries.
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Insert extra rows as needed

Checklist for submitting comments

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- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted,

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please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Comments on NICE Appraisal Consultation Document for the Single Technology Appraisal on lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

British Association of Dermatologists
Therapy & Guidelines sub-committee

[redacted]

Hereditary angioedema (HAE) is due to C1 esterase inhibitor deficiency (Types 1 or 2) but also occurs in patients with normal C1 esterase inhibitor. HAE with normal inhibitor has been linked with mutations in genes for Factor XII, plasminogen and angiopoeitin but the underlying mutation in other patients is unknown. The HELP-03 study population was drawn from patients with Type 1 or Type 2 HAE so the analysis and implementation of the technology appraisal should be confined to HAE types 1 and 2 and clearly stated as such.

HAE presents with angioedema without weals. Angioedema without weals may also be a presentation of chronic spontaneous urticaria (CSU). CSU is considerably more common than HAE but angioedema probably never results in asphyxiation and can be expected to remit naturally whereas HAE may cause death from asphyxiation in a few individuals[1] and is potentially life long.

The aim of treatment of HAE should be complete disease control to prevent a risk of asphyxiation and improve quality of life.

The only licensed treatment for long-term prophylaxis of patients 6 years and older with HAE types 1 and 2 in the UK is **Cinryze** (C1 esterase inhibitor) by intravenous administration. Berinert (C1 esterase inhibitor) is licensed for treatment and pre-procedure prevention of acute attacks of HAE but not for long-term prophylaxis even though it is commonly used off licence for this. The correct financial comparator for lanadelumab should therefore be Cinryze rather than Berinert, despite estimated lower NHS usage (section 3.12).

Self-administration by subcutaneous injection is much easier for patients than repeated intravenous cannulation and safer in the context of poor peripheral access requiring long-term central lines. The subcutaneous route is likely to be an increasing advantage over a lifetime as venous access becomes more difficult and the ability of patients to self-cannulate becomes less with age.

As a further confounder, in the calculation of cost, it should not be forgotten that acute breakthrough episodes still require emergency treatment with C1 inhibitor (Berinert, Cinryze or Ruconest) or icatibant +/- supportive medical care so the total costs to the NHS of lanadelumab will not be limited to prophylactic administration. Furthermore, the need for high frequency administration may be reduced by co-administration of oral prophylaxis (danazol or tranexamic) where tolerated and appropriate. The HELP-03 study provides no data to estimate any advantage of concurrent oral treatment in terms of attack frequency, severity or optimal treatment frequency.

Concentrated C1 esterase inhibitor (Haegarda™) by subcutaneous injection has recently been approved by the FDA for long-term prophylaxis based presumably on data from the COMPACT trial[2]. Guidance on using lanadelumab in the NHS in England should be revisited if EMA approval for its use in Europe is granted or pending.

1. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol 2012;130:692-7.
2. Longhurst H, Cicardi M, Craig T, Bork K, Grattan C, Baker J et al. Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. N Engl J Med. 2017;376:1131-1140.

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Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Royal college of Pathologists**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**No links to disclose**]
Name of commentator person completing form:	[redacted]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
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1	We would like to point out that there are promising oral Kallikrein inhibitors in Phase 2 and phase 3 trials for prophylaxis and acute attacks that will probably be entering the market within the next 5 years. The impact of these medications on management of HAE has not been taken into account.
2	The long half-life (weeks) of Lanadelumab which is probably one of the contributing factors to its efficacy, results in long term inhibition of plasma Kallikrein and reduction in bradykinin (BK) production. The long term effect of reduction in BK production is not known as the use of Lanadelumab in human is limited to a maximum of 3-4 years. The effect of Kallikrein inhibition on cardiovascular events is not known and could only be established after long term post-marketing surveillance. Lanadelumab has been considered as an orphan drug in a disease in which for majority of patients there are many effective treatments such as C1Inhibitor replacement therapy which would supplement the physiological deficit of C1Inhibitor. Lanadelumab would effectively create a second knock out in this disease resulting in absence of C1Inhibitor function in addition to reduction in Kallikrein activity. Until a reasonable post-marketing period, we believe that the use of Lanadelumab should be limited to very severe and/or frequent disease for which alternative medications do not exist.
3	HAE is a rare disease and most clinical centres have a small number of patients with HAE. Initiation of C1-Inh prophylaxis, based on the department of health commissioning policy, requires a multidisciplinary decision and approval from two consultant immunologist from different. Patients who are considered to be appropriate for Lanadelumab, should be reviewed (virtually or in person) by designated national centres with large cohorts of HAE patients where alternative treatments may be considered before embarking on treatment with Lanadelumab.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**United Kingdom Primary Immunodeficiency Network (UKPIN)**
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Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that this recommendation does not take into account the actual amount of Berinert and Cinryze used in clinical practice for prophylaxis. UKPIN has completed a snap survey of immunology centres to determine this. 82% (28 out of 34) of immunology centres responded in time, contributing data from 66 patients on prophylaxis with C1 inhibitor. Patients on Berinert (n=33) were using an average of 2781 units per week for prophylaxis and patients on Cinryze (n=31) were using an average of 2343 units per week for prophylaxis. Two patients on Ruconest were on 8400 units per week prophylaxis. The average usage per week for prophylaxis is higher than the licensed dose of Cinryze and the assumed fixed dose of 1000 units of Berinert twice per week. We would like to know what the cost-effectiveness data looks like with these figures. This data also indicates that the actual usage of Berinert for prophylaxis is higher than the fixed dose used in the model.
2	We are concerned the model does not seem to take into account the additional costs associated with treatment of breakthrough attacks for patients on prophylaxis (i.e. medication, additional hospital visits etc). We would expect there to be a greater reduction in breakthrough attacks in patients treated with lanadelumab rather than iv C1 inhibitor. The average number of breakthrough attacks in HAE patients in the UKPIN snap survey was 2.4 per month (data on breakthrough attacks available for 27 patients), which is a lot higher than the number of breakthrough attacks for patients in the HELP study. We would be like to see the additional costs associated with this included in the cost-effectiveness analysis.
3	We would also like to stress that lanadelumab is a genuinely innovative prophylactic treatment for patients with HAE, and has the potential to reduce both burden of treatment (significantly less injections) and burden of illness (less attacks compared to iv C1 inhibitor prophylaxis). The reduced burden of treatment and burden of illness means less days off work/school (reduced economic impact) and reduced anxiety for patients – these are factors which would not necessarily be accounted for in the model used.
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reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

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NICE National Institute for Health and Care Excellence

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Immunology and Allergy CRG]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**No links to the tobacco industry**]
Name of commentator person completing form:	[Sinisa Savic]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	UK Primary immunodeficiency network has recently completed a survey looking at the usage of plasma derived C1 concentrates for long-term prophylaxis in patients with HAE. The findings of this survey suggest higher usage then what was originally considered when compared to cost effectiveness of lanadelumab. I hope that this new information can be taken into account.
2	I would like to express my support here for the additional comments made by the UKPIN regarding the likely significant reduction in cost of on-demand therapy if lanadelumab is introduced into routine clinical practice. Furthermore, it is worthwhile highlighting innovative nature of this treatment, which has a potential to truly transform how we look after the patients with HAE
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Rachel Annals, patient representative (HAE UK)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Pharmaceutical funding for the charity, HAE UK, from various pharmaceutical companies
Name of commentator person completing form:	Rachel Annals

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	This medication will be a life changer for many patients, especially those suffering severe attacks who cannot self-infuse medication due to poor vein access.
2	Even patients who have prophylactic medication have breakthrough attacks and have to either self-administer an acute attack medication or visit A&E for emergency treatment.
3	HAE has a big impact on mental health too. Stress is one of the main triggers for attacks and the fear of an attack and the unpredictability can cause a lot of stress, not only when an attacks is presenting, but every day. Having a treatment that will stop attacks will be hugely life changing, patients will feel more relaxed and have the confidence to live a normal life.
4	This medication will be much easier to administer, being a sub-cut medication. I myself have very good veins but having to treat twice weekly for a number f year has caused much scaring on my veins and it becomes much more difficult being able to self-treat effectively without problems. Having this medication will also save time for administration – my current medication takes time to prepare as well as time to infuse. It also needs to be administered in a sterile environment which is not always possible at short notice when an attacks presents.
5	
6	

Insert extra rows as needed

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transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Organisation	Hereditary Angioedema International
Comments on the ACD:	

[redacted], the umbrella organization that represents the world's HAE patient groups. The critiques associated with using QALYs as the basis for healthcare utilization decisions are well known so I won't recount those arguments here. What I will present, however, is an alternative perspective on the value of a highly effective subcutaneous prophylaxis treatment based on a pharmaco-economic study performed by one of our member organizations--the United States Hereditary Angioedema Association. 737 HAE patients with HAE types I and II responded to a survey that asked questions on quality of life (using the validated Angioedema Quality of Life questionnaire) and a variety of other topics including direct and socioeconomic costs associated with HAE. The American Academy of Asthma, Allergy, and Immunology accepted the study for a poster presentation at their February 2019 annual meeting in San Francisco, California. A manuscript containing the study findings has been prepared and will be submitted to a medical journal later this month. Below we present the principle findings from the study, ""A Comprehensive Approach to Assessing the Value of Treating an Ultra Rare Disease: Hereditary Angioedema."" Two internationally recognized, well published HAE expert physician/scientists are co-authors.

Study Overview and Highlights
--Recent clinical trials evaluating new, subcutaneous (SC) prophylaxis therapies reveal significant reductions in the number of HAE attacks and improvement in QoL. Moreover, SC prophylaxis treatments, for the first time, offer HAE patients an opportunity for a normal, attack-free life. Despite the clear advantages to patients, questions have been raised regarding the value of new SC prophylaxis therapies when compared to an on-demand only treatment model.

--Our study assessed the value of the new SC prophylaxis therapies compared to on-demand only treatment using real world patient data to quantify QoL, pharmacoeconomic, and socioeconomic impact.

--Members of the US HAE Association were invited to complete an anonymous online survey designed to obtain a comprehensive profile of education, employment, attack frequency, treatments, comorbidities, caregiver economic costs, and actual billed costs for attack-related hospitalizations, physician office visits or emergency room admissions. In addition, QoL was measured by the validated Angioedema Quality of Life (AE-QoL) questionnaire (where 0 = no impact and 100 = severe impact).

QoL
-Use of prophylaxis therapy led to significant reductions in median QoL impairment score when compared to either on-demand treatment alone (42.6 vs 50.0, $p<.01$) and periods of time when prophylaxis was not available (42.6 vs 73.5, $p<.01$).
--Fewer HAE attacks led to a clinically relevant and statistically significant reduction in QoL impairment.

-- Patients using the newest SC prophylaxis therapy who (1) were attack free in the last 3 months and (2) reported a period without access to prophylaxis showed a 83.3% reduction in median QoL impairment score (11.8 vs. 70.6; p<.01).

Economic Analysis
--A comprehensive health economics analysis of patients using on-demand only treatment revealed costs of
$417,100 per patient per year as follows:
--Direct costs - including on-demand only treatment (assuming only 7 out of 10 attacks are treated); ER visits, hospital stays, and HAE-linked co-morbidities totaled $364,500.
-- Indirect socioeconomic costs, calculated using the cost of missed work due to sick days, reduced wages, and under employment, totalled $52,600.

Conclusions
--The survey of 737 patient members of the US HAEA community is the largest ever sample of HAE Type I and II patients.
--Recent data indicate that the population of patients achieving zero attack status increases with sustained exposure to a SC prophylaxis therapy.
--a post hoc analysis performed as part of the lanadelumab clinical trial indicated that treatment efficacy increases over time and that a substantial majority of patients on the new therapies will be attack free.
--The value of a SC prophylactic HAE treatment should be assessed in the context that:
-- a substantial majority of patients using the newest SC prophylaxis therapies are likely to become attack free,
-- there is potential for remarkable improvements in health outcomes, quality of life and potential socioeconomic gain,
--the on-demand only treatment model is associated with high direct and indirect costs.

Why should HAE patients be left to suffer from a dramatically reduced quality of life from attacks when there is an easy to use and highly effective medicine available to prevent the physical and mental anguish associated with this painful, disfiguring, and potentially fatal ultra rare disease? Moreover, as the US pharmaco-economic study shows, when looked at from a comprehensive perspective (direct and socioeconomic costs), on-demand only therapy is quite expensive.

Name	[redacted]
Comments on the ACD	
Response 1: New treatment option This sounds like it will be life changing especially for us who cannot treat at home plus save valuable time being treated in A&E **Response 2: Proposed date for review of guidance** 3 years will feel like a lifetime with us but will still be life changing treatment	

Name	[redacted]

Comments on the ACD:

Response 1:
Question: Has all of the relevant evidence been taken into account?

I have HAE and was on the clinical trial for this medication and have subsequently been on it open label for the last 2 1/2 years. This medication has made an enormous difference in my life. I was in the process of being considered for the C1-INH when I joined the trial. My sister (who lives in another country) has been on C1-INH before, so I have some awareness of what is involved. Since been on Lanadelumab, the number of attacks I have has reduced dramatically and the attacks I have had were much milder. What's more, my mental health has improved because I'm not worried or anxious now about when my next attack is coming or what that will mean to my colleagues at work and the ability to do my job and keep social commitments. Finally, my overall health has improved. When I'm not constantly about to have an attack, having an attack or recovering from an attack, I can eat better and exercise more and enjoy an overall much-higher quality of life. Thanks to this medication, I am working to my full potential and living with joy. I could not stress enough what a difference this medication has made to me and the ripple-effects of this difference to my family, friends, colleagues and beyond.
I cannot speak to whether or not I would have had the same results with C1-INH, but I do know that a sub-cutaneous injection every two weeks is much less daunting to me than finding a vein and self-injecting every few days with a medication that is also somewhat complex and time-consuming to prepare and does carry with it the risk of an infection like hepatitis.

Response 2:
Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I think it is difficult to know the true cost-effectiveness of a whole group of people being well who formerly were not. The difference in cost isn't just between the price of different medical treatments. If one treatment does significantly increase quality of life, then the benefits to well-being of someone as a whole, society as a whole, the NHS as a whole, the economic system as a whole are difficult to quantify. That being said, £12,420 per 300 mg vial is very high, and though I support100% the medication being widely available to HAE patients with moderate to severe levels of attacks, I would also support NICE in further price negotiations.

Response 3:
Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

I would like to see a positive recommendation to the NHS from NICE.
It is a valuable product which significantly enhances wellness and quality of life for patients suffering with HAE.

Response 4:
Question: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

None that I am aware of.

Name	[redacted]
Comments on the ACD:	
I suffers with Hereditary Angioedema which predisposes me to get sporadic swelling of the peripheries (hands, feet, arms, legs, torso or genitals) which can be painful and limit the ability to use my hands or feet when they get swollen. In addition, I get sporadic abdominal swellings with abdominal distension, pain, vomiting or diarrhoea. I also get life threatening swellings involving the face in particular the airways. These swellings need to be treated promptly. I have been trained to self-inject Icatibant for peripheral or abdominal swellings but on quite a few occasions I have need to go to the nearest emergency department for un-resolving swellings, in particular for swellings of my face to be given intravenous Berinert to replenish the depleted C1 esterase inhibitor. Even though I have been trained to self-inject Icatibant subcutaneously, at times I am unable to given the injection if my hands are particularly swollen or my abdomen is swollen too much. Under these circumstances I have to get help from my sister in injecting the drug (she has also been trained to inject Icatibant into me). At other times when my feet or legs are swollen I will have difficulty in mobilising, walking, using stairs, going to the toilet, etc. If my hands are swollen I find it difficult to feed myself, take other medication, operate doors, use my mobile phone as my dexterity is severely compromised. The frequency of these episodes are variable, and my attacks can last anywhere from 2-5 days or so. I believe this medication will enable provision of a more comfortable life taking into account the condition and the limitations it puts on my mobility and functionality.	

Name	[redacted]
Comments on the ACD:	
This new medication would be amazing, been hoping for something for so long to bring a quality of life back. I have 2 to 3 attacks a week and sometimes can end up having 5 injections a week to treat attacks as it stands. I am a single mum with a little girl who has the same condition who is experiences swells early. Every day is a struggle. I am finding it impossible to administer I.V C1 to myself despite attempting training so this could be a life changer for me and my little girl.	

Name	[redacted]
Comments on the ACD:	
Response 1 Question: Are the recommendations sound and a suitable basis for guidance to the NHS? I have been closely involved with the medical care of hereditary angioedema (HAE) patients for many years and was an investigator in the lanadelumab trial. depPatients with HAE still cry when they are told that their child has HAE. This is because almost everyone continues to have some breakthrough swellings, which are greatly feared, despite currently available prophylaxis. In the trial, lanedelumab prevented attacks to a much greater extent that I have seen with any other agent, with resulting transformation in the lives of those participants, who were some of my most severely affected patients. For example, one lady, was able to go on holiday for the first time and to do her job without the special provisions for	

unexpected absence that needed previously to be in place. Her relatives with HAE are unable to work because of frequent attacks and are semi-reclusive as a result. It is imperative hat we gain access to this medication for the widest possible range of HAE patients.

Response 2
Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

I have been closely involved with the medical care of hereditary angioedema (HAE) patients for many years and was an investigator in the lanadelumab trial. depPatients with HAE still cry when they are told that their child has HAE. This is because almost everyone continues to have some breakthrough swellings, which are greatly feared, despite currently available prophylaxis. In the trial, lanedelumab prevented attacks to a much greater extent that I have seen with any other agent, with resulting transformation in the lives of those participants, who were some of my most severely affected patients. For example, one lady, was able to go on holiday for the first time and to do her job without the special provisions for unexpected absence that needed previously to be in place. Her relatives with HAE are unable to work because of frequent attacks and are semi-reclusive as a result. It is imperative hat we gain access to this medication for the widest possible range of HAE patients.

Response 3
Question: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

In my experience, access to effective medical care for HAE is much more likely for those not disadvantaged by social circumstances (who may be overrepresented in racial minorities or the disabled community). In fact those most disabled by HAE often do not get the treatment required, because of the difficulties they have engaging with medical care because of unpredictable disabling/disfiguring attacks and the psychological consequences of these. Current prophylaxis is too complex (or ineffective) for them to cope with.

Name	[redacted]
Comments on the ACD:	
I experience Type 1 HAE. For many years I had to go to A&E to be treated every time I had an attack. It had an impact on both my work and my social life. I can remember going to London for the day, buying a theatre ticket, having a coke and realising I had a fast moving attack coming, and having to forget the theatre, catch a train home, camped out in the toilet. My brother who also experiences HAE has had a similar experience, passing out on a platform and people just stepping over him, assuming he was drunk. He was also airlifted once from Hever Castle due to an attack in his larynx. I had another fast moving attack and had to drive 30 minutes to hospital. By the time I reached the car park I couldn't walk, colapsed on the floor, vomited, my limbs locked, my vision went completely (I believe due to hyperventilation tetany as part of an acute attack) Thankfully someone ran to get help and hospital staff were able to get me in and to recognise me as I was so regular there, and treat me. This is a really stressful and dangerous way to live. I currently have 1-2 attacks a week. I take tranexamic acid and treat attacks with Berinert. I am now able to treat at home (or indeed out and about, which I've had	

to do on many occasions) Without this safety net, I had to constantly be thinking about how far away I was from hospital and whether I could get to treatment in time. Being able to treat attacks myself is so much better. It has made a huge difference in my quality of life. I suspect that with my attacks as regular as they currently are, if I had to go to hospital every time for treatment, I'd struggle to remain working (I'm a counsellor so this would mean lots of last minute cancellations, a damage to the therapeutic relationship, and ultimately impacting whether I am safe to practice) I don't have enough attacks to proactively treat with Berinert, but I would love to be in a position to be able to treat proactively, and be less concerned about when my next attack will come and how I might find time and appropriate space to be able to treat. I am aware through HAE UK that treatments that for some are really effective, for others are much less so or have difficult side effects. To have an increase in options available would be extremely benefitial in managing what is a very difficult condition.

Name	[redacted]
Comments on the ACD:	
This drug is a life changer for the likes of myself who suffer from HAE. I have been able to live my life and forget that I have hae. I've been able to plan days out with my family. I've also been abroad on holidays. This drug has just not changed my life but it's changed the lives of my family to. Time away from work due to hae attacks is a thing of the past due to this drug. I cannot shout this out enough and say how brilliant it is. But it's simply fantastic.	

Name	[redacted]
Comments on the ACD:	
I have very severe HAE and am on C1 injections in my veins every day. My veins are not good and they are getting painful. This new medication would change my life as I am now 67 and can't go on this way. My mental health has deteriorated and my husband is 71 with a heart condition an d the stress on both of us is immense. We would be able to do so much more with0ut the restrictions of daily infusions. My anxiety and depression would definitely improve. We know people in other countries that have told us the difference in their lives this news medication has made. One person said they were on the brink of suicide and now have a happy and fulfilled family life. Please, please consider the life changing effect this would make to people as seriously affected as I am. No other treatment works so please give us hope for the future. Yours in hope [redacted]	

Lanadelumab for preventing recurrent attacks of hereditary angioedema

ERG critique of new evidence and revised economic analyses submitted by the company in response to the ACD

Produced by Aberdeen HTA Group

Prepared by Andrew Walker[1]
Graham Scotland[1,2]

1 Health Economics Research Unit, University of Aberdeen, UK
2 Health Services Research Unit, University of Aberdeen, UK

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Date completed 26 July 2019

Confidential data redacted [redacted]

This document provides a brief commentary and critique of the new evidence that the company have submitted in their response to the ACD on Lanadelumab for preventing recurrent attacks of hereditary angioedema. It should be read in conjunction with the company submitted responses and updated economic analysis.

ERG commentary on Shire/Takeda revised CEA in response to ACD: Berinert dosing

Evidence	ERG commentary
Company state Berinert dose is based on patient weight	Agreed
SmPC is for acute attacks only at a dose of 20 IU per kg	Agreed
The prophylactic weekly dose of Berinert calculated in the company revised submission was based on a target dose of [redacted] but with rounding to the nearest 500 IU vial to avoid wastage. The company apply the [redacted]. The rounding assumption is based on the clinical advice from one of the experts present at the first committee meeting, and further advice from the clinicians that the company has engaged with in further advisory boards (detailed in their ACD response).	The ERG believes the rounding assumption appears reasonable but notes that it does not appear to be applied in all cases according to clinical data the company received. The ERG notes that application of the company's revised dosing assumptions, using the individual weights of patients in WRAP-IT (mean = [redacted]), results in a mean rounded Berinert dose of [redacted] IU per administration ([redacted] IU/week). The ERG accept that this is the appropriate figure given the assumptions made. However, the Appraisal Committee judged this to be "highly uncertain" (ACD paragraph 3.13)
NHS England were not able to provide more dosing information	
The company reports clinical experts they consulted (further details at foot of this table) after ACM1 confirm [redacted].	The company's evidence shows that of [redacted] patients on prophylactic Berinert under the management of 22 consulted clinicians, [redacted]. Where actual doses were calculable, [redacted]).
In the same sample of 22 clinical experts, data on dose and frequency of Berinert were reported by clinicians for [redacted] patients. For the weight-based doses, it doesn't seem that the clinical experts reported the actual weekly dose for each patient; this was calculated in the company's research, seemingly using the weight of patients in the HELP-03 RCT ([redacted]kg). Given the estimated doses for all [redacted] patients, the average dose came to [redacted] IU per patient per week.	The ERG note the figure of [redacted] IU is approximately [redacted] lower than the base case rounded figure in the company's submission. The ERG note that the company appear to have assumed the body weight of the 37 NHS patients was the same as in the average in HELP-03 RCT. No evidence was offered to support this assumption. In the calculation, seen in Table 1 of the company's document "Revised cost-effectiveness analyses in response to [the ACD]", it can be seen in row 3, column 3 that a dose of [redacted]

	[redacted]. It was not clear why this figure was used, but the ERG assume it is to account for dose rounding.
	In their response the company also make the claim their 'base case' figure for the Berinert rounded dose ([redacted] IU) could be too low as higher doses can be used in patients experiencing attacks. However, the reported data suggest the figure in NHS clinical practice is actually below the base case and the suggested 'could be higher' factor does not apply.
In the ACD consultation responses, the UK Primary Immunodeficiency Network reported a survey of 34 immunology centres, 28 of whom responded (82%). Of 33 patients on prophylaxis with Berinert the average dose was 2781 units per week.	The ERG note this is approximately [redacted] lower than the base case figure in the company's submission. It is not clear if the dose suggested by UKPIN already accounts for dose rounding to avoid wastage. If it does, then Berinert costs based on this scenario would be lower than in the company's clinical dosing scenario.
	It was not clear what overlap there was between the company's survey and the UK PIN sample, in terms of participating centres or the patients reported on.
	The UKPIN survey question appears to be what dose patients on prophylactic Berinert currently receive; it is not clear whether this varies other than by weight (e.g. recent history of attacks could be a factor). Using this figure assumes lanadelumab would be appropriate for all Berinert patients, which may not be appropriate.
	With these caveats, the ERG proposes the most plausible dose is between [redacted] and 2781 IU.
	It is not clear how more evidence could be collected to resolve this uncertainty other than to survey the doses for all patients on Berinert in England, taking account of whether they would be candidates for lanadelumab or not.

Footnote: The clinical experts surveyed by the company: N=22, i.e. 13 consultant immunologists plus 9 nurse specialists; Working in 34 centres in England and Wales; This represents 72% of specialist centres; Their clinical practice included [redacted] patients who were on prophylactic treatment with Berinert; Dosing information was available for [redacted]

Proportion of lanadelumab patients switching to less frequent dose of lanadelumab

Evidence	ERG commentary
Lanadelumab can be dosed every two weeks or every four weeks. The company assumed patients would start with doses every two weeks	Agreed
Neither HELP-03 or HELP-04 had the option of switching lanadelumab frequency from every 2 weeks to every 4 weeks so there is no directly observed data on the proportion who would reduce frequency	Agreed
The company assumed 77% of patients would switch to dosing every four weeks after 1 year of treatment. 77% was based on the proportion of patients on lanadelumab every two weeks who were attack free between days 70 and 182 after commencing treatment	Clinical experts at ACM1 described 77% as plausible but difficult to predict (ACD 3.14). The Appraisal Committee accepted 77% as an upper bound but said the true figure could be lower as not all patients would want to switch. The Committee described the uncertainty as "substantial" (ACD 3.14)
After ACM1 company consulted 22 clinical experts (sample as reported above) – they confirmed they would offer a less frequent dose if appropriate. For those able to predict a percentage the range was [redacted]	Only [redacted] clinical experts made an estimate ([redacted]) For those who did make an estimate, it was not clear what they based their estimate upon – the ERG would prefer to give more weight to the answers of those who have prescribed lanadelumab. The ERG note that if 77% of patients could switch then a range of [redacted] actually doing so suggests between [redacted] of patients who could switch actually do so. The ERG propose that the higher figure is implausible.
Company also point out the 77% figure was based on a strict interpretation of 'attack free' at Day 70. The company argue in practice patients with [redacted], hence the upper limit is above 77%	The sample of 22 clinical experts would have factored this into their estimates, but according to the company's report none of them suggested a figure above 77%. The ERG propose retaining the Appraisal Committee's view of 77% as being the upper limit.
	The lower bound on the range is not known. In the company research provided in response to the ACD, the 22 clinical experts said while they would consider reducing the frequency of lanadelumab it would be discussed with the patient and the decision would be a joint one taking account of many different factors. This suggests the company's lower limit of [redacted] switching could still be high.

	One option for reducing this uncertainty would be for the company to submit data on lanadelumab prescribing in practice, focusing on the proportion changing frequency. However, this would most likely be from other countries and there could be doubts about the relevance of data based on different clinical practice.
	Another option to address the uncertainty would be for NHS England to negotiate with the company to agree data collection in England as lanadelumab is used with reimbursement linked to the proportion actually changing dosing frequency.

Other issues

ITC vs Poisson regression

In their revised base case analysis the company estimated the effect of lanadelumab by applying the hazard ratios from NMA for both lanadelumab versus and placebo and CI-INH versus placebo. This is in line with the appraisal committee conclusion as stated in the ACD: "The committee considered both approaches and concluded that using the indirect treatment comparison to inform attack rates for both lanadelumab and C1-INH is the more consistent and robust approach".

The company have disagreed with this conclusion in their response to the ACD and reiterated their arguments for using the Poisson regression to model attack rates directly for lanadelumab. They have therefore provided a scenario analysis where this approach in retained.

Tender pricing

In response to the statement in the ACD: "*discounted price of C1-INH treatments paid by the NHS is not currently included in the cost-effectiveness results. Therefore, all estimates of cost effectiveness for lanadelumab compared with C1-INH are highly uncertain*." The company argue that tender prices are agreed for defined periods of time and are subject to fluctuation, particularly when supply constraints may have an impact on pricing. They also note that there will be a new C1-INH tender in place for the start of 2020 and that current C1-INH prices are likely to be updated.

With the above caveats in mind, upon the request of NICE, the ERG have rerun the company's revised set of analysis using the currently available discounted prices for Cinryze and Berinert. These apply for both prophylactic treatment and for the treatment of breakthrough attacks in the model (see confidential appendix). In addition, discounted prices were also included for icatibant and Ruconest, which are applied for the treatment of acute attacks in the lanadelumab arm of the model.

To implement the above, changes were made to the company's revised model, in the "DrugAdminCosts" worksheet as follows: cell E21 for the price of Cinryze; cell E25 for the price of Berinert (1500 IU), cell E26 for the price of Berinert 500 IU, cell F95 for the price of Icatibant, and cell F96 for the price of Ruconest.

Revised cost-effectiveness analysis for lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268], based on revised PAS

Takeda UK Ltd

22 August 2019

Thank you for the opportunity to submit the updated economic analyses based on the revised patient access scheme (PAS) (August 2019) for the single technology appraisal (STA) for lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268].

While we acknowledge the uncertainty expressed by the committee with regard to the proportion of patients who will switch to the 4-weekly administration, we believe the value used in the revised base case is realistically achievable in clinical practice. Furthermore, as discussed and acknowledged at the first committee meeting, the cost-effectiveness analysis presented by the company is conservative in a series of elements:

- no survival benefits due to the prevention of potentially fatal laryngeal attacks; this was raised as an important issue at the first appraisal committee meeting
- no impact of lanadelumab on the severity of attacks, while trial data showed a significant reduction in severe attacks with lanadelumab
- no benefits in terms of caregiver quality of life (QoL), which at the first appraisal committee meeting was described by the patient experts as a significant aspect
- the selection of the shortest duration of attacks ([redacted]) vs longer estimates from other arms of the HELP-03 trial or from the CHANGE trial, also considering the testimony of the patient representatives at the committee meeting (over 2 days of duration, as reported in section 3.1 of the ACD)
- Cinryze is used in the model at its licensed dose, [redacted], also evident from the data submitted by UK PIN as part of the ACD consultation.

We hope that the additional discount offered, and the relative cost-effectiveness results will ensure that a positive recommendation is now achievable.

Yours sincerely,

Shire, now part of Takeda

Revised base case analysis

Upon consideration of the committee-preferred analysis following the second appraisal committee meeting (ACM) on 7th August 2019, the company has revised the original base-case settings of the cost-effectiveness analysis; these are detailed in Table 1 below.

Table 1 - Company's base-case revisions following second ACM

Assumption	Base-case presented at second ACM	Revised base-case	Rationale
Lanadelumab price	Simple PAS discount of [redacted] on list price	Simple PAS discount of [redacted] on list price	Company's new offer
Population	Full HELP-03 population and severe subgroup from HELP-03 with at least 8 attacks over 4 weeks	Full HELP-03 population	Committee's preference for more robust data available for the full population
Proportion of patients receiving Berinert or Cinryze in the C1-INH arm	64% Berinert 36% Cinryze	73% Berinert 27% Cinryze	Data provided by NHS England
Berinert dosing	All patients have a target dose of [redacted] with pragmatic dose rounding applied to ensure there is no vial wastage	Berinert clinical practice dosing as presented in scenario analysis by the company at the 2nd ACM, based on weighted average of specific dosing regimens reported by 22 clinical experts participating in advisory board meetings and series of interviews	Data reflective of clinical practice
C1-INH prices	List prices	List prices	Tender prices are confidential, therefore the company's revised base case is based on list prices
Proportion of patients switching to lanadelumab 300mg every 4 weeks (q4w) in the long term	76.9%	60.9%	More conservative estimate reflecting uncertainty on the actual proportion of patients that will switch in clinical practice

The results of the new base-case analysis are presented in Table 2 below and show that lanadelumab is more effective and less costly than treatment with C1-INH.

Table 2: Revised base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NMB (£)
C1-INH	[redacted]	21.48	[redacted]	[redacted]	[redacted]	Dominant	£602,395
Lanadelumab	[redacted]	21.48	[redacted]				

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

Dear NICE

This is just to confirm that the ERG has checked all the ICERs that NICE has produced and confirm that they are all correct.

It should just be noted that the last scenario on slide 3 (clinical practice dosing) will have originally (in the post ACD company submission and ERG CPAS appendix) assumed [redacted] on Berinert rather than the [redacted] you have applied. The [redacted] was in line with the percentage of patients on Berinert ([redacted]) reported by clinicians that the company surveyed post ACD to estimate the Berinert dose. The company did not make this clear in their post-ACD submission and I hadn't noticed this change in the model for this scenario.

It is also worth noting that for the clinical dosing scenario, the calculated dose of [redacted] per week is based on the data reported by clinicians and assuming an average weight of [redacted]. The calculation in the model uses the average of the calculated rounded dose (to the nearest vial) based on the weight of each individual patient in HERP-03. The average dose for this scenario in the model thus comes out slightly higher at [redacted] per week.

Hope this is clear.

Yours sincerely

Aberdeen HTA Group
University of Aberdeen