

Single Technology Appraisal

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Contents:

The following documents are made available to stakeholders:

[Access the **final scope** and **final stakeholder list** on the NICE website.](#)

- 1. Company submission from Otsuka Pharmaceuticals UK:**
 - a. Full submission
 - b. Summary of Information for Patients (SIP)
- 2. Clarification questions and company responses**
- 3. Patient group, professional group, and NHS organisation submissions from:**
 - a. HAE UK – written by patient expert, Angela Metcalfe
 - b. British Society for Immunology Clinical Immunology Professional Network (BSI-CIPN)
 - c. The Royal College of Pathologists
 - d. NHS England (NHSE) Clinical Reference Group (CRG) in Immunology and Allergy – written by clinical expert, Dr Matthew Buckland
- 4. Expert personal perspectives from:**
 - a. Dr Anthony Dorr – clinical expert, nominated by Otsuka Pharmaceuticals UK
 - b. Dr Matthew Buckland – clinical expert, nominated by NHSE Blood and Infection
 - c. Patient expert, nominated by HAE UK
- 5. External Assessment Report** prepared by Birmingham Centre for Evidence and Implementation Science (BCEIS), University of Birmingham
 - a. External Assessment Report
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Donidalorsen for preventing hereditary angioedema attacks in people 12 years and over [ID6457]

Company evidence submission

October 2025

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angioedema attacks in people 12 years and over [ID6457]

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Abbreviations

ACE	Angiotensin-converting enzyme
AE	Adverse event
AECT	Angioedema Control Test
AE-QoL	Angioedema Quality of Life Questionnaire
AIC	Akaike information criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BMI	Body mass index
BNF	British National Formulary
BSACI	British Society for Allergy and Clinical Immunology
C1-INH	C1-esterase inhibitor
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CrI	Credible interval
CSR	Clinical study report
CUA	Cost-utility analysis
DSU	Decision Support Unit
EAACI	European Academy of Allergy and Clinical Immunology
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5 Dimensions-5 Levels
FAS	Full analysis set
FDA	Food and Drug Administration
FE	Fixed effects
FSH	Follicle-stimulating hormone
GalNAc3	Triantennary N-acetylgalactosamine
GI	Gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HAE	Hereditary angioedema
HCRU	Health care resource use
HRQoL	Health-related quality of life
HTA	Health technology appraisal
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
ITC	Indirect treatment comparison
ITT	Intention to treat
IU	International unit
IV	Intravenous
kg	kilogram
KM	Kaplan-Meier
LICA	Ligand-conjugated antisense
LLN	Lower limit of normal

LSM	Least squares mean
LTP	Long-term prophylaxis
m	metre
Max	Maximum
mg	milligram
Min	Minimum
mL	millilitre
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	Messenger ribonucleic acid
N/A	Not applicable
NC	Not calculated
Nf	Nano filtered
NHS(E)	National Health Service (England)
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OLE	Open label extension
OWSA	One-way sensitivity analysis
P25	25th percentile
P75	75th percentile
PAS	Patient access scheme
pdC1-INH	Plasma-derived C1-inhibitor
PKK	Prekallikrein
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q1M	Once every month
Q2	Second quarter
Q4	Fourth quarter
Q2M	Once every two months
Q2W	Once every two weeks
Q4W	Once every four weeks
Q8W	Once every eight weeks
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RE	Random effects
rhC1-INH	Recombinant C1-inhibitor
RNA	Ribonucleic acid
RR	Rate ratio
SAE	Serious adverse event
SAS	Safety analysis set
SC	Subcutaneous
SD	Standard deviation
SE	Standard error

SEM	Standard error of the mean
siRNA	Small interfering ribnucleic acid
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SoC	Standard of care
STA	Single technology appraisal
STP	Short-term prophylaxis
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
TTD	Time to discontinuation
TTO	Time trade-off
U	Unit
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USD	United States Dollars
VAT	Value added tax
WAO	World Allergy Organization
WPAI	Work Productivity and Impairment Questionnaire

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

- The objective of this appraisal is to evaluate the clinical and economic benefit of donidalorsen as a treatment for patients aged 12 years and older experiencing attacks of hereditary angioedema (HAE).
 - The comparators considered relevant to this appraisal are berotralstat, lanadelumab, and C1-esterase inhibitors (C1-INH) (intravenous [IV] Cinryze and IV Berinert).
 - A cost-comparison analysis is presented as the base case in the company appraisal.
- HAE is a rare, chronic, debilitating genetic disorder characterised by recurrent, unpredictable and potentially life-threatening swelling episodes, commonly occurring in the hands, feet, stomach, face, and throat.¹
- The symptom burden associated with HAE attacks is considerable. Patients experience substantial pain and functional impairment not only during acute episodes but also in the periods between them.² Some patients describe the pain as so severe that they are unable to leave their bed.³
- The unpredictability of HAE attacks contributes to persistent psychological distress, with patients frequently reporting extreme anxiety, stress and depression.^{3–5}
- HAE attacks substantially restrict patients' ability to perform daily activities and are associated with higher rates of absenteeism, presenteeism and work productivity losses.⁶ Patients describe swelling episodes as sufficiently debilitating to prevent them from undertaking basic self-care tasks such as washing themselves, getting dressed or even feeding themselves without discomfort, anxiety and stress.³
- The burden associated with HAE extends beyond patients' quality of life, substantially impacting carers and family members.^{7,8}
- There is an unmet need among patients experiencing between two to eight attacks per month; currently, access to standard-of-care long-term prophylaxis

(LTP) therapy is limited to berotralstat only, which may not be suitable for all patients due to tolerability concerns and limited efficacy.^{9,10}

- Donidalorsen is an innovative, first-in-class LTP option, intended as a treatment for adults and adolescents aged 12 years and older who experience ≥ 2 attacks per month.¹¹
- Donidalorsen is an efficacious, well-tolerated and convenient LTP option with the potential to improve patients' quality of life and reduce their burden of disease through improved HAE control.¹²
- Donidalorsen addresses the unmet need for an efficacious, well-tolerated and less frequently administered LTP.
 - For patients who are well-controlled (e.g., attack-free), the option to reduce to a once every two months (Q2M) dosing regimen represents a less frequent and potentially more convenient dosing regimen compared with existing LTPs (berotralstat, lanadelumab and C1-INHs).^{12–17}

1.1 Decision problem

The objective of this single technology appraisal (STA) is to evaluate the clinical and economic benefit of donidalorsen as a treatment for patients aged 12 years and older for the routine prevention of recurrent of HAE attacks. The proposed position in the HAE treatment pathway is as follows:

- Patients with HAE aged 12 or older who experience two or more attacks per *month* (≥ 2 attacks per month), as an alternative treatment to berotralstat;
- Patients with HAE aged 12 or older who experience two or more attacks per *week* (≥ 8 attacks per month), as an alternative treatment to lanadelumab or IV C1-INHs.

The appraisal is in line with the technology's full marketing authorisation for this indication, that is, for [REDACTED]

[REDACTED].¹⁶ In the UK, donidalorsen is anticipated to be positioned in a subgroup of the marketing authorisation population in patients experiencing ≥ 2 attacks per month. This positioning reflects where donidalorsen offers the greatest clinical benefit: for patients with a clear unmet need for a well-tolerated and convenient LTP option that reduces attack frequency, supports disease control and enables continuation of normal daily activities. The full decision problem addressed in the appraisal is presented in Table 2.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People 12 years and over with hereditary angioedema	People 12 years and over with hereditary angioedema	N/A
Intervention	Donidalorsen	Donidalorsen	N/A
Comparator(s)	Established clinical management for preventing hereditary angioedema attacks, which may include: • C1-esterase inhibitors (this includes Cinryze, Berinert and Ruconest) • Attenuated androgens • Antifibrinolytics • Lanadelumab for people eligible for preventative C1-esterase inhibitor treatment in line with NHS England's commissioning policy • Berotralstat • Garadacimab (subject to NICE evaluation)	Established clinical management for preventing hereditary angioedema attacks, which may include: • Plasma-derived, intravenous C1-esterase inhibitors (this includes IV Cinryze, IV Berinert) • Lanadelumab for people eligible for preventative C1-esterase inhibitor treatment in line with NHS England's commissioning policy • Berotralstat	The comparators considered relevant to this appraisal are berotralstat, lanadelumab, and C1-INHs (IV Cinryze and IV Berinert). SC Berinert, Ruconest, attenuated androgens, and antifibrinolytics have not been included as comparators in the decision problem for the reasons outlined below. Only IV Berinert is considered an appropriate comparator to donidalorsen; SC Berinert is not a comparator as no plasma-derived SC C1-INH therapies are reimbursed in the UK for LTP.¹⁸ This exclusion is further supported by clinical expert opinion, sought as part of clinical validation meetings held in September 2025; clinical experts noted that any use of SC Berinert has been largely replaced with lanadelumab.¹⁹ Ruconest is predominantly used as an on-demand therapy for the treatment of acute attacks and is therefore not considered to be an appropriate comparator for donidalorsen. The marketing authorisation of Ruconest states that: <i>"Ruconest is indicated for treatment of acute angioedema attacks in adults, adolescents, and children (aged 2 years and above) with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency"</i>.²⁰ Furthermore, Ruconest is neither recommended by NICE nor commissioned by NHS England for use as an LTP.^{20–22}

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			The NHS commissioning policy for C1-INH treatment specifically discusses plasma derived C1-INHs, in contrast to Ruconest which is a recombinant treatment.^{20–22} This has been established in previous technology appraisals for lanadelumab and berotralstat (TA606 and TA738).^{9,18} Androgens are not licensed as LTP, nor are they recommended by NICE for the long-term prevention of HAE attacks. Although off-label use of androgens such as danazol was historically considered standard of care for prophylaxis in HAE, since the availability of licensed and commissioned treatments in England has improved, androgens are no longer considered a treatment option when patients are initiated on an LTP or require an alternative LTP. An algorithm of commissioned treatment options for the management of HAE, published by NHS England, states <i>“Some adult patients are treated with androgens as oral prophylactic treatment. However, evidence is limited and accessing treatment is difficult so this is not recommended as first line for patients newly starting on prophylaxis. Where existing patients are established on androgen therapy, this may continue if considered clinically appropriate; if established patients do cease treatment with androgen therapy then review the need for any prophylaxis. An individualised assessment to withdrawal of androgens and commencing new prophylaxis should be taken. If a historical attack frequency is documented, it can be used as the basis for selecting other prophylaxis treatment options.”</i>²³

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			Additionally, clinical expert feedback in berotralstat TA738 stated that patients under the age of 18 should not be treated with androgens. Therefore, androgens are not considered to be an appropriate comparator for donidalorsen, for which patients aged 12 years and above are included in the anticipated licence. Androgens are also associated with adverse androgenic and anabolic effects, drug interactions and contraindications.⁹ Furthermore, danazol has been discontinued in the UK and current treatment directives state not to start new patients on androgens.^{23,24} Similarly, anti-fibrinolytics were historically considered standard of care but these are not indicated as LTPs for patients with HAE and the marketing authorisation for tranexamic acid specifically indicates “short term use”.^{24,25} In addition, WAO and EAACI guidelines do not recommend anti-fibrinolytics due to the limited efficacy data available.²⁶ Following recent NICE guidance in October 2025, garadacimab is recommended for patients with two or more HAE attacks per month. However, as implementation of the guidance is still in progress, garadacimab is not considered established standard of care in UK clinical practice at the time of this appraisal.²⁷ As per the NICE process and methods, garadacimab is therefore not considered a relevant comparator in this appraisal and has been excluded from the company’s decision problem.²⁸

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • angioedema attacks (including frequency, severity, location and duration) • attack-free period • time to first attack • need for acute treatment • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).	The outcome measures to be considered include: • angioedema attacks (including frequency, severity, location and duration) • need for acute treatment • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).	‘Attack-free period’ and ‘time to first attack’ were not included as the primary or secondary outcome measures in the pivotal phase III trial (OASIS-HAE) of donidalorsen and have therefore not been included in the company’s decision problem.^{12,29} Furthermore, ‘attack-free period’ and ‘time to first attack’ are not considered principal outcome measures for the economic analysis, and these endpoints do not inform the analysis.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to	A cost-comparison analysis is presented in the base-case in patients with HAE aged 12 years and over who experience ≥ 2 clinically significant attacks per month, comparing donidalorsen against berotralstat, lanadelumab, and C1-INHs (IV Cinryze and IV Berinert). Please see Section 3 for	The efficacy of donidalorsen is assumed equal to the relevant comparators of this appraisal because there were no statistically significant differences observed between donidalorsen Q4W and comparator LTPs in the results of the indirect treatment comparison. Please see Section 2.10 for further details.

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	further details. A cost-utility analysis in the same population is presented as a scenario analysis. Please see Appendix K for further details.	
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	As per draft scope.	N/A

Abbreviations: C1-INH – C1 esterase inhibitor; EAACI – European Academy of Allergy and Clinical Immunology; HAE – Hereditary angioedema; IV – Intravenous; LTP – Long-term prophylaxis; N/A – Not applicable; NHS – National Health Service; NICE – National Institute for Health Care and Excellence; Q4W – Once every four weeks; SC - Subcutaneous; TA – Technology appraisal; UK – United Kingdom; WAO – World Allergy Organisation

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1.2 Description of the technology being evaluated

A description of donidalorsen is presented in Table 2.

Table 2: Technology being evaluated

UK approved name and brand name	Donidalorsen (brand name: Dawnzera®)
Mechanism of action	Donidalorsen is a first-in-class, ribonucleic acid (RNA)-targeted antisense oligonucleotide that binds to prekallikrein (PKK) messenger ribonucleic acid (mRNA) in the liver, the primary site of plasma PKK production, thereby promoting the degradation of PKK-encoding mRNA.^{11,12,30,31} By preventing PKK protein synthesis and reducing circulating PKK levels, donidalorsen inhibits the plasma kallikrein-kinin system.³⁰ This prevents the production of bradykinin which causes vasodilation and increased vascular permeability, leading to angioedema.³² Donidalorsen is conjugated to GalNAc3 (a triantennary N-acetylgalactosamine), which increases the potency up to 30-fold, compared to unconjugated molecules, by enabling its uptake into liver cells.^{31,33}
Marketing authorisation/CE mark status	Donidalorsen is currently undergoing assessment by the EMA with an expected licence date of [REDACTED]. Donidalorsen is also undergoing assessment by the Medicines and Healthcare products Regulatory Agency (MHRA) through [REDACTED] with an anticipated licence date of [REDACTED].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated marketing authorisation for donidalorsen is [REDACTED] No restrictions are anticipated or described in the draft SmPC.
Method of administration and dosage	Donidalorsen is administered subcutaneously (SC) via an auto-injector pen. The recommended starting dose in adult and adolescent patients is [REDACTED]¹⁶
Additional tests or investigations	No tests or investigations are required.

List price and average cost of a course of treatment	List price: [REDACTED] per 80 mg pre-filled pen The cost of a course of treatment over one year for patients treated with donidalorsen at the anticipated list price, assuming a proportional split of [REDACTED] patients treated with donidalorsen once every month (Q1M) and [REDACTED] of patients treated with donidalorsen Q2M, is [REDACTED].
Patient access scheme (PAS) (if applicable)	A simple PAS discount of [REDACTED] % will be applied to the anticipated list price of donidalorsen, resulting in a net price of [REDACTED] per pre-filled pen. The discounted cost of a course of treatment over one year for patients treated with donidalorsen, assuming a proportional split of [REDACTED] patients treated with donidalorsen Q1M and [REDACTED] of patients treated with donidalorsen Q2M is [REDACTED]. All costs exclude value added tax (VAT).

Abbreviations: EMA – European Medicines Agency; GalNAc3 - Triantennary N-acetylgalactosamine; HAE – Hereditary angioedema; mg – milligram; MHRA – Medicines and Healthcare products Regulatory Agency; mRNA – Messenger ribonucleic acid; PAS – Patient access scheme; PKK – Prekallikrein; Q1M – Once per month; Q2 – Second quarter; Q2M – Once every two months; Q4 – Fourth quarter SC - Subcutaneous; SmPC – Summary of product characteristics; VAT – Value added tax

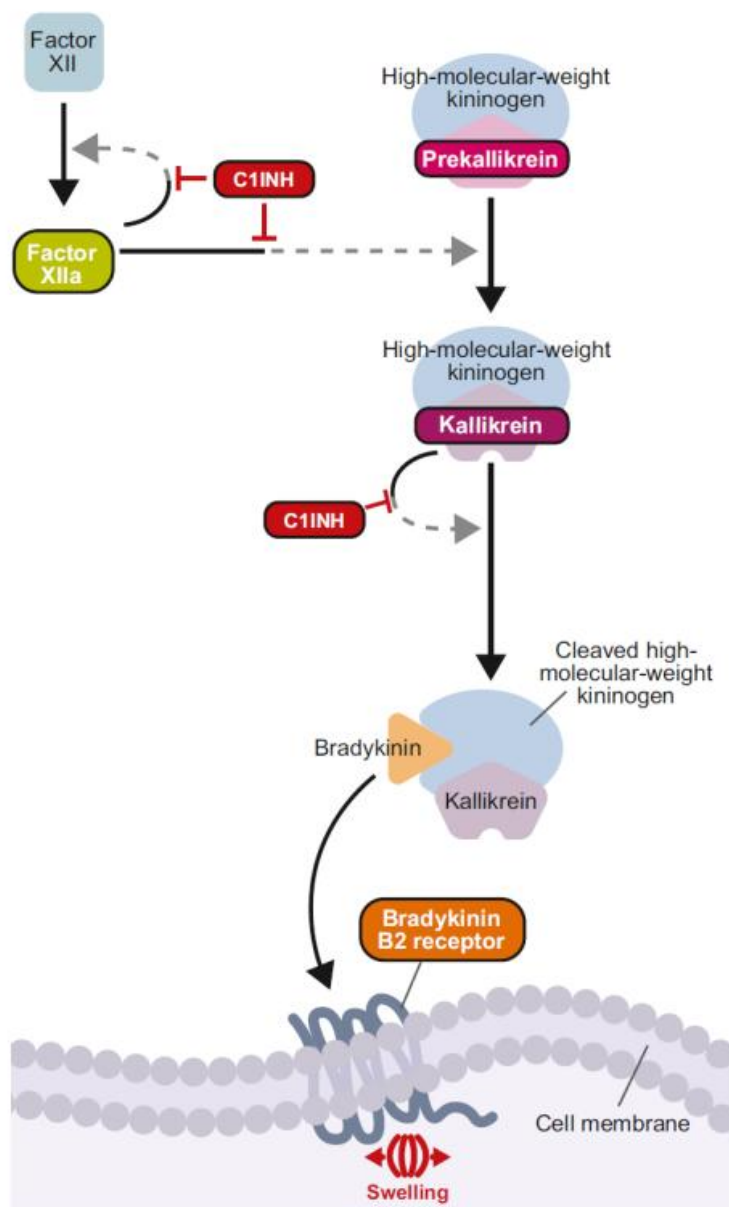
1.3 Health condition and position of the technology in the treatment pathway

1.3.1 Disease overview

HAE is a rare, chronic and potentially life-threatening genetic disorder (autosomal dominant), characterised by recurrent and unpredictable swelling attacks, commonly occurring in the hands, feet, stomach, face and throat.¹ HAE attacks have a debilitating impact on the quality of life (QoL) of patients, both during and between episodes.² Patients experience significant pain, anxiety, depression, absenteeism and work productivity losses, as well as being limited in their daily functioning due to the severe and unpredictable nature of attacks.^{3–6} These attacks most often result from C1-INH deficiency or dysfunction. C1-INH is a key regulatory protein that controls coagulation, vascular permeability, and inflammation in the contact activation system and complement pathway.³⁴ Dysfunction or deficiency of C1-INH leads to uncontrolled activation of the kallikrein-kinin system which causes overproduction of bradykinin, a potent vasodilator and primary mediator of increased

vascular permeability and fluid extravasation, ultimately causing angioedema.³² A summary of C1-INH regulatory pathways is presented in Figure 1.

Figure 1: Summary of C1-INH regulatory pathways



Abbreviations: C1-INH – C1-esterase inhibitor; FXII – Factor XII; FXIIa – Factor XIIa

Source: Adapted from Riedl et al. 2024³⁵, Tachdijan et al. 2024³⁶ Source: Adapted from Riedl et al. 2024³⁵, Tachdijan et al. 2024³⁶

HAE comprises of three types:³⁷

- **HAE-C1INH-Type1 (Type I):** Defined by patients with a loss of the C1-INH protein and accounts for 80-85% of patients.
- **HAE-C1INH-Type2 (Type II):** Defined by patients with improper function of C1-INH and accounts for 15-20% of patients.
- **HAE-nC1INH (previously referred to as Type III)** is not a result of the deficiency of the protein C1-esterase inhibitor. However, type is not yet fully understood.³⁸

Type I and Type II are caused by a mutation in the *SERPING1* gene, which codes for C1-INH.²⁶ Currently, more than 700 different *SERPING1* variants are known to be linked to Type I and Type II.²⁶

1.3.1.1 Diagnosis, epidemiology and risk factors

Type I and Type II HAE have a prevalence of at least 1 in 59,000 of the UK population and can affect people of any ethnic group or gender.³⁹ While the age of HAE onset varies, it usually presents in childhood with around 50% of patients experiencing an attack before the age of 10 years and the mean age of onset being between only 8 and 12 years.^{40,41} Most patients experience their first attack before the age of 18 and, although attacks have been reported in children as young as 1 year old, attacks rarely occur before two years of age and are less frequent before adolescence.^{40,41} Early onset of symptoms is linked to a more severe disease course.

Despite this, due to the rarity of the disease, HAE remains extremely challenging to diagnose; patients typically experience symptoms for an average of 10 to 18 years before a diagnosis of HAE Type I and Type II, respectively.⁴²

The British Society for Allergy and Clinical Immunology (BSACI) guidelines recommend taking a detailed history of angioedema, including frequency, circumstances of onset, triggers, timing, pattern of recurrence and duration of

attacks.⁴³ The BSACI as well as the World Allergy Organization (WAO)/ European Academy of Allergy and Clinical Immunology (EAACI) guidelines state that diagnosis of HAE relies on clinician suspicion, which should be validated through laboratory tests, particularly tests for C1-INH function, C1-INH protein, and C4.^{26,43,44} Patients are typically diagnosed and managed in secondary/tertiary care centres.⁴³

Given the autosomal dominant inheritance pattern of HAE, family history is a key symptom for diagnosis; each child of a person with HAE has a 50% chance of inheriting the disease themselves.³⁷ However, it is estimated that *de novo* genetic variations are responsible for up to 25% of all unrelated cases.⁴⁵ Recurrent skin swelling and gastrointestinal (GI) attacks are also key symptoms that can aid diagnosis. Other factors include:^{26,41}

- Onset of symptoms in childhood/adolescence
- Recurrent and painful abdominal symptoms
- Occurrence of upper airway oedema
- Failure to respond to standard anti-allergy treatments such as antihistamines, glucocorticoids, omalizumab, or epinephrine
- Presence of prodromal signs or symptoms before swelling
- Absence of wheals (raised, itchy bumps on the skin)

1.3.2 Burden of HAE

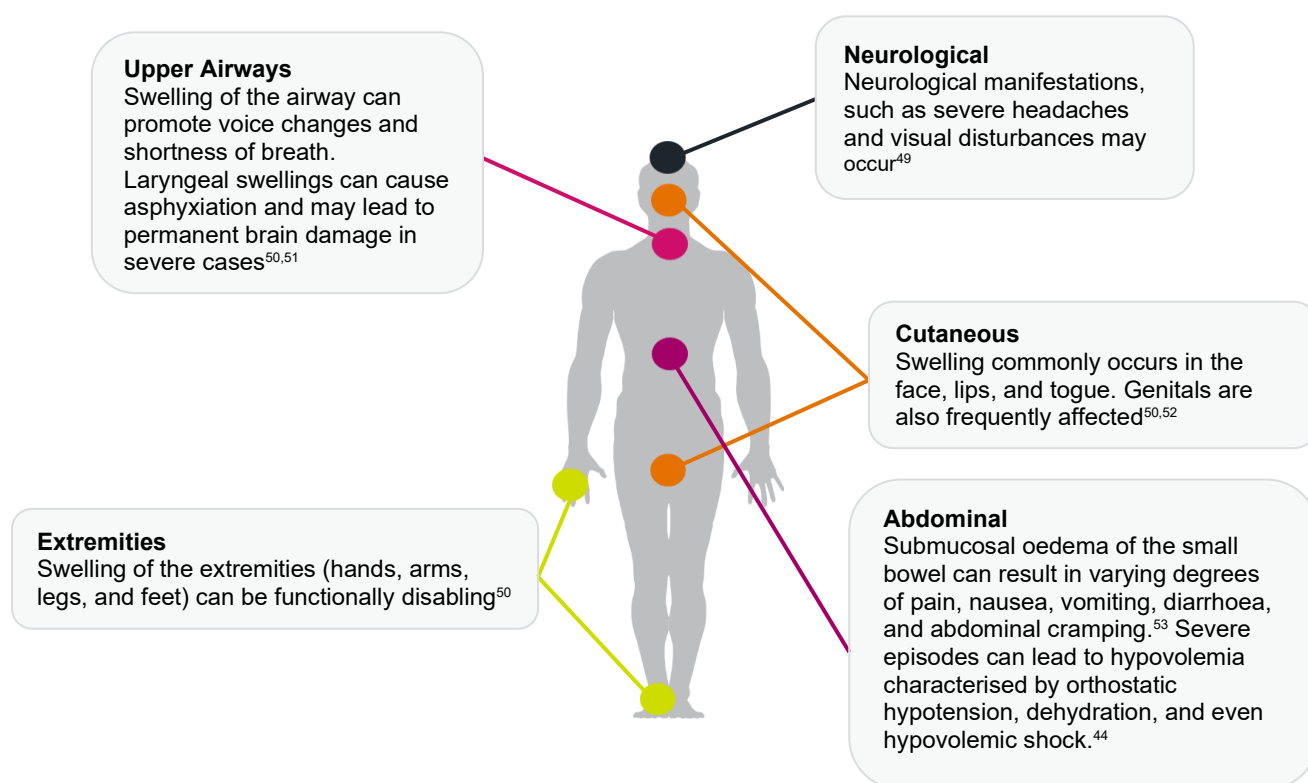
1.3.2.1 Symptom burden

HAE is characterised by swelling attacks in subcutaneous and submucosal tissues around the body, such as swelling of the face, lips and tongue, extremities, upper airways, and abdomen.³⁷ HAE attacks can cause substantial pain, limit daily functioning and place a serious burden on patients, considerably impacting their QoL. As discussed above, people with HAE can often go long periods with their disease misdiagnosed or undetected, experiencing these life-threatening attacks for an average of over 10 years due to a misunderstanding of symptoms and general

lack of disease awareness.^{46,47} The often long wait that patients experience to receive a diagnosis can delay patients beginning their treatment journey, which can exacerbate all aspects of the burden of HAE, and is associated with decreased physical function, increased risk of mortality, negative psychological impact, and higher direct and indirect costs.⁴⁷ A United States (US)-based study of 214 patients with HAE who died found that 70 (32.7%) had died due to asphyxiation resulting from laryngeal attacks, with a mean age of death of 40.6 years, representing a significant reduction to the length of life.⁴⁸ In a UK audit of HAE patient data from 2010 to 2012, family history records showed that there were 55 deaths related directly to an HAE attack across 33 families, highlighting the significant risk of death associated with the disease.⁴²

The burdensome symptoms of HAE are dependent on the location of the attack, as outlined in Figure 2.

Figure 2: Symptoms of HAE in the body



Abbreviations: HAE – hereditary angioedema

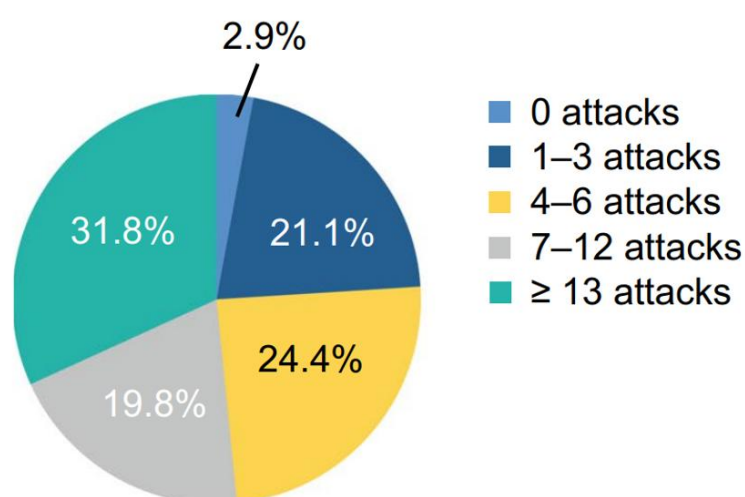
Source: Jacobs et al. 2021⁴⁹, FDA, 2018⁵⁰, Mar et al. 2023⁵¹, Farkas. 2010⁵², Santacroce et al. 2021⁵³, Caballero. 2021⁴⁴

Angioedema in the larynx is the most severe location for a swelling attack, due to the risk of asphyxia and death, or permanent brain damage.⁵² In particular, it is essential to diagnose this promptly in paediatric cases as asphyxiation can occur rapidly due to their narrow airways.⁴⁹ Laryngeal attacks occur in more than 50% of patients with HAE at least once in their lifetime.² If left untreated, HAE can lead to potentially fatal outcomes. As detailed above, one study of 214 patients with HAE who died found that 70 (32.7%) had died due to asphyxiation resulting from laryngeal attacks; importantly, in 90% of these cases, the fatalities occurred before C1-INH-HAE had been diagnosed.⁴⁸ Swelling of the face and lips accounts for roughly 3% of subcutaneous oedema episodes; importantly, up to 30% percent of upper airway oedema episodes are preceded by facial or lip oedema.⁵⁴

Abdominal attacks occur in up to 90% of patients diagnosed with HAE and can cause severe pain, vomiting, diarrhoea and abdominal cramping.² During an abdominal attack, 34% of patients with HAE received a misdiagnosis that led to appendectomies, exploratory laparotomies or both.² Symptoms often resemble those of acute abdominal emergencies like acute appendicitis, often leading to unnecessary emergency surgeries in affected patients.² In a Food and Drug Administration (FDA) 'Voice of the Patient' meeting on HAE, one patient said "*During these attacks, I can't eat, I can't drink, you basically vomit every little bit that is in you*".⁵⁰ Cutaneous attacks of the extremities are the most common, affecting 97% of patients, and can cause discomfort and mobility limitations.⁵⁵ One patient from the FDA's 'Voice of the Patient' meeting described these attacks as "*...if the bottoms of your feet are swollen, you cannot walk anywhere. And if your hands swell up like a balloon... you cannot pick stuff up, you cannot pull up your pants... you cannot do anything, dress yourself, feed yourself... When both your hands and your feet are swollen, you cannot do anything except just sit there*".⁵⁰ A survey of HAE patients, including those in the UK, found that patients reported an average of 12.5 attacks in the past six months, and 47% of patients experienced their most recent attack in the last seven days, as presented in Figure 3 and Figure 4, respectively. Of these surveyed patients, 62.4% were using LTP, and 76.4% had used on-demand medication to treat their most recent attack.⁴ These findings reflect a high disease

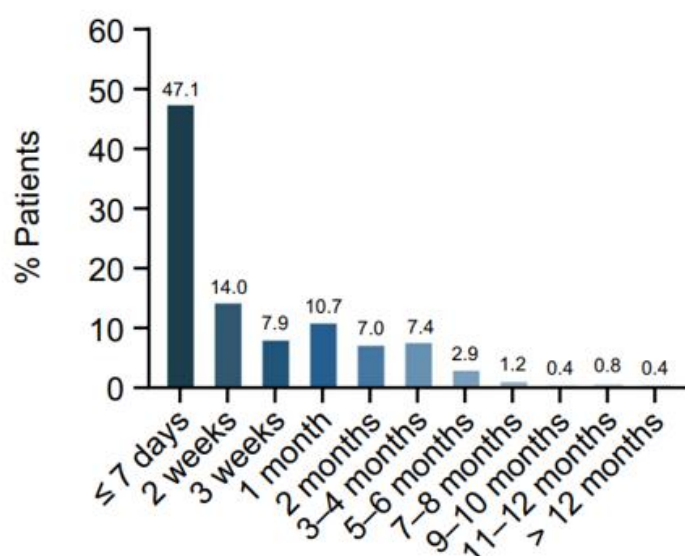
burden, even among patients who are receiving treatment such as LTP, or acute therapy. Among patients who are not receiving treatment, this burden can be especially severe, with debilitating symptoms lasting for up to 100 days annually.^{56–58} Furthermore, many acute attacks remain undertreated. In the Icarian Outcome Survey study, patients in the UK experienced a median of 2.0 untreated attacks per year, despite the availability of on-demand treatments.⁵⁹ Patients with HAE can experience devastating symptoms, even when receiving currently available LTPs, highlighting the ongoing need for effective LTP in patients with HAE to ensure better disease control.¹⁸

Figure 3: Number of HAE attacks over the past 6 months, patient survey by Mendivil et al.



Abbreviations: HAE – hereditary angioedema
Source: Mendivil et al. 2021⁴

Figure 4: Time since most recent attack^a, patient survey by Mendivil et al.



^aPatients were asked “When was your most recent angioedema attack?” and selected the answer closest to the time when the first symptom of attack appeared.

Source: Mendivil et al. 2021⁴

Although HAE attacks are unpredictable, around half of attacks seem to be triggered by various external factors including physical exertion, mental stress, surgical and dental procedures and infection.^{49,60} However, the severity of response to a particular trigger is patient dependant, and the same trigger may not always cause an attack for a patient.² Even when patients are able to recognise potential triggers, the unpredictable nature of HAE persists, as attacks can still occur without clear cause, or vary in response to known factors.^{61,62}

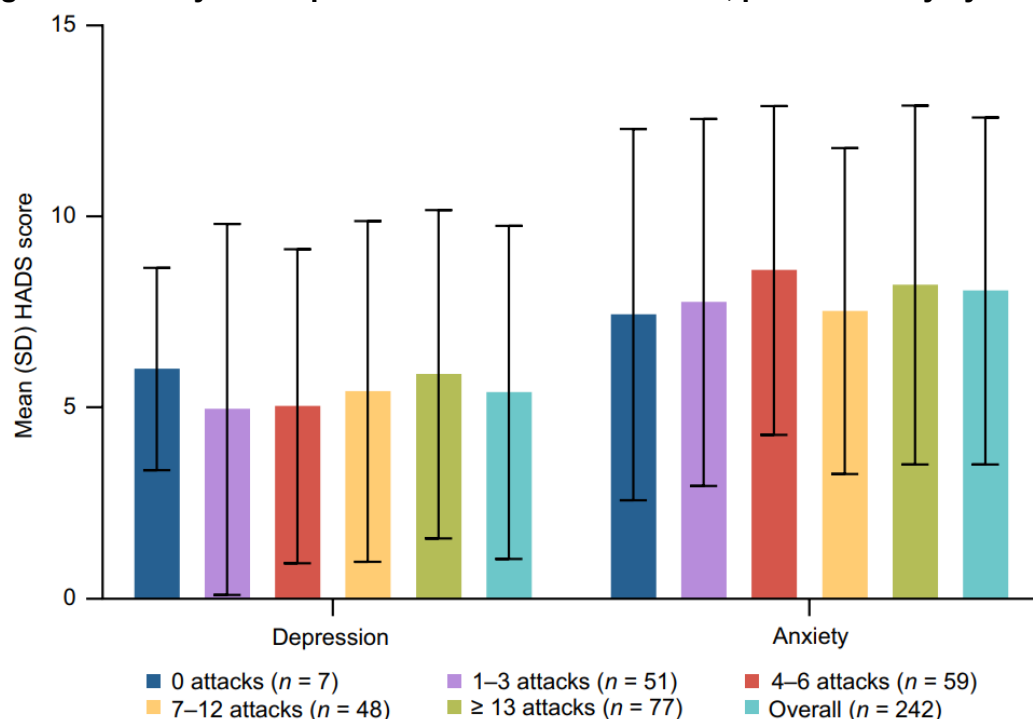
1.3.2.2 Quality of life burden

HAE impacts almost all aspects of patients’ lives, such as their physical and mental wellbeing, school or work life, and family life, and the consequences are lifelong.^{6,58} Attacks can have a substantially negative impact on the QoL for patients, both during and between episodes.⁵⁸ In a survey of 445 patients with HAE, almost 50% had some degree of anxiety and 24% exhibited depressive symptoms.⁶ These emotional challenges likely stem from the unpredictable nature, frequency, and severity of swelling episodes, which can have adverse effects on an individual’s work, social interactions, and family life. In the FDA’s ‘Voice of the Patient’ meeting on HAE, one

patient describes the unpredictability as *“And then you think okay, this one is done, when is the next one going to happen? And so, you live with this constant fear of it looming over you”*.⁵⁰ Market research conducted by the company, in collaboration with Healthcare Research Worldwide, to understand the HAE emotional patient journey, presented UK patients who have described the anxiety and fear associated with HAE as *“It is always on my mind...When will my next attack be and where on my body?”* and *“I get the “dark” thoughts like, when would I be discovered if anything serious occurred?”*.³ Patients’ families also share this burden, with family members describing how they live *“...in absolute dread of the next attack”*, and struggle to *“live without fear and without worry”*.⁵⁰

One survey assessing HAE burden in eight countries, including the UK, found that 38.0% and 17.4% of HAE patients reported moderate-to-severe anxiety and depression, respectively.⁴ Decreased QoL was associated with the severity of anxiety and depression, as measured by the Angioedema Control Test (AECT) and the Hospital Anxiety and Depression Scale (HADS) scores. The results of the HADS score are presented in Figure 5 and demonstrate that anxiety and depression are largely not impacted by the frequency of attacks, suggesting that patients are likely to experience anxiety and depression, regardless of how many attacks they have each month, emphasising the continual burden on patients, no matter how severe their disease.⁴

Figure 5: Anxiety and depression associated with HAE, patient survey by Mendivil et al.

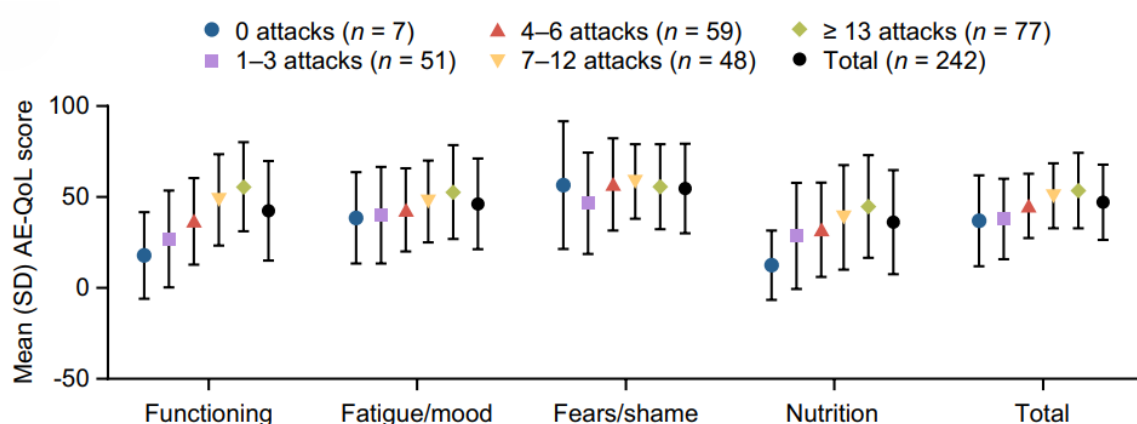


Abbreviations: HADS – Hospital anxiety and depression score; HAE – Hereditary angioedema; SD – Standard deviation

Source: Mendivil et al. 2021⁴

In the same patient survey, the Angioedema Quality of Life Questionnaire (AE-QoL) was used to assess the impact on QoL of HAE patients over 4 weeks.⁴ The results presented in Figure 6 show that scores were highest in the fears/shame category (mean [standard deviation [SD]]: 54.68 [24.67]), highlighting the significant emotional burden patients experience – particularly due to the unpredictability of attacks and fear of their consequences. Use of the AECT in this survey also demonstrated that almost half of survey respondents reported being “much” or “very much” bothered by the unpredictability of their HAE.⁴

Figure 6: Mean AE-QoL scores, patient survey by Mendivil et al.



Abbreviations: AE-QoL – Angioedema Quality of Life Questionnaire; HAE – Hereditary angioedema; SD – Standard deviation
Source: Mendivil et al. 2021⁴

Overall, the results from this study evidence that although on-demand and LTPs are available, patients still experience significant disease burden, particularly with respect to mental health. Reducing the frequency of attacks is crucial to alleviating not only the physical but also the mental burden that repeated attacks impose on patients. The results in Figure 6 demonstrate that a reduced number of attacks is associated with improvements in patient nutrition, fatigue and mood, and functioning. Donidalorsen offers an effective and well-tolerated treatment that has demonstrated an ability to reduce the frequency of HAE attacks, improving patient disease control and patient QoL.

1.3.2.3 Socioeconomic and carer burden

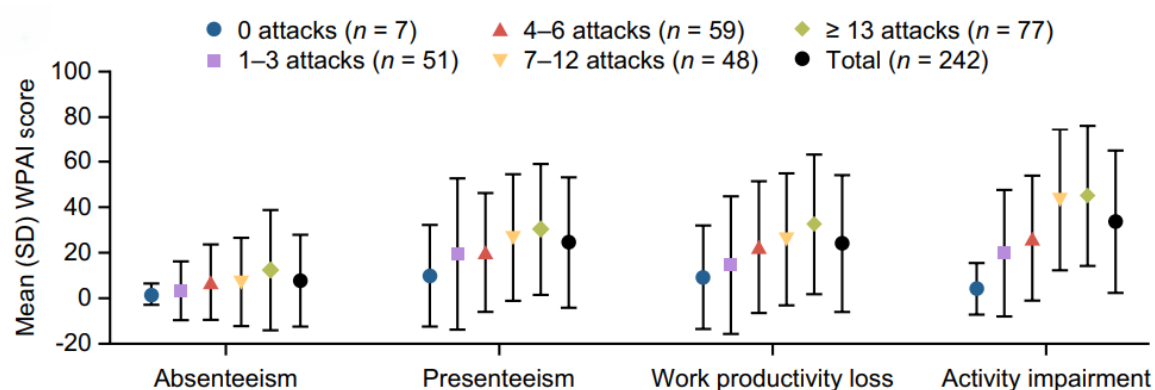
Due to the unpredictable nature of attacks, patients with HAE are severely limited in their ability to engage in daily activities with HAE attacks associated with higher rates of absenteeism, presenteeism and work productivity losses.⁶

A study into the socioeconomic burden of HAE in European countries (HAE-BOIS-Europe) discovered that 56% of patients reported missing time from school or work during their most recent attack, 40.5% of patients felt that HAE prevented them from going as far in school as they would have liked, and 69.1% felt that they could not consider certain jobs because of their disease.⁸ This unpredictability and its impact

on daily life leads people with HAE to experience fear, anxiety and depression between attacks, occurring not only due to the attacks themselves but also about reduced work/school productivity and limited career/educational achievement.^{4,5}

In one study of HAE across eight countries, including the UK, work impairment was measured using the Work Productivity and Impairment Questionnaire (WPAI), where higher scores indicate greater impairment.⁴ The mean (SD) percentage impairment measured by the WPAI was 24.59% (28.65) for presenteeism, 24.18% (30.03) for work productivity loss, and 33.88% (31.20) for activity impairment, as shown in Figure 7. These data demonstrate that as the frequency of attacks per year increases, the impairment experienced by patients increases. This highlights the increasing burden to patients when HAE is not adequately managed.⁴

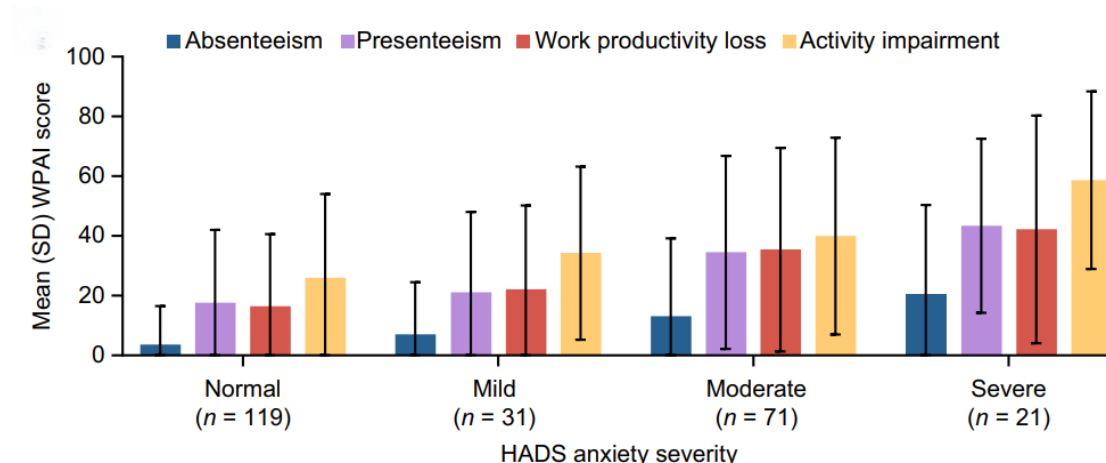
Figure 7: WPAI Scores, patient survey by Mendivil et al.



Abbreviations: HAE – Hereditary Angioedema; SD – Standard deviation; WPAI - Work Productivity and Impairment Questionnaire
Source: Mendivil et al. 2021⁴

Furthermore, higher mean WPAI scores were observed in patients with increasing anxiety, demonstrating the psychological and economic burden from HAE as presented in Figure 8.⁴

Figure 8: WPAI scores based on HADS anxiety levels, patient survey by Mendivil et al.



Abbreviations: HADS – Hospital Anxiety and Depression Scale; HAE – Hereditary Angioedema; SD – Standard deviation; WPAI - Work Productivity and Impairment Questionnaire
Source: Mendivil et al. 2021⁴

HAE also poses a substantial economic burden. A survey of patients with Type I and Type II HAE across eight countries, including the UK, found that 97.1% had regularly visited a medical professional during the past year, with some requiring HAE-related emergency department visits, urgent care visits, and hospitalisation.⁴ This healthcare resource use, alongside use of current treatments, contributes to a great financial burden to the NHS that can potentially be lessened through use of effective LTPs that reduce the frequency of attacks in patients.

In addition to the burden to patients, HAE also impacts carers and family members. Results from the HAE-BOIS-Europe study showed that 59% of patients required carer help over the past 6 months while 52% required assistance from a carer during an attack.⁸ The proportion of patients who require support increases with the severity of the attacks with 69% of those with severe pain, 64% with moderate and 26% with no or mild pain reporting requiring assistance from a carer ($p < 0.001$). Caregiving responsibilities lead to a decrease in work and/or leisure time for carers, with an average of 1.2 days of work/leisure missed for severe attacks, 1.2 days for moderate and 1 day for mild.⁸ In a multinational survey of carers of adult patients with HAE, respondents reported providing care for an average of 14.4 days per month.⁷ Carers reported facing disruption to daily activities such as sleeping (28.8%), work (28.8%), and recreation (27.3%) due to their responsibilities as a caregiver, with almost 40%

of respondents reporting that their future planning was also impacted. Furthermore, 92.4% of carers reported being impacted emotionally due to their concerns about the patient's health.⁷ These findings demonstrate that HAE places a substantial burden on those who care for patients with HAE, in addition to the burden faced by patients themselves. Demands are placed on the personal and professional lives of carers and family members that could be lessened or prevented through more effective and accessible HAE management strategies.

1.3.3 Overview of treatment landscape

There is currently no cure for HAE.⁶³ Treatment plans for HAE include LTP, short-term (pre-procedure) prophylaxis (STP), and on-demand treatment to manage attacks, with the frequency of on-demand treatment varying according to disease control. On-demand treatment is used at onset of a HAE attack to stop the progression of swelling during attacks.²⁶ STP is a preventative treatment given to patients before triggers, such as medical and dental procedures, to reduce the risk of swelling attacks.^{23,26} LTP treatment involves regular use of medication to prevent or reduce the frequency and severity of swelling attacks. As per the final scope, this appraisal concerns LTP treatment and as such, STP is not discussed further in this appraisal.⁶⁴

The ultimate goal of HAE treatment is to achieve total control of the disease and allow patients to continue with normal daily living.⁶⁵ This can currently only be achieved by LTP, i.e., the regular use of medication that reduces the burden of the disease by reducing the risk of attacks.²⁶ The availability of new LTPs has improved HAE management, however, there remains a substantial unmet need for a well-tolerated and effective treatment that has minimal impact on the daily lives of patients.

Donidalorsen is anticipated to be indicated for the routine prevention of HAE attacks as an LTP. The remit of this appraisal is to evaluate the clinical and cost benefit of donidalorsen for preventing recurrent HAE attacks, with currently available standard of care LTPs as the comparators for this appraisal.

Current NHS England (NHSE) clinical commissioning policies and National Institute for Health and Care Excellence (NICE) recommendations present distinct treatment pathways for the prophylactic treatment of HAE, based on the frequency of patient attacks.^{9,18,21} The frequency of HAE attacks experienced by a patient is an important factor in treatment choice and shared decision-making between patients and clinicians. The frequency of attacks helps determine whether a patient should receive LTP or on-demand therapy alone. However, access to LTPs is restricted by specific reimbursement criteria, which vary by treatment. As a result, some patients with frequent attacks may not qualify for certain LTPs, despite clear clinical need. The reimbursement criteria for each LTP are outlined in Section 1.3.3.2.

1.3.3.1 On-demand treatment

On-demand treatment does not prevent attacks but is used at the onset of a HAE attack to stop and/or reduce the progression of swelling.²⁶ Frequent attacks, despite on-demand treatment, can substantially affect patients' QoL, increase anxiety and require patients to actively avoid triggers and adjust their lifestyle. Based on the latest NHSE treatment algorithm, patients who experience less than two attacks per month are not eligible for treatment with LTPs, and are treated with on-demand therapy only, resulting in high unmet need in this patient population.²³ As per the final scope, this appraisal concerns LTP treatment, as such on-demand treatments are not considered as comparators for this appraisal.⁶⁴ On-demand treatments are, however, considered in this appraisal as part of the management of acute HAE attacks.

In the UK, icatibant, a subcutaneous bradykinin-receptor antagonist, and intravenous C1-INHs (Berinert and Cinryze) are licensed for treatment of acute attacks of HAE.^{22,66} Sebetralstat is an oral plasma kallikrein inhibitor currently undergoing NICE health technology appraisal (HTA) for treatment of acute attacks.⁶⁷

1.3.3.2 Long-term prophylaxis

LTP involves the regular use of medication to prevent or reduce the frequency and severity of swelling attacks, aiming to achieve total control of the disease and allow patients to continue with normal daily living.²⁶

In the UK, eligibility for specific LTPs is determined by patients' attack frequency, based on the current NHS commissioning policy for plasma-derived C1-INHs and the NICE recommendations for berotralstat and lanadelumab.^{9,18,21} Under these criteria, patients experiencing ≥ 2 attacks per month are eligible for only one LTP option: berotralstat. Access to additional LTP options, C1-INHs and lanadelumab, is restricted to patients experiencing a higher attack frequency of ≥ 8 attacks per month.²³ An overview of these LTPs is provided below, with further details presented in Table 3.

Following recent NICE guidance in October 2025, garadacimab is recommended for patients with two or more HAE attacks per month. However, as implementation of the guidance is still in progress, garadacimab is not an established standard of care in UK clinical practice at the time of this appraisal.⁶⁸ As per the NICE process and methods, garadacimab is therefore not considered a relevant comparator in this appraisal and has not been included in the company's decision problem.²⁸

Two or more attacks per month

Berotralstat

Berotralstat is the only standard of care LTP recommended for use in patients who experience ≥ 2 attacks per month.

Berotralstat is an oral, small molecule inhibitor of plasma kallikrein indicated for routine prevention of recurrent HAE attacks in adult and adolescent patients aged 12 years and older.¹⁷ In England, berotralstat is recommended by NICE for patients who experience at least two attacks per month; treatment is stopped if the number of attacks per month does not reduce by at least 50% after 3 months.⁹ See Section 1.3.3.3 for the limitations of berotralstat in current clinical practice.

Eight or more attacks per month

There are currently two recommended standard of care LTPs for patients who experience ≥ 8 attacks per month: C1-INH and lanadelumab.

Plasma-derived C1-INHs

Routine injections of plasma derived C1-INHs, such as IV Cinryze and IV Berinert, are used as LTPs. Under current NHS guidelines, C1-INH treatments are commissioned as an LTP for patients with HAE 'who fail oral prophylaxis and who experience ≥ 2 clinically significant attacks *per week*, despite oral prophylaxis over a period of at least 56 days, requiring treatment with C1-INHs or icatibant' or for 'individuals in whom oral prophylaxis is contraindicated, for example pregnant women'.²¹

In England, IV Cinryze is licensed for routine prevention of HAE attacks, in patients aged six years old and above with severe recurrent HAE attacks who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment.¹³ IV Berinert is licensed for acute treatment and short-term prophylaxis and is used off-label as an LTP for patients who experience ≥ 2 attacks *per week* (i.e., ≥ 8 attacks per month) who have either failed or have a contraindication for oral prophylaxis.^{14,22} SC Berinert is licensed in the UK for the prevention of recurrent HAE attacks in adolescent and adult patients with HAE, but is not commercially available and the NHSE commissioning policy for plasma derived C1-INH only discusses the use of IV treatments.²² This is further supported by clinical expert opinion, sought as part of clinical validation meetings held in September 2025; clinical experts noted that any use of SC Berinert has been largely replaced with alternative LTPs.¹⁹ As such, SC Berinert is not a comparator for this appraisal.

Lanadelumab

Lanadelumab is a plasma kallikrein inhibitor licensed for the routine prevention of recurrent attacks for HAE in patients aged two years and older.¹⁵ In England,

lanadelumab is reimbursed for preventing recurrent attacks of HAE in people aged 12 and over who experience ≥ 2 attacks clinically significant attacks *per week* over eight weeks despite oral preventative therapy, or where oral therapy is contraindicated or not tolerated.¹⁸

Table 3: Overview of standard of care LTPs in the UK

Medicine Name	IV Berinert ^{14,21}	IV Cinryze ^{13,21}	Lanadelumab ^{15,18}	Berotralstat ^{9,17}
Treatment class	C1-INH	C1-INH	Plasma kallikrein inhibitor	Plasma kallikrein inhibitor
Marketing authorisation status as LTP in UK	Off-label	Licensed	Licensed	Licensed
Dosing schedule and licensed dose	N/A, not licensed. Assumption of dosage for the economic model is set to a distribution of either 1,000 or 1,500 IU every three to four days, based on feedback from clinical experts (see Section 3.2.7)	Starting dose of 1,000 IU every three or four days, the dosing interval may need to be adjusted according to individual response.	Patient weight >40kg: Starting dose of 300 mg every two weeks; patients who are stably attack-free may be considered for dosing every four weeks Patient weight <40kg: Starting dose of 150 mg every two weeks, patient who are stably attack-free may be considered for dosing every four weeks	150 mg once-daily
Administration	IV injection; can be self-administered at doctor's discretion after suitable training by a healthcare professional	IV injection; can be self-administered at doctor's discretion after suitable training by a healthcare professional	SC injection with a pre-filled syringe; can be self-administered after suitable training by a healthcare professional	Oral tablet
NICE recommendations/NHS England commissioning policy	Not appraised by NICE Commissioned by NHS England for the routine prevention of angioedema attacks in individuals who fail oral prophylaxis and who experience ≥ 2 attacks clinically significant attacks per week, despite oral prophylaxis over a period of at least 56 days, requiring on-demand treatment		Recommended by NICE for preventing recurrent attacks of HAE in patients aged 12 years and older, only if patients are having ≥ 2 clinically significant attacks per week over eight weeks despite oral preventative therapy, or oral therapy is contraindicated or not tolerated	Recommended by NICE for preventing recurrent attacks of HAE in adult and adolescent patients aged 12 years and older, only if: patients experience at least two attacks per month, and it is stopped if the number of attacks per month does not reduce by at least 50% after three months

Abbreviations: C1-INH – C1-inhibitor; HAE – Hereditary angioedema; IU – International unit; IV – Intravenous; kg – kilogram; LTP – Long-term prophylaxis; mg – milligram; N/A – Not applicable; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; SC – Subcutaneous; UK – United Kingdom

Company evidence submission template for donidalorsen for preventing hereditary angioedema attacks in people 12 years and over [ID6457]

1.3.3.3 Limitations of current LTPs and unmet need

Despite advances in LTPs for HAE, currently available treatments are associated with a number of limitations, such as frequent and invasive administration, potential adherence issues, and patients still experiencing breakthrough attacks.⁶⁹ An online discrete-choice experiment survey of 250 patients with HAE showed that among multiple features of treatment, patients' strongest preferences included reduction in attack frequency, reduced risk of gastrointestinal side effects, mode of administration, and less frequent dosing.⁷⁰ Overall, there remains a significant unmet need for a well-tolerated and effective treatment that has minimal impact on the daily lives of patients.

Berotralstat

Berotralstat is the only treatment option for patients experiencing ≥ 2 attacks per month. There exists substantial unmet need for these patients as there are currently no other standard of care treatments, limiting choice for patients and clinicians when considering alternatives. This is compounded by the limitations associated with berotralstat treatment:

- Patients treated with berotralstat must discontinue treatment if they fail to achieve a reduction in attack frequency of at least 50% within three months of treatment initiation.⁹ This accounted for 42% of patients in the ApeX-2 placebo-controlled trial.⁷¹ Patients who do not respond to berotralstat have severely limited options, as there are currently no other recommended LTPs available for this patient population. Androgens and anti-fibrinolytics are suboptimal alternatives with poor efficacy and safety profiles, which are not recommended as first line for patients newly starting on prophylaxis.^{23,26}
- Berotralstat must be administered daily which can lead to adherence issues and therefore long-term efficacy of treatment.^{17,72}
- There are tolerability concerns associated with berotralstat. In particular, it is associated with poor GI tolerability, with 50% of patients experiencing GI

abdominal treatment-emergent adverse events (TEAE) when receiving 150 mg berotralstat in the pivotal APeX-2 trial.⁷¹ In addition, of the patients who subsequently enrolled into the open-label extension (OLE) of APeX-2, 39% experienced GI abdominal adverse events deemed to be drug related.¹⁰ Furthermore, in the cohort of patients who enrolled into the OLE, the patients who were re-randomised from placebo to berotralstat in the blinded active phase (Week 24 to Week 48) of the APeX-2 trial experienced GI abdominal adverse events deemed to be drug-related in 57% of cases.¹⁰

- In an advisory board conducted by the company with UK clinical experts in May 2025, and subsequent clinical validation meetings in June 2025, the experts agreed that real-world use of berotralstat is perceived as variably effective and unable to achieve adequate disease control in certain patients. In addition, the side effect profile is a barrier to many patients, with GI issues in particular frequently leading to early discontinuation as patients do not want to persevere on treatment when they are facing debilitating side effects.^{19,72}

The limitations of berotralstat highlight the lack of favourable LTP options for patients who seek an alternative LTP; those who do not benefit from or tolerate berotralstat, and are not eligible for lanadelumab or C1-INHs, are left with no standard of care treatment options under the current commissioning landscape for HAE.^{9,18,22}

C1-INHs

Under the NHS commissioning policy, only IV C1-INHs are commissioned for use as LTPs in patients experiencing ≥ 8 attacks per month.²¹ The limitations of IV C1-INHs treatment are described below:

- The restricted population for which C1-INHs are available means only a small proportion of people with HAE in the UK would be eligible to receive C1-INHs as LTP; in a 2019 survey across 37 UK centres by Yong et al., just 8% of patients with HAE were treated with C1-INHs.³⁹ As such, there remains a significant unmet need for patients who experience ≥ 8 attacks per month who are not suitable for IV therapy.

- The intravenous route of C1-INH administration is a more invasive route compared with other treatment options, which are administered orally or subcutaneously. IV administration of medicines is associated with a higher risk of complications, including infection and direct microbial entry into the blood stream, compared to SC administration.⁷³
- Twice-weekly dosing may be inconvenient for patients and impact their daily lives; this dosing schedule does not align with patient preferences, which tend to favour less frequent treatment, such as once every two months, rather than more frequent administration.⁷⁰ Additionally, some patients' fear of needles may make twice-weekly injections an unsuitable or unsustainable treatment option.¹⁸

Lanadelumab

Lanadelumab provides the only alternative standard of care LTP to IV C1-INHs, used in patients experiencing ≥ 8 attacks per month.¹⁹ The limitations of lanadelumab treatment listed below illustrate the significant unmet need for patients who experience this number of attacks:

- As with C1-INHs, the restricted population for which lanadelumab is available means there is a substantial population with significant unmet need. Based on the estimates from Yong et al. (2023) detailed above for plasma-derived C1-INHs, only ~8% are expected to experience a sufficient number of attacks (≥ 2 per week) to be eligible for LTP with lanadelumab.³⁹
- Lanadelumab requires SC administration once every two weeks (Q2W), and is associated with a significant incidence of injection site reactions (52%) and injection site pain (43%).^{15,74} Patients typically place high importance on, and express greater preference for, LTPs that offer less frequent dosing schedules, such as once every two months, and a lower risk of injection site reactions.⁷⁰ The frequency, pain, and discomfort associated with lanadelumab administration can therefore exacerbate patient treatment burden, limiting patient satisfaction.

In summary, given the significant burden of disease and limitations of current LTPs, there is a clear unmet need for a well-tolerated and convenient LTP option that can demonstrate efficacy in reducing patients' attack frequency, allowing patients to achieve control of the disease and to continue with normal daily living. Donidalorsen has been comprehensively demonstrated to be an effective LTP and offers an alternative therapy option that addresses the unmet need for patients who seek an efficacious, well-tolerated and less frequently administered LTP than those currently available in the treatment pathway.

1.3.4 Place of donidalorsen in treatment pathway

Donidalorsen is a first-in-class, RNA-targeted PKK inhibitor, intended for the [REDACTED]

[REDACTED].^{11,16} The intended positioning of donidalorsen in the current treatment pathway is as a treatment for prevention of recurrent attacks of HAE for adults and adolescents aged 12 years and older who experience ≥ 2 attacks per month, as presented in Figure 9.

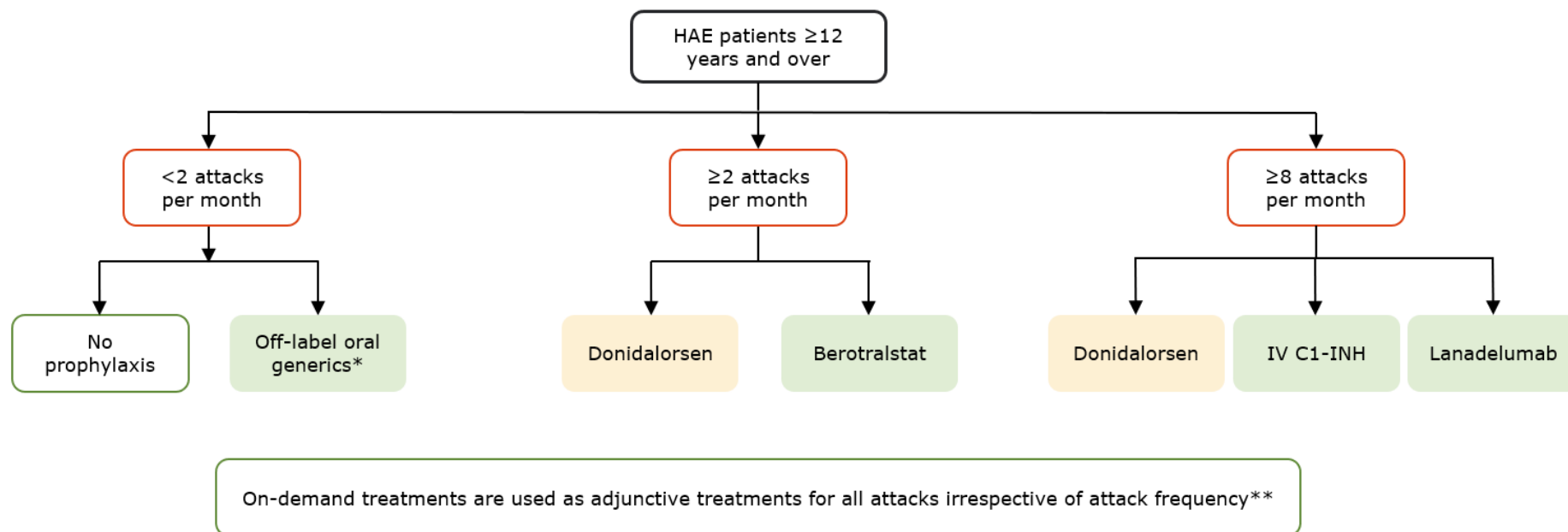
The efficacy and safety of donidalorsen were comprehensively evaluated through a randomised, placebo-controlled phase III trial over a 24-week treatment period (OASIS-HAE) and an ongoing open-label, long-term extension (OASISplus).^{12,75} For further details on the clinical data for donidalorsen, please see Section 2.6. In addition to the demonstrated clinical efficacy and well-tolerated safety profile, [REDACTED]

[REDACTED], offers a reduced dosing regimen compared to C1-INHs, lanadelumab, and berotralstat.^{12–17,33} Donidalorsen is administered subcutaneously via an auto-injector pen, which offers patients the benefit of being able to self-administer at home. For patients who can self-administer at home and do not require injection support in clinics, the need for continued hospital visits following the first administration training appointment can be minimised or potentially eliminated. As a result, the burden of treatment on their daily lives compared to IV C1-INHs can be reduced.

In addition to the ability to self-administer donidalorsen at home, patients can travel with their pre-filled injection pens as they can be left unrefrigerated for up to six weeks in the original carton when stored below 30°C.¹⁶ By comparison, lanadelumab pre-filled syringes may be left unrefrigerated below 25 °C for two weeks.¹⁵ C1-INH must be reconstituted using aseptic technique before IV administration within three hours.¹³

Donidalorsen provides an effective and well-tolerated alternative to berotralstat, lanadelumab, and C1-INHs in patients with HAE and addresses several key treatment gaps, such as the need for a less frequent and burdensome administration, with a proven efficacy and tolerability profile. Furthermore, it addresses an unmet need as a treatment option offered to patients experiencing ≥ 2 attacks per month or < 8 attack per month, as patients in both these populations have limited LTP options under the existing treatment landscape.

Figure 9: HAE treatment pathway



Abbreviations: C1-INHs – C1 esterase inhibitors; IV – intravenous

The proposed positioning of donidalorsen within the existing treatment pathway is indicated by gold boxes

*Off-label oral generics include tranexamic acid and attenuated androgens

**On-demand therapy is used as an adjunct therapy in all patients for the acute treatment of HAE attacks, irrespective of attack frequency or concurrent use of LTPs

Adapted from NHSE hereditary angioedema algorithm, 2025²³

1.4 Equality considerations

The company politely asked the committee to consider the implications of patients' religion, as a protected characteristic under the Equality Act 2010, as an equity or equality consideration forming part of the appraisal of donidalorsen. Two currently available C1-INHs (IV Cinryze and IV Berinert) included as comparators in this appraisal are derived from human plasma, with which some religious groups may be unwilling to be treated as blood-derived products. Accordingly, treatment options for individuals who decline human-derived products on the grounds of religious belief should be carefully considered to ensure that recommendations do not, directly or indirectly, result in discrimination on the basis of religion. Donidalorsen is not derived from human plasma.

2 Clinical effectiveness

- A systematic literature review (SLR) was conducted in April 2025 to identify published clinical, cost-effectiveness, health-related quality of life, cost and resource use, and burden of disease studies conducted in HAE.
- The relevant clinical evidence to demonstrate the efficacy of donidalorsen for the treatment of HAE in patients aged 12 years and older is the phase III, randomised, placebo-controlled, trial OASIS-HAE.⁷⁶
 - The long-term safety and clinical efficacy of donidalorsen is being evaluated through the ongoing long-term, open-label OASISplus study.^{36,77}
- The clinical evidence demonstrates that donidalorsen is an effective and well-tolerated, LTP option for patients with HAE.
 - In OASIS-HAE, donidalorsen significantly reduced mean HAE attack rates compared to placebo from Week 1 to Week 25. Patients treated with donidalorsen once every four weeks (Q4W) demonstrated a statistically significant reduction of 81% ($p<0.001$) in HAE attack rates, with a 55% ($p=0.004$) reduction observed in patients treated with donidalorsen once every eight weeks (Q8W).⁷⁶
 - Long-term data from OASISplus demonstrated that the reduced mean HAE attack rate was sustained from Week 1 to Week 53 of the OLE treatment period, with a 92% reduction in patients treated with donidalorsen Q4W and a 93% reduction for patients treated Q8W in the OASISplus OLE cohort.³⁶
 - In the OASISplus switch cohort, patients with HAE receiving donidalorsen Q4W after treatment with other LTPs demonstrated reductions in mean HAE attack rate from Week 1 to Week 17 of 73% (berotralstat), 65% (lanadelumab), and 41% (C1-INHs).⁷⁷
 - Donidalorsen provided clinically meaningful improvements in patient AE-QoL scores, with mean reductions of 24.8 (Q4W) and 19.9 (Q8W) points from Week 1 to Week 25 in OASIS-HAE.¹² In the OASISplus OLE

cohort, mean reductions of 28 (Q4W) and 24 (Q8W) points were observed from Week 1 to Week 25, while patients switching from other LTPs in the OASISplus switch cohort achieved a 10.4 point improvement.⁷⁷

- Donidalorsen can improve patients' lives by significantly reducing attack rates, versus placebo. Treatment with donidalorsen can therefore preserve patient's overall well-being, and emotional and physical functioning, allowing them to continue with work, school, and normal daily living and reducing the psychological burden associated with HAE.^{12,76}
- In the absence of head-to-head studies comparing donidalorsen with other LTPs, a network meta-analysis (NMA) was conducted to estimate the comparative efficacy and effect on quality of life of donidalorsen against berotralstat, lanadelumab, and plasma-derived IV C1-INHs.
 - No statistically significant difference was observed between donidalorsen Q4W and comparator LTPs in the mean number of HAE attacks per month, or in the change from baseline in AE-QoL score between donidalorsen Q4W and lanadelumab, and C1-INHs, indicating donidalorsen provides similar efficacy and quality of life benefits compared to existing LTPs.
- Donidalorsen addresses the unmet need for a well-tolerated and efficacious treatment option in patients who experience [REDACTED].¹²

2.1 Identification and selection of relevant studies

See Appendix B for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

An SLR was performed in April 2025, to identify published existing clinical, cost-effectiveness, health-related quality of life (HRQoL), cost and resource use, and burden of disease studies conducted in HAE. Searches to identify clinical studies

were conducted in EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Clinical Answers databases. In line with NICE and the Centre for Reviews and Dissemination methods, following the removal of duplicate records across the databases searched, two independent reviewers assessed the relevance of identified studies, based on title and abstract, for inclusion using the eligibility criteria.^{28,78} Disagreements were discussed and a third reviewer was involved if required. The SLR identified 18 randomised controlled trials (RCTs) that evaluated relevant LTP treatments, including one key study investigating donidalorsen, the OASIS-HAE trial, which is presented in Section 2.2. Of the comparator studies, two were identified that were suitable for the NMA. These studies, as well as the NMA methodology, are presented in Section 2.10.

2.2 List of relevant clinical effectiveness evidence

The relevant clinical evidence for donidalorsen for the treatment of HAE in patients aged 12 years and older is the phase III, multi-centre, double-blind, randomised, placebo-controlled study, OASIS-HAE.^{12,76} A summary of the study is presented in Table 4.

Table 4: Clinical effectiveness evidence – OASIS-HAE

Study	OASIS-HAE: NCT05139810 ^{12,76}
Study design	OASIS-HAE was a phase III, multi-centre, double-blind, randomised, placebo-controlled study.
Population	Patients aged 12 years or older with confirmed hereditary angioedema Type I or Type II who had at least two angioedema attacks in up to 8 weeks in the run-in period.
Intervention(s)	Donidalorsen 80 mg – Q4W (n=45) Donidalorsen 80 mg – Q8W (n=23)
Comparator(s)	Placebo (n=22)
Indicate if study supports application for marketing authorisation	OASIS-HAE presents the pivotal, regulatory and clinical evidence in support of donidalorsen in the population directly relevant to the decision problem.
Indicate if study used in the economic model	Yes
Rationale if study not used in model	NA
Reported outcomes specified in the decision problem	Monthly angioedema attack rate Angioedema attack severity Need for acute treatment

	Mortality Adverse effects of treatment Health-related quality of life
All other reported outcomes	Number of patients with a $\geq 50\%$, $\geq 70\%$, or $\geq 90\%$ reduction in attack rate from baseline Percentage of attack-free patients

Abbreviations: HAE – Hereditary angioedema; mg – milligrams; NA – Not applicable; Q4W – Once every four weeks; Q8W – Once every eight weeks.

Source: OASIS-HAE CSR,⁷⁶ Riedl et al. 2024¹²

In addition to the phase III OASIS-HAE trial, the long-term safety and clinical efficacy of donidalorsen was evaluated through the OASISplus study – the study is ongoing at the time of this appraisal.^{36,77} OASISplus is a multicentre, open-label, long-term phase III study of donidalorsen which consists of two study arms: patients who rolled over from the OASIS-HAE phase III trial (i.e. OASISplus OLE cohort) and a *de novo* cohort of patients who switched from a commercially available alternative HAE LTP to donidalorsen (OASISplus switch cohort).^{36,77} The study included a qualification period of up to four-weeks, a 52-week treatment period, and a 13-week post-treatment period.⁷⁶ Following Week 53, participants were able to receive donidalorsen for an extended treatment period (Week 54 to Week 157).⁷⁶ The OASISplus study was not used to populate the economic model but is included in Sections 2.2 to 2.6 as the results of this study support the investigation of the long-term efficacy and safety of donidalorsen. This study was not included in the economic model because mature data were unavailable at the time of model generation. Additionally, the data from the randomised, placebo-controlled phase of the OASIS-HAE trial were considered more robust to inform the efficacy data in the economic model compared to the OLE data.

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 OASIS-HAE

Trial design

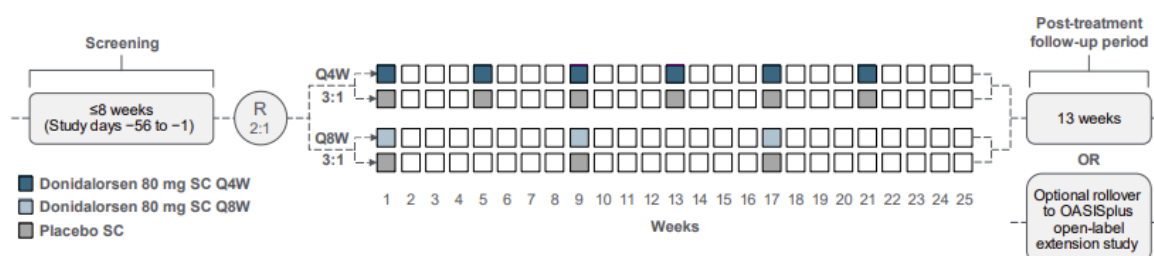
Company evidence submission template for donidalorsen for preventing hereditary angioedema attacks in people 12 years and over [ID6457]

The clinical efficacy of donidalorsen was evaluated through the OASIS-HAE study (NCT05139810); a phase III, multi-centre, double-blind, randomised, placebo-controlled study.¹² The study consisted of a screening period (up to 8 weeks) followed by a 24-week treatment period after which patients could complete up to 13-weeks post-treatment period or could enrol in the OLE arm of the OASISplus study (ISIS 721744-CS7), hereafter referred to as the 'OASISplus OLE cohort' of the OASISplus study.⁷⁶ The study included 21 sites in the European Union countries, 11 in North America, 5 in the Middle East and 3 in the UK.⁷⁶ Two dosing regimens were evaluated for donidalorsen in OASIS-HAE: 80 mg Q4W and 80 mg Q8W.⁷⁹

In total 116 patients were screened, 91 met the eligibility criteria and were randomised to receive either donidalorsen Q4W (n=46), donidalorsen Q8W (n=23) or placebo (n=22).⁷⁶ One patient in the donidalorsen Q4W group withdrew consent prior to receiving the study drug. Following the double-blind period, 94% of eligible patients in OASIS-HAE enrolled in the OASISplus OLE cohort.^{12,80}

A schematic presenting the design of OASIS-HAE is presented below in Figure 10.

Figure 10: OASIS-HAE study design



Abbreviations: HAE – Hereditary angioedema; mg; milligrams; Q4W – Once every four weeks; Q8W – Once every eight weeks; R – Randomisation; SC – Subcutaneous
Source: Riedl et al. 2024¹²

Randomisation

A total of 91 patients with Type I or Type II HAE were randomised 2:1 to receive either 4-week dosing interval or 8-week dosing interval of donidalorsen over a 24-week treatment period.⁷⁶ Within each dosing cohort, patients were then randomised

3:1 to receive 80 mg donidalorsen or a matching volume (0.8 mL) of placebo, administered subcutaneously. Patients were randomised via the Interactive Response Technology system and initiated treatment as soon as they experienced ≥ 2 HAE attacks during the screening period, assuming all other inclusion criteria were met.

All study participants, including clinical trial personnel were blinded throughout, until all patients had completed the study. In the event of a serious adverse event (SAE), the treatment assignment was revealed for that patient.⁷⁹

Eligibility

Eligible patients included males and females aged 12 years and over with a confirmed diagnosis of Type I or Type II HAE, and with at least two investigator-confirmed HAE attacks during the run-in period (56 days to one day before randomisation).⁷⁶ Patients also had to have access and the ability to use on-demand medication to treat any HAE attacks. Any patient with a concurrent diagnosis of Type III HAE or anticipated use of short-term prophylaxis for pre-planned procedures was excluded.⁷⁶

Trial drugs and concomitant medications

The donidalorsen dose of 80 mg Q4W was selected based on the safety and tolerability profile of donidalorsen from two previous trials, ISIS 721744-CS1 and ISIS 721744-CS2.⁷⁶ The marketing authorisation of donidalorsen 80 mg is anticipated to stipulate [REDACTED]¹⁶

No difference in outcomes data for donidalorsen Q1M compared to donidalorsen Q4W is anticipated, as the marginal difference in dosing frequency is expected to have a negligible difference to clinical outcomes for patients. ISIS 721744-CS1 evaluated doses of donidalorsen at 20, 40, 60, and 80 mg Q4W that were administered to healthy volunteers for a total of 12 weeks.⁷⁶ The highest dose level of 80 mg Q4W produced a mean decrease in plasma PKK levels of [REDACTED]% from baseline on [REDACTED].⁷⁶ A second dosing regimen of 80mg Q8W was also selected based on safety and tolerability data from

two other trials; ISIS 721744-CS2 OLE study and ISIS 721744-CS3.⁷⁶ Similarly, the marketing authorisation of donidalorsen 80 mg is anticipated to stipulate [REDACTED]

[REDACTED]¹⁶ No difference in outcomes data for donidalorsen Q2M compared to donidalorsen Q8W is anticipated. Administration of donidalorsen was carried out as subcutaneous injections either in a study centre or at home by a healthcare professional.⁷⁶ Self-administration was allowed after instructions and training were provided by qualified site personnel, and a Home Healthcare professional had to be available to complete all pre-dose procedures.

During the course of the study, the use of on-demand HAE medications (plasma-derived or recombinant C1-INH concentrates, bradykinin 2-receptor antagonists, or kallikrein inhibitors) to treat angioedema attacks were allowed, as determined by their treating physician. All other stable medications (if not excluded below) were allowed, so long as the dose and type were not expected to change during the study.⁷⁶

Disallowed concomitant therapy included:⁷⁶

- Chronic prophylaxis for angioedema attacks, except for a stable dose of androgens or tranexamic acid. Any use of other HAE prophylactic agents such as lanadelumab or berotralstat was not permitted during the treatment period.
- Angiotensin-converting enzyme (ACE) inhibitors or any oestrogen-containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy)
- Any oligonucleotides (including small interfering ribonucleic acid [siRNA]) other than donidalorsen
- Any other investigational drug or device

Endpoints

The primary endpoint was the time-normalised number of investigator-confirmed HAE attacks per four weeks from Week 1 to Week 25 for the donidalorsen Q4W group compared to placebo.⁷⁹ Investigator-confirmed HAE attacks were continuously collected until Week 25, with the time-normalised attack rate of all patients who discontinued the treatment period early included in the analysis.⁷⁹

To calculate the 4-week attack rate for each patient from Week 1 to Week 25, the number of attacks for a patient was divided by the number of days the patient contributed to the study and multiplied by 28 days.⁷⁹ The investigator-confirmed attacks were grouped into 28-day intervals by the start time of the attack.⁷⁹ These intervals were defined by the time of the first dose, with each subsequent interval beginning 28 days later, from the end of the previous interval.⁷⁹

Secondary endpoints included:⁷⁹

- Time-normalised number of investigator-confirmed HAE attacks from Week 1 to Week 25 for the donidalorsen Q8W group compared to placebo. This endpoint was analysed in the same way as the primary endpoint, with the analysis including the time-adjusted attack rate of patients who discontinued the treatment period between Week 1 and Week 25. For patients who withdrew before Week 1, the baseline HAE attack rate in the run-in period was used.
- Time-normalised number of investigator-confirmed HAE attacks from Week 5 to Week 25 compared to placebo. This endpoint was analysed in the same way as the primary endpoint, with the analysis including time-adjusted attack rate of patients who discontinued the treatment period between Week 5 to Week 25. For patients who withdrew before Week 5, the baseline HAE attack rate in the run-in period was used.
- The time-normalised number of moderate or severe investigator-confirmed HAE attacks from Week 5 to Week 25 compared to placebo. This endpoint

was analysed in the same way as the primary endpoint, with the analysis including time-adjusted attack patients who discontinued the treatment period between Week 5 to Week 25. For patients who withdrew before Week 5, the baseline rate of moderate or severe attacks in the run-in period was used.

- Number of participants with a clinical response defined as $\geq 50\%$, $\geq 70\%$, or $\geq 90\%$ reduction from baseline in investigator-confirmed HAE attack rate from Week 5 to 25 compared to placebo. Clinical response was analysed by calculating the percentage reduction of attack rate for each patient relative to the baseline attack rate. For patients who discontinued treatment before Week 25, the HAE attack rate was considered as the same before and after withdrawal.
- Change in AE-QoL Questionnaire total score at Week 25. Patient QoL was assessed during screening (baseline), Week 13 and 25 of the treatment period, and Week 13 of the post-treatment period (Week 17 for UK patients). The questionnaire contains 17 questions across four domains: functioning, fatigue/mood, fears/shame, and food. Each question has five response choices: never = 0, rarely = 1, occasionally = 2, often = 3, very often = 4. Scores are determined for each individual domain and a total score by calculating the percentage score from the maximum sum score for all completed questions. Patients who discontinued treatment due to adverse events or lack of efficacy were considered non-responders, while those who withdrew for other reasons were excluded from the analysis. Patients with missing baseline scores were also excluded from analysis for this endpoint.
- Percentage of participants who are well-controlled on the AECT at Week 25. This was assessed at Week 5, 9, 13, 17, 21, and 25 of the treatment period, as well as Week 4, 8 and 13 (Week 17 for UK patients) of the post-treatment period. The questionnaire consisted of four questions based on frequency, QoL, unpredictability and control of HAE, with each question having five response choices: very often = 0, often = 1, sometimes = 2, seldom = 3, and

not at all = 4. The total score is a sum of the four questions and a cutoff score of 10 was used to determine whether patients had poorly controlled disease (patients with scores less than 10 points have poorly controlled disease).⁸¹ For patients who discontinued treatment before Week 25, their total AECT score at Week 25 was taken as their most recent post-baseline score.

- Number of investigator-confirmed HAE attacks requiring on-demand HAE therapy from Week 5 to 25.
- Percentage of investigator-confirmed HAE attack-free patients from Week 5 to Week 25 compared to placebo. Attack freedom was analysed as a clinical response. The percentage reduction of attack rate for each patient was calculated by the difference between the attack rate from Week 5 to Week 25 and the attack rate during the run-in period (baseline), which was then divided by the baseline rate and multiplied by 100. For patients who discontinued treatment before Week 25, the HAE attack rate was considered as the same before and after withdrawal. The results for this outcome are reported in Appendix J.

The safety of donidalorsen was monitored throughout the study by the Investigator or Sponsor Medical Monitor. Safety was assessed by means of clinical laboratory findings and the incidence of adverse events (AE) in relation to the trial regimen.⁷⁶ Safety endpoints included assessment, type and severity of AEs, clinical laboratory parameters, vital signs and electrocardiograms.⁷⁹ The patient-reported exploratory endpoints included:

- Generalised Anxiety Disorder-7 questionnaire score
- Patient Global Impression of Severity
- WPAI questionnaire activity impairment score

Any of the following reasons would have led to the study being halted:⁷⁶

- Death in any patient in which the cause of death was judged to be probably or definitely related to the study drug by the treating investigator.
- The occurrence in any patient of a life-threatening SAE that was assessed to be related to the study drug by the treating investigator.
- Two occurrences of Grade ≥ 3 toxicities that were assessed to be related to the study drug by the treating investigator.
- Two occurrences of a clinically significant Grade ≥ 3 laboratory abnormality assessed to be related to the study drug by the treating investigator.

Table 5: Summary of methodology of OASIS-HAE

Trial number (acronym)	NCT05139810 (OASIS-HAE)
Location	The study was conducted at 39 centres in four areas: Europe, North America, Middle East and the UK.
Trial Design	OASIS-HAE is a phase III, multicentre, randomised, double-blind, placebo-controlled study of donidalorsen 80 mg or matching placebo administered Q4W or Q8W for 24 weeks in patients with HAE.
Eligibility criteria for participants	Inclusion criteria: • Patients, or their legally appointed and authorised representatives, must have provided a written and signed ICF, and when appropriate, an assent form, and any authorisations required by local law, and been able to comply with all study requirements for the duration of the study. • Patients must have been aged 12 years or over at the time of informed consent and, as applicable, assent • Patients must have had a documented diagnosis of HAE-1/HAE-2 based upon ALL of the following: ○ Documented clinical history consistent with HAE (subcutaneous or mucosal, non-pruritic swelling episodes without accompanying urticaria). ○ Diagnostic testing results that confirmed HAE-1/HAE-2: C1-INH functional level < 40% normal level. Patients with a functional level of 40% to 50% of normal could be enrolled if their complement factor C4 level was below the LLN or when a known pathogenic mutation in the <i>SERPING1</i> gene had been demonstrated. ○ At least 1 of the following: age at reported HAE onset ≤ 30 years; a family history consistent with HAE-1/HAE-2; or complement component 1q within the normal range. • Patients must have had the following: ○ Experienced a minimum of 2 HAE attacks (confirmed by the Investigator) during the Screening Period. ○ Be willing to complete the PRO assessments throughout the study as described in Study Protocol. ○ Had access to, and the ability to use, ≥ 1 on-demand medication(s) (e.g., plasma derived, or recombinant C1-INH concentrate or a bradykinin 2-receptor antagonist) to treat angioedema attacks. • Female patients had to be nonpregnant (and not planning a pregnancy during the study) and non-lactating, and been either: ○ Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy). ○ Post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years of age, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the post-menopausal range for the laboratory involved). ○ Abstinent (only acceptable as true abstinence, i.e., when in line with the preferred and usual lifestyle of the

Company evidence submission template for donidalorsen for preventing hereditary angioedema attacks in people 12 years and over [ID6457]

	patient; periodic abstinence [e.g., calendar, ovulation, symptothermal, or post ovulation methods], declaration of abstinence for the duration of the study, or withdrawal are not acceptable methods of contraception). ○ If engaged in sexual relations of childbearing potential, agreed to use acceptable contraceptive methods from the time of signing the ICF and, as applicable, assent form until at least 24 weeks after the last administration of study drug (donidalorsen or placebo). • Male patients had to be surgically sterile or, if engaged in sexual relations with a female of childbearing potential, the patient must have agreed to use an acceptable contraceptive method from the time of signing the ICF until at least 24 weeks after the last administration of study drug (donidalorsen or placebo). Exclusion criteria: • Anticipated use of short-term prophylaxis for angioedema attacks for a preplanned procedure during the Screening, Treatment or Post-Treatment Periods. • Concurrent diagnosis of any other type of recurrent angioedema, including acquired, idiopathic angioedema or HAE with normal C1-INH (also known as HAE Type 3). • Anticipated change in the use of concurrent androgen prophylaxis used to treat angioedema attacks. • Any clinically significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion in the study. The following laboratory values were exclusionary: ○ Alanine aminotransferase or aspartate aminotransferase $> 3 \times \text{ULN}$. ○ Total bilirubin $> 1.5 \times \text{ULN}$ OR, if due to Gilbert's syndrome, $> 5 \text{ mg/dL}$. ○ Platelet count $< 130 \text{ K/mm}^3$. ○ For patients ≥ 18 years old: $\text{eGFR} < 45 \text{ mL/min}$ (as determined by the Chronic Kidney Disease Epidemiology Collaboration formula for creatinine clearance). ○ For patients 12 and < 18 years old: $\text{eGFR} < 60 \text{ mL/min}$ (as determined by the Bedside Schwartz formula for creatinine clearance). • Patients with a history of acquired coagulopathies or bleeding diathesis (e.g., thrombocytopenia, disseminated intravascular coagulation, coagulopathy of liver disease, drug-induced platelet dysfunction, hyperfibrinolysis, acquired clotting factor inhibitors) and inherited bleeding disorders (e.g., hemophilia A, hemophilia B, other clotting factor deficiencies, qualitative platelet disorders, inherited thrombocytopenia, vascular abnormalities) and hypercoagulability. • Any clinically significant renal or hepatic diseases. • Active infection requiring systemic antiviral or antimicrobial therapy that would not have been completed prior to

	Study Day 1. • Active infection with human immunodeficiency virus, hepatitis C or hepatitis B diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C. Patients at Screening who tested positive by serology, but negative by RNA could be allowed in consultation with the Sponsor Medical Monitor. • Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that had been successfully treated. • Treatment with another investigational drug or biological agent within 1 month or 5 half-lives, whichever was longer, of Screening. • Participated in a prior donidalorsen study. • Exposure to any of the following medications: ○ ACE inhibitors or any oestrogen containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy) within 4 weeks prior to Screening. ○ Chronic prophylaxis with Takhzyro® (lanadelumab), Haegarda® (C1-esterase inhibitor SC), Cinryze® and Ruconest® (C1 esterase inhibitor) or Orladeyo® (berotralstat) within 5 half-lives prior to Screening (i.e., Takhzyro within 10 weeks prior to Screening, Haegarda/Beriner 2000/3000 subcutaneously/Cinryze/Ruconest within 2 weeks prior to screening, Orladeyo within 3 weeks prior to Screening). ○ Oligonucleotides (including siRNA) within 4 months of Screening if single administration received, or within 12 months of Screening if multiple doses received. This exclusion did not apply to vaccines. • Any condition that, in the opinion of the Investigator or designee, may have compromised the patient's safety or compliance, precluded successful conduct of the study, or interfered with the interpretation of results. • Recent history (3 years) of, or current drug or alcohol abuse.
Settings and locations where the data were collected	A total of 39 sites enrolled and randomised at least 1 patient including: 21 in European Union countries, 11 in North America, 5 sites in the Middle East and 2 in the UK. Efficacy and safety assessments were conducted at specified study centre visits by the study site personnel and confirmed by the Investigator. Site personnel contacted the patients approximately weekly to inquire about any attack that may have occurred. Patients were also requested to complete scheduled AE-QoL, other PRO questionnaires, and reported healthcare utilisation data.
Trial drugs	Patients received a single SC dose of donidalorsen or placebo Q4W or Q8W during the 24-week treatment period. Patients were randomised to receive any of the following dosing regimens: • Donidalorsen 80 mg Q4W (n=45). • Donidalorsen 80 mg Q8W (n=23).

	• Placebo (n=22). Patients were randomly assigned in a 2:1 ratio to Cohort A (donidalorsen 80 mg Q4W or matched placebo) or Cohort B (donidalorsen 80 mg Q8W or matched placebo), respectively. Within each cohort, patients were randomly assigned in a 3:1 ratio to receive donidalorsen or a matching volume of placebo.
Permitted and disallowed concomitant medication	Allowed concomitant medications included: • The use of on-demand HAE medication (plasma-derived or recombinant C1-INH concentrate, bradykinin 2-receptor antagonist, or kallikrein inhibitor) to treat angioedema attacks was allowed as medically indicated. All other stable medications were allowed if dose and type was not expected to change during the study. • Disallowed concomitant therapies included: • Chronic prophylaxis for angioedema attacks, except for a stable dose of androgens or tranexamic acid. Any use of other HAE prophylactic agents such as lanadelumab or berotralstat was not permitted during the Treatment Period. • ACE inhibitors or any oestrogen-containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy). • Any oligonucleotides (including siRNA) other than donidalorsen. • Any other investigational drug or device.
Primary outcomes	Time-normalised number of investigator-confirmed HAE attacks (per 4 weeks) from Week 1 to Week 25 compared to placebo for the donidalorsen 80 mg Q4W.
Other outcomes used in the economic models	• The time-normalised number of investigator-confirmed HAE attacks (per 4 weeks) from Week 1 to Week 25 compared to placebo for the donidalorsen 80 mg Q8W • The time-normalised number of investigator-confirmed HAE attacks (per 4 weeks) from Week 5 to Week 25 compared to placebo. • The percentage of investigator-confirmed HAE attack-free patients from Week 5 to Week 25 compared to placebo. • The time normalised number of moderate or severe investigator-confirmed HAE attacks (per 4 weeks) from Week 5 to Week 25 compared to placebo.
Pre-planned subgroups	Subgroup analyses were planned to evaluate the consistency of analysis in the primary endpoint over parameters such as demographic and baseline characteristics: • Age Category (12-17, 18-39, 40–64, ≥ 65 years of age). • Sex (Male, Female). • Race (Caucasian, Other). • Regions (North America, Europe, Middle East)

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	• Use of predefined prophylactic therapy, including lanadelumab, berotralstat, C1-esterase inhibitor. (Yes, No).

Abbreviations: ACE – Angiotensin converting enzyme; AECT – Angioedema control test; AE-QoL – Angioedema quality of life questionnaire; ALT - Alanine aminotransferase; AST - Aspartate aminotransferase; C1-INH – C1-erastase inhibitor; eGFR - Estimated glomerular filtration rate; FSH - Follicle-stimulating hormone; HAE – Hereditary angioedema; ICF - Informed consent form; LLN - Lower limit of normal; mg – milligrams; PRO – Patient-reported outcomes; Q4W – Once every four weeks; Q8W – Once every eight weeks; SC – Subcutaneous; siRNA; small interfering ribonucleic acid; UK – United Kingdom; ULN – Upper limit of normal
Source: OASIS-HAE CSR⁷⁶, Riedl et al. 2024¹²

Baseline characteristics

Patient characteristics across treatment groups were generally well balanced.⁷⁶ HAE type was similar across the treatment groups, with most patients having a Type I diagnosis in the donidalorsen Q4W (93%), Q8W (96%) and placebo (91%) groups.⁷⁶ Similarly, mean age of onset was similar across groups in the Q4W (age 12), Q8W (age 11), and placebo (age 13) groups.⁷⁶ However, there was some variation in predefined prophylactic therapy use between treatment groups, with a higher percentage of reported use in the placebo (23%) and the donidalorsen Q8W (22%) groups, compared to the donidalorsen Q4W group (13%).⁷⁶ Furthermore, there was a higher proportion of patients with a family history of HAE in the donidalorsen Q4W (91%) and Q8W groups (87%) compared to placebo the group (77%).⁷⁶ A summary of the patient demographics and baseline characteristics is presented in Table 6.

Table 6: Summary of patient demographics and baseline characteristics (full analysis set), OASIS-HAE

Demographics/ baseline characteristics	Placebo (N =22)	Donidalorsen 80 mg every 4 weeks (N=45)	Donidalorsen 80 mg every 8 weeks (N=23)
Age (years)			
Mean (SD)	██████████ ██████████	██████████ ██████████	██████████ ██████████
Age Group (years)			
12 to 17	0	4 (8.9)	3 (13.0)
18 to 39	15 (68.2)	19 (42.2)	12 (52.2)
40 to 64	7 (31.8)	21 (46.7)	7 (30.4)
≥ 65	0	1 (2.2)	1 (4.3)
Sex, n (%)			
Male	14 (63.6)	17 (37.8)	11 (47.8)
Female	8 (36.4)	28 (62.2)	12 (52.2)
Ethnicity n (%)			
Hispanic or Latino	██████████	██████████	██████████
Not Hispanic or Latino	██████████	██████████	██████████
Race n (%)			
American Indian or Alaskan Native	2 (9.1)	0	1 (4.3)
Asian	0	1 (2.2)	0

Demographics/ baseline characteristics	Placebo (N =22)	Donidalorsen 80 mg every 4 weeks (N=45)	Donidalorsen 80 mg every 8 weeks (N=23)
Black or African American	1 (4.5)	1 (2.2)	0
White	18 (81.8)	42 (93.3)	22 (95.7)
Multiple	1 (4.5)	0	0
Other	0	1 (2.2)	0
Mean BMI, kg/m ² (SD) ^a	28.88 (9.22)	28.03 (6.74)	26.97 (5.40)
Family History of HAE, n (%)			
Yes	██████	██████	██████
No	██████	██████	██████
Mean number of attacks in past 12 months, (SD)	29.1 (21.13)	45.7 (43.04)	33.3 (21.95)
Historical C1-INH Activity (%)			
N	██	██	██
Mean (SD)	██████ ██████	██████ ██████	██████ ██████
Mean years from diagnosis to informed consent, (SD)	██████ ██████	██████ ██████	██████ ██████
Age at Onset (Years)			
N	██	██	██
Mean (SD)	12.9 (7.19, 1.57)	11.6 (9.85, 1.47)	10.9 (7.73, 1.61)
HAE Type, n (%)			
HAE-1	20 (90.9)	42 (93.3)	22 (95.7)
HAE-2	2 (9.1)	3 (6.7)	1 (4.3)
Types of Attacks Experienced, n (%)			
Peripheral	██████	██████	██████
Abdominal	██████	██████	██████
Laryngeal	██████	██████	██████
Any Predefined Prophylactic Therapy Use, n (%)^b			
Yes	██████	██████	██████
No	██████	██████	██████
Mean run-in period attack rate per 4 weeks, (SD) ^c	2.90 (1.66)	3.61 (2.24)	3.18 (2.15)

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Demographics/ baseline characteristics	Placebo (N =22)	Donidalorsen 80 mg every 4 weeks (N=45)	Donidalorsen 80 mg every 8 weeks (N=23)
Run-in period HAE Attack Rate, n (%)			
≤ 2 attacks/4-weeks	██████	██████	██████
2 to 5 attacks/4-weeks	██████	██████	██████
> 5 attacks/4-weeks	██████	██████	██████

Abbreviations: BMI – Body mass index; C1-INH – C1-inhibitor; CI – Confidence interval; HAE – Hereditary angioedema; kg – kilogram; m – metre; mg – milligrams; SD – Standard deviation

Notes: ^a Total number of patients analysed for BMI in placebo group n = 21, which makes the total in the 'All Patients' group = 89.

^bFirst-line prophylactic agents and excluded attenuated androgens and tranexamic acid.

^cThe run-in period (Screening) HAE attack rate for each patient was calculated as the number of investigator-confirmed HAE attacks occurring during the run-in period divided by the number of days the patient contributed to the run-in period and then multiplied by 28.

Source: OASIS-HAE CSR⁷⁶, Riedl et al. 2024¹²

2.3.1.1 Discontinuation

Eight patients discontinued treatment early: two (4.3%) in the donidalorsen Q4W group, two (8.7%) in the donidalorsen Q8W group, and four (18.2%) in the placebo group. The most common reason for discontinuation was lack of efficacy, defined as patients who experienced at least five HAE attacks per month for two consecutive months after Week 5 (one [2.2%] in the donidalorsen Q4W group, one [4.3%] in the donidalorsen Q8W group and three [13.6%] in the placebo group).^{12,76} One patient in the donidalorsen Q4W group discontinued due to voluntary withdrawal before the first administration of the study drug, one patient in the donidalorsen Q8W group discontinued due to an AE of alanine aminotransferase (ALT) increase, and one patient in the placebo group discontinued due to pregnancy. Overall, a higher proportion of patients in the donidalorsen Q4W group (44 [95.7%]) and the donidalorsen Q8W group (21 [91.3%]) completed treatment compared with the placebo group (18 [81.8%]).⁷⁶ A summary of patient discontinuation and disposition is provided in Table 7.⁷⁶ A Consolidated Standards of Reporting Trials (CONSORT) diagram of patient flow is presented in Appendix B.

Table 7: Patient disposition (All screened patients)

Patient Disposition	Placebo (N = 22) n (%)	Donidalorsen 80 mg Q4W (N = 46) n (%)	Donidalorsen 80 mg Q8W (N = 23) n (%)	All Patients (N = 116) n (%)
Patients Randomised ^a	22	46	23	91
Patients Dosed ^b	22 (100)	45 (97.8)	23 (100)	90 (98.9)
Patients Who Completed the Study Treatment	18 (81.8)	44 (95.7)	21 (91.3)	83 (91.2)
Patients Who Terminated Early from the Study Treatment	4 (18.2)	2 (4.3) ^b	2 (8.7)	8 (8.8)
Primary Reason for Early Termination of Study Treatment				
Voluntary Withdrawal	0	1 (2.2) ^b	0	1 (1.1)
Pregnancy	1 (4.5)	0	0	1 (1.1)
Adverse Event or SAE	0	0	1 (4.3) ^d	1 (1.1)
Lack of Efficacy ^c	3 (13.6)	1 (2.2)	1 (4.3)	5 (5.5)

Abbreviations: AE – Adverse event; ALT – Alanine aminotransferase; HAE – Hereditary angioedema; mg – milligrams; OLE – Open-label extension; SAE – Serious adverse event(s)

Note: ^a The denominator of the percentages in the table are the number of randomised patients.

^b One patient in the donidalorsen Q4W group withdrew consent prior to receiving study drug.

^c Lack of efficacy was defined per protocol as patients who experienced at least 5 HAE Investigator-confirmed attacks per month for 2 consecutive months after Week 5. These patients terminated treatment early in the current study and enrolled into the OLE arm of Study ISIS 721744-CS7.

^d One patient in the donidalorsen Q8W group discontinued due to an AE of ALT increased. Although the stopping rule was not met in the donidalorsen Q8W group, study drug was permanently discontinued due to the AE of ALT increased per Investigator's decision.

Source: Riedl et al. 2024¹²

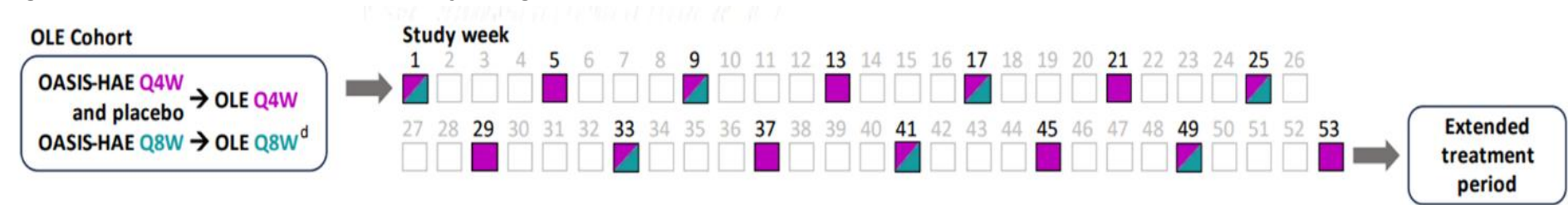
2.3.2 OASISplus

Trial design

The long-term safety and clinical efficacy of donidalorsen was evaluated through the OASISplus study, which is still ongoing at the time of this appraisal.^{36,77} OASISplus consisted of two cohorts: an OLE cohort comprising patients from the OASIS-HAE trial, referred to as the OASISplus OLE cohort; and a *de novo* cohort of patients receiving donidalorsen after treatment with other LTPs, hereafter referred to as the OASISplus switch cohort.

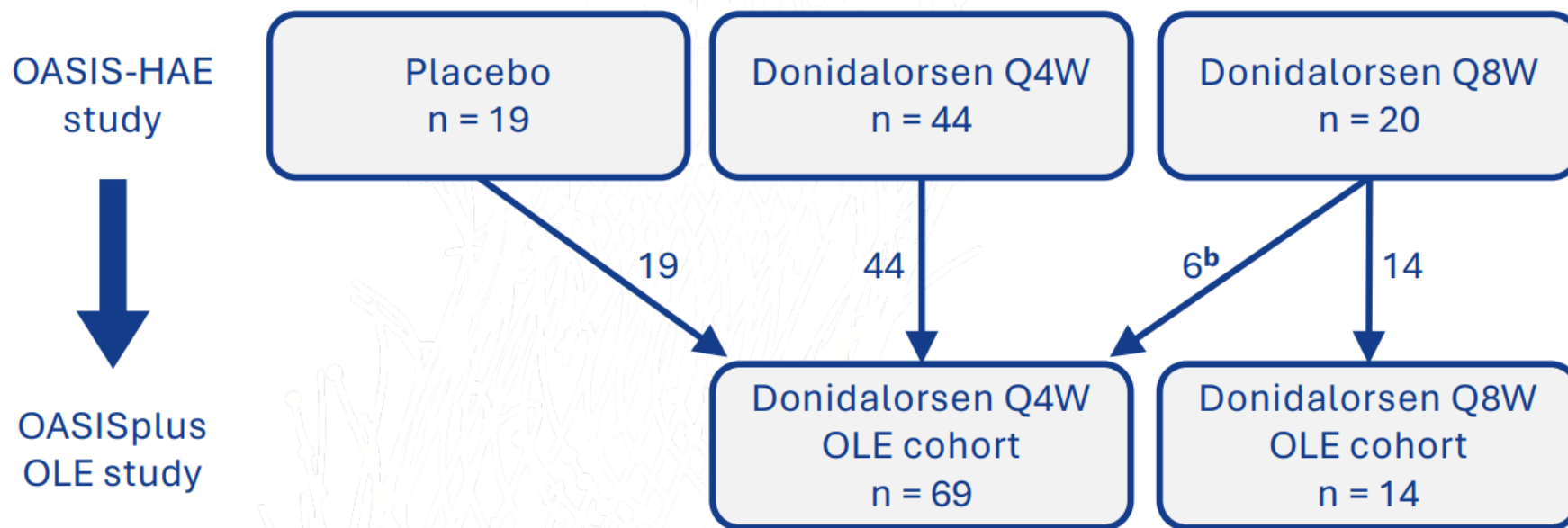
After completion of the double-blind OASIS-HAE study, 83 patients were enrolled into the OASISplus OLE cohort.³⁶ Here, patients received donidalorsen 80 mg Q4W (n=69) or Q8W (n=14) for a 52-week OLE treatment period, for up to 157 weeks in total. All patients randomised to placebo or Q4W donidalorsen dosing in OASIS-HAE received Q4W dosing in the OASISplus OLE cohort.³⁶ Patients randomised to Q8W dosing who were *not* attack-free for ≥ 8 weeks also received Q4W dosing (n=6); all other patients receiving Q8W dosing remained on this dose (n=14). Schematics presenting the study design and patient flow from OASIS-HAE for the OASISplus OLE cohort are presented below in Figure 11 and Figure 12, respectively.

Figure 11: OASISplus OLE cohort study design



Abbreviations: HAE – Hereditary angioedema; OLE – Open-label extension; Q4W – Once every four weeks; Q8W – Once every eight weeks
Source: Tachdjian et al. 2024³⁶

Figure 12: OASISplus OLE cohort patient flow



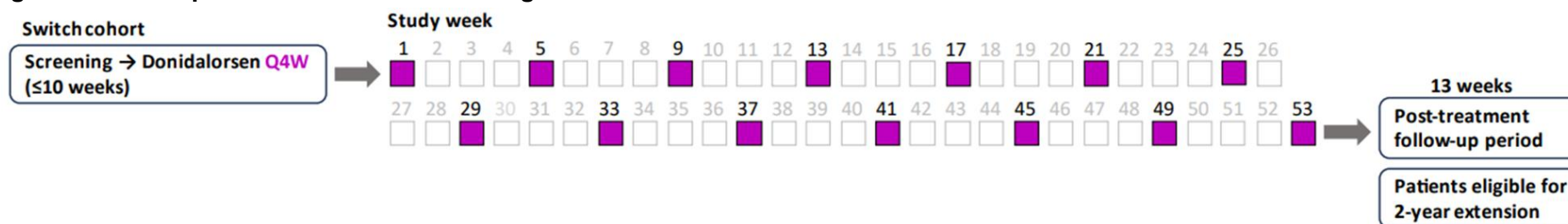
^a83 of 88 eligible patients rolled over into the OASISplus study. ^bPatients who were not attack-free for ≥ 8 weeks (Weeks 17–25 in OASIS-HAE) received donidalorsen 80 mg SC Q4W

Abbreviations: HAE – Hereditary angioedema; OLE – Open-label extension; Q4W – Once every four weeks, Q8W – Once every eight weeks

Source: Tachdjian et al. 2024³⁶

In addition to the OASISplus OLE cohort, a further 64 patients were enrolled into the OASISplus switch cohort to receive donidalorsen 80 mg Q4W following a stable dose of lanadelumab (N = 31), berotralstat (N = 11), or C1-INH (N = 22) for at least 12 weeks prior to the screening period.⁷⁷ After screening, patients followed a consolidated switching protocol from prior LTP to donidalorsen, which is detailed in Appendix J. A schematic presenting the design of the OASISplus switch cohort study is presented below in Figure 13.

Figure 13: OASISplus switch cohort trial design



Abbreviations: HAE – Hereditary angioedema; Q4W – Once every four weeks

Source: Riedl et al. 2024⁷⁷

Endpoints

The primary objective of OASISPlus was to evaluate the safety of long-term dosing with donidalorsen in patients with HAE.^{36,77} The primary endpoint was the incidence and severity of TEAEs while secondary endpoints evaluated the long-term efficacy and effects of donidalorsen on number of HAE attacks (HAE attacks per month) and QoL (AE-QoL).^{36,77} The percentage of patients with well-controlled disease over 52 weeks assessed by the AECT was an exploratory endpoint.^{36,77}

Baseline characteristics

A summary of patient demographics and disposition for the OASISplus OLE cohort, and patient baseline characteristics and disposition for the OASISplus switch cohort is presented in Appendix J.

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

OASIS-HAE

Statistical analysis of the primary endpoint was conducted on the full analysis set (FAS), which includes all patients who received at least one dose of donidalorsen or placebo. Analyses or summaries were conducted by randomised treatment group. The safety analysis set (SAS) was equal to the FAS. The FAS was used as the basis for the primary efficacy analysis whereas the SAS was used for assessment of the safety outcomes. Exploratory subgroup analyses were conducted for the primary endpoint by sex, age, race, region and predefined prophylactic therapy, as in Section 2.8.⁷⁶ A summary of the statistical analysis and methods is outlined in Table 8.⁷⁶

OASISplus

The primary outcome was assessed in the safety population, which is defined as all patients enrolled in the OLE who received at least one dose of donidalorsen.⁸² Secondary outcomes were assessed in the intention to treat (ITT) population, defined as enrolled patients, and the per-protocol population, defined as patients in the ITT population who were treated according to the protocol.⁸² Due to the absence

of a control group in this study, no formal statistical testing was conducted, and all efficacy data were presented as descriptive statistics.

Table 8: Summary of statistical analysis of OASIS-HAE

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculations	Data management, patient withdrawal
NCT05139810 (OASIS-HAE)	The primary efficacy endpoint was the time-normalised number of Investigator-confirmed HAE attacks (per 4-weeks) from Week 1 to Week 25 compared to placebo for the donidalorsen 80 mg once Q4W group ¹²	The primary analysis was performed using a Poisson regression model and Pearson chi-square scaling of standard errors to account for potential overdispersion on the FAS. The model includes fixed effect for treatment group (categorical), Baseline (the time-normalised run-in period attack rate, continuous), and the Treatment-by-Baseline interaction as covariates, and the logarithm of time in every-4-week that each patient was observed from Week 1 to Week 25 was used as an offset variable.⁷⁹ From this model, the LSM rate, the SE and the corresponding 95% confidence interval for each treatment group as well as the model adjusted mean rate ratios of donidalorsen Q4W 80 mg relative to the pooled placebo group and the corresponding 95% confidence interval were estimated. These estimates were reported as mean event rates per every-4-week by transforming the estimates using the exponential function. The p-value of the Wald-based chi-square test were reported for testing the hypothesis.⁷⁹ The primary efficacy endpoint was tested using the following hypothesis: $H_0: \lambda_{\text{ISIS 721744}} / \lambda_{\text{placebo}} = 1$ versus $H_1: \lambda_{\text{ISIS 721744}} / \lambda_{\text{placebo}} \neq 1$ $\lambda_{\text{ISIS 721744}}$ refers to the Investigator-confirmed HAE attack rate from Week 1 to Week 25 in the donidalorsen 80 mg Q4W group and λ_{placebo} refers to the investigator-confirmed HAE attack rate in the placebo group. The null hypothesis was that the Investigator-confirmed HAE attack rate ratio from Week 1 to Week 25 is 1 (no difference between treatment groups), versus the alternative hypothesis that the Investigator-confirmed HAE attack rate ratio is not 1. Estimated attack rate ratios less than 1 would indicate that patients treated with donidalorsen 80 mg Q4W, on average, have a lower incidence of Investigator-confirmed HAE attacks from Week 1 to Week 25. The hypothesis was tested using a Poisson regression model.⁷⁹ The percentage difference in mean Investigator-confirmed HAE attack	The power and sample size estimations were calculated using simulations based on a generalised linear model for count data assuming a Poisson distribution. Assuming an HAE attack rate of 13.26 attacks per 6-month period in the placebo group and an HAE attack rate of 1.38 attacks per 6-month period in the donidalorsen Q4W group, the sample size of 54 patients (2:1 ratio) would provide at least	An electronic case report form using an Electronic Data Capture application was used in this study.

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Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculations	Data management, patient withdrawal
		rate between donidalorsen 80 mg Q4W and the pooled placebo was calculated as $100\% \times (\text{model adjusted mean rate ratio} - 1)$. Similarly, the estimated upper and lower confidence limits for the model adjusted mean rate ratio were transformed by subtracting 1 and multiplying by 100% to calculate 95% confidence intervals for the percentage change. In the case when the Poisson regression model could not be converged, e.g., when all patients within one treatment group have 0 post-baseline Investigator-confirmed HAE event, Fisher's Exact Test was used for the analysis instead of Poisson regression. The odds ratio, corresponding 95% CI, and p-value was provided⁷⁹. The secondary endpoints were analysed using the same method as the primary analysis. All statistical tests were conducted using 2-sided tests with 5% Type I error rate unless otherwise stated. All report outputs were produced using SAS® version 9.4 or higher. To control for multiplicity, a hierarchical testing procedure was applied to a fixed sequence of 24 end points.	90% power for the primary endpoint, with a 0.05 significance level. A total of approximately 84 patients (42 per 4 weeks group, 21 in the placebo group, and 21 in the donidalorsen Q8W group) were planned to be enrolled in this study to account for potential early dropouts and to facilitate some general safety evaluations⁷⁹.	

Abbreviations: CI – Confidence interval; eCRF – Electronic case report form; FAS – Full analysis set; HAE – Hereditary angioedema; LSM – Least squares mean; mg – milligrams; Q4W – Once every four weeks; Q8W – Once every eight weeks; SE – Standard Error

Source: Riedl et al. 2024¹²; OASIS-HAE CSR⁷⁶

2.5 Critical appraisal of the relevant clinical effectiveness evidence

The robustness and reliability of OASIS-HAE was assessed using the Cochrane risk of bias tool for RCTs.⁸³ No signs of significant bias were identified during the critical appraisal. Randomisation of patients was clearly described, and baseline characteristics were well balanced across cohorts. The full assessment for the study can be found in Appendix B.

2.6 Clinical effectiveness results of the relevant studies

The following section describes the results of the pivotal OASIS-HAE trial and the subsequent OASISplus study. As outlined in Section 2.3.1, the dosing regimens selected for donidalorsen in OASIS-HAE were Q4W and Q8W.⁷⁶ The anticipated marketing authorisation for donidalorsen stipulates [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED].¹⁶ The trial data are therefore presented as donidalorsen Q4W and donidalorsen Q8W; [REDACTED]
[REDACTED]
[REDACTED].

2.6.1 OASIS-HAE primary endpoint

2.6.1.1 Investigator-confirmed HAE attack rate, donidalorsen 80 mg Q4W compared to placebo, Week 1 to Week 25

The mean (SD) time-normalised investigator-confirmed HAE attack rate (per 4 weeks) was [REDACTED] for the donidalorsen Q4W group compared with [REDACTED] for the placebo group.⁷⁶ The least squares mean (LSM) time-normalised investigator-confirmed HAE attack rate was 0.44 (95% CI: 0.27, 0.73) for the donidalorsen Q4W group and 2.26 (95% CI: 1.66, 3.09) for the placebo group, representing an 81% (95% CI: -89.3%, -64.9%) reduction relative to placebo for the donidalorsen Q4W ($p < 0.001$).⁷⁶

Table 9: Investigator-confirmed HAE attack rate (per 4 weeks) from Week 1 to Week 25 for the donidalorsen Q4W group (FAS)

Time-normalised HAE attacks	Placebo (N=22)	Donidalorsen 80 mg Q4W (N=45)
Run-in period HAE attack rate^a		
Mean (SD)	2.90 (1.66)	3.61 (2.24)
Time-normalised HAE attack rate from Week 1 to Week 25^b		
Mean (SD)	██████████	██████████
Poisson Regression^c		
Least square mean rate (95% CI)	2.26 (1.66, 3.09)	0.44 (0.27, 0.73)
Model Adjusted Mean Rate ratio (95% CI)	-	██████████
P-value	-	<0.001
Percent difference relative to placebo (95% CI) ^d	-	-81% (-89.3%, -64.9%)

Abbreviations: CI – Confidence interval; FAS – Full analysis set; HAE – Hereditary angioedema; mg – milligrams; SD – Standard deviation

Notes: ^aThe run-in period (Screening) HAE attack rate (per 4 weeks) for each patient was calculated as the number of Investigator-confirmed HAE attacks that occurred during the run-in period divided by the number of days the patient contributed to the run-in period and then multiplied by 28.

^bThe time-normalised HAE attack rate (per 4 weeks) was calculated as number of Investigator-confirmed HAE attacks that occurred from Week 5 to Week 25, divided by the number of days the patient contributed to that period, and then multiplied by 28.

^cThe Poisson regression model included treatment groups, Baseline (the run-in period HAE attack rate), the Treatment-by-Baseline interaction as a covariate, and the logarithm of time per 4 weeks that each patient was observed from Week 1 to Week 25 used as an offset variable (e.g., log (6) if the patient stayed in the study for 24 weeks). Pearson chi-square scaling of standard errors was used to account for potential overdispersion.

^d The percentage difference in mean Investigator-confirmed HAE attack rate between donidalorsen 80 mg and placebo groups were calculated as 100% * (mean rate ratio -1). Similarly, the estimated upper and lower confidence limits for the mean rate ratio can be transformed by subtracting 1 and multiplying by 100% to calculate 95% confidence intervals for the percentage change.

Source: Riedl et al. 2024¹²; OASIS-HAE CSR⁷⁶

2.6.2 OASIS-HAE secondary endpoints

2.6.2.1 Investigator-confirmed HAE attack rate (per 4 weeks), donidalorsen 80 mg Q8W compared to placebo, Week 1 to Week 25

The mean (SD) time-normalised HAE attack rate (per 4 weeks) from Week 1 to Week 25 was ██████████ for the donidalorsen Q8W group compared to ██████████ for the placebo group.⁷⁶ The LSM time-normalised investigator-confirmed HAE attack rate was 1.02 (95% Confidence interval [CI]: 0.65, 1.59) for the donidalorsen Q8W group and 2.26 (95% CI: 1.66, 3.09) in the placebo group, demonstrating a 55% reduction (95% CI: -73.9%, -22.3%) in the donidalorsen Q8W group 80 mg relative to placebo (p=0.004).⁷⁶

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Table 10: Investigator-confirmed HAE attack rate (per 4 weeks) from Week 1 to Week 25 for the donidalorsen Q8W group (FAS)

Time-normalised HAE attacks	Placebo (N=22)	Donidalorsen 80 mg Every 8 Weeks (N=23)
Run-in period HAE attack rate^a		
Mean (SD)	2.90 (1.66)	3.18 (2.15)
Time-normalised HAE attack rate from Week 1 to Week 25^b		
Mean (SD)	██████████	██████████
Poisson Regression^c		
Least square mean rate (95% CI)	2.26 (1.66, 3.09)	1.02 (0.65, 1.59)
Model adjusted mean rate ratio (95% CI)	-	██████████
P-value	-	0.004
Percent difference relative to placebo (95% CI) ^d	-	-55% (-73.9%, -22.3%)

Abbreviations: CI – Confidence interval; FAS – Full analysis set; HAE – Hereditary angioedema; mg – milligrams; Q8W – Every eight weeks; SD – Standard deviation

Notes: ^a The run-in period (Screening) HAE attack rate (per 4 weeks) for each patient was calculated as the number of Investigator-confirmed HAE attacks that occurred during the run-in period divided by the number of days the patient contributed to the run-in period, and then multiplied by 28.

^b The time-normalised HAE attack rate (per 4 weeks) was calculated as number of Investigator-confirmed HAE attacks that occurred from Week 1 to Week 25, divided by the number of days the patient contributed to that period, and then multiplied by 28.

^c The Poisson regression model included treatment groups, Baseline (the run-in period HAE attack rate), the Treatment-by-Baseline interaction as a covariate, and the logarithm of time in every 4 weeks that each patient was observed from Week 1 to Week 25 used as an offset variable (e.g., log (6) if the patient stayed in the study for 24 weeks). Pearson chi-square scaling of standard errors was used to account for potential overdispersion.

^d The percentage difference in mean Investigator-confirmed HAE attack rate between donidalorsen 80 mg and placebo groups were calculated as 100% * (mean rate ratio -1). Similarly, the estimated upper and lower confidence limits for the mean rate ratio can be transformed by subtracting 1 and multiplying by 100% to calculate 95% confidence intervals for the percentage change.

Source: Riedl et al. 2024¹²; OASIS-HAE CSR⁷⁶

2.6.2.2 Investigator-confirmed HAE attack rate (per 4 weeks), from Week 5 to Week 25

The LSM time-normalised investigator-confirmed HAE attack rate from Week 5 to Week 25 was 0.30 (95% CI: 0.15, 0.58) for the donidalorsen Q4W group and 2.25 (95% CI: 1.59, 3.18) for the placebo group, representing an 87% (95% CI: -93.8%, -71.9%,) reduction relative to placebo ($p < 0.001$).⁷⁶ An improvement was also observed in the donidalorsen Q8W group, with LSM time-normalised investigator-confirmed HAE attack rate from Week 5 to Week 25 of 0.90 (95% CI, 0.53, 1.52) and 2.25 (95% CI: 1.59, 3.18) for the placebo group, representing a 60% (95% CI: -78.8%, -25.2%) reduction relative to placebo ($p = 0.004$).⁷⁶

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Table 11: Investigator-confirmed HAE attack rate (per 4 weeks) from Week 5 to Week 25 (FAS)

Time-normalised HAE attacks	Placebo (N=22)	Donidalorsen 80 mg Q4W (N=45)	Donidalorsen 80 mg Q8W (N=23)
Run-in period HAE attack rate^a			
Mean (SD)	2.90 (1.66)	3.61 (2.24)	3.18 (2.15)
Time-normalised HAE attack rate from Week 5 to Week 25^b			
Mean (SD)			
Poisson Regression^c			
Least square mean rate (95% CI)	2.25 (1.59, 3.18)	0.30 (0.15, 0.58)	0.90 (0.53, 1.52)
Model adjusted mean rate ratio (95% CI)	-		
P-value	-	<0.001	0.004
Percent difference relative to placebo (95% CI) ^d	-	-87% (-93.8%, -71.9%)	-60% (-78.8%, -25.2%)

Abbreviations: CI – Confidence interval; FAS – Full analysis set; HAE – Hereditary angioedema; mg – milligrams; Q4W – Once every four weeks; Q8W – Once every eight weeks; SD – Standard deviation

Notes: ^a The run-in period (Screening) HAE attack rate (per 4 weeks) for each patient was calculated as the number of Investigator-confirmed HAE attacks that occurred during the run-in period divided by the number of days the patient contributed to the run-in period, and then multiplied by 28.

^b The time-normalised HAE attack rate (per 4 weeks) was calculated as number of Investigator-confirmed HAE attacks that occurred from Week 1 to Week 25, divided by the number of days the patient contributed to that period, and then multiplied by 28.

^c The Poisson regression model included treatment groups, Baseline (the run-in period HAE attack rate), the Treatment-by-Baseline interaction as a covariate, and the logarithm of time in every 4 weeks that each patient was observed from Week 1 to Week 25 used as an offset variable (e.g., log (6) if the patient stayed in the study for 24 weeks). Pearson chi-square scaling of standard errors was used to account for potential overdispersion.

^d The percentage difference in mean Investigator-confirmed HAE attack rate between donidalorsen 80 mg and placebo groups were calculated as 100% * (mean rate ratio -1). Similarly, the estimated upper and lower confidence limits for the mean rate ratio can be transformed by subtracting 1 and multiplying by 100% to calculate 95% confidence intervals for the percentage change.

Source: Riedl et al. 2024¹²; OASIS-HAE CSR⁷⁶

2.6.2.3 Investigator-confirmed moderate or severe HAE attack rate (per 4 weeks) from Week 5 to Week 25

The LSM time-normalised investigator-confirmed number of moderate or severe HAE attacks rate (per 4 weeks) from Week 5 to Week 25 was 0.12 (95% CI: 0.04, 0.35) for the donidalorsen Q4W group and 1.15 (95% CI: 0.72, 1.83) for the placebo group, representing a reduction of 89% (95% CI: 66.1%, 96.5%) in the moderate or severe HAE attack rate relative to placebo for the donidalorsen Q4W group ($p < 0.001$).⁷⁶ A reduction in moderate or severe HAE attacks of 41% (95% CI: -72.4%, 26.0%) was also observed in the donidalorsen Q8W group compared to placebo.⁷⁶

Table 12: Investigator-confirmed moderate or severe HAE attack rate (per 4 weeks) from Week 5 to Week 25 (FAS)

Time-normalised HAE attacks	Placebo (N=22)	Donidalorsen 80 mg Q4W (N=45)	Donidalorsen 80 mg Q8W (N=23)
Run-in period HAE attack rate^a			
Mean (SD)			
Time-normalised HAE attack rate from Week 5 to Week 25^b			
Mean (SD)			
Poisson Regression^c			
Least square mean rate (95% CI)	1.15 (0.72, 1.83)	0.12 (0.04, 0.35)	0.68 (0.37, 1.23)
Model adjusted mean rate ratio (95% CI)	-		
P-value	-	<0.001	0.173
Percent difference relative to placebo (95% CI) ^d	-	-89% (-96.5%, -66.1%)	-41% (-72.4%, 26.0%)

Abbreviations: CI – Confidence interval; FAS – Full analysis set; HAE – Hereditary angioedema; mg – milligrams; Q4W – Once every four weeks; Q8W – Once every eight weeks; SD – Standard deviation

Notes: ^a The run-in period (Screening) HAE attack rate (per 4 weeks) for each patient was calculated as the number of Investigator-confirmed HAE attacks that occurred during the run-in period divided by the number of days the patient contributed to the run-in period, and then multiplied by 28.

^b The time-normalised HAE attack rate (per 4 weeks) was calculated as number of Investigator-confirmed HAE attacks that occurred from Week 1 to Week 25, divided by the number of days the patient contributed to that period, and then multiplied by 28.

^c The Poisson regression model included treatment groups, Baseline (the run-in period HAE attack rate), the Treatment-by-Baseline interaction as a covariate, and the logarithm of time in every 4 weeks that each patient was observed from Week 1 to Week 25 used as an offset variable (e.g., log (6) if the patient stayed in the study for 24 weeks). Pearson chi-square scaling of standard errors was used to account for potential overdispersion.

^d The percentage difference in mean Investigator-confirmed HAE attack rate between donidalorsen 80 mg and placebo groups were calculated as 100% * (mean rate ratio -1). Similarly, the estimated upper and lower confidence limits for the mean rate ratio can be transformed by subtracting 1 and multiplying by 100% to calculate 95% confidence intervals for the percentage change.

Source: OASIS-HAE CSR⁷⁶

2.6.2.4 Number of patients with a $\geq 50\%$, $\geq 70\%$, or $\geq 90\%$ reduction from Baseline in investigator-confirmed HAE attacks (per 4 weeks) from Week 5 and Week 25

Although all thresholds were considered secondary endpoints, only $\geq 70\%$ was included in the efficacy hierarchical testing; therefore, the $\geq 50\%$ and $\geq 90\%$ reduction analyses were considered exploratory and the p-values were considered nominal.⁷⁶

The percentage of patients with a $\geq 50\%$ reduction from Baseline in investigator-confirmed HAE attacks from Week 5 and Week 25 was 93.3% and 82.6% for the

donidalorsen Q4W group and the donidalorsen Q8W group, respectively, compared with 27.3% in the placebo group.⁷⁶ These differences were nominally significant (p [REDACTED] for both groups).⁷⁶

The percentage of patients with a $\geq 70\%$ reduction from Baseline in investigator-confirmed HAE attacks from Week 5 and Week 25 was 82.2% and 65.2% for the donidalorsen Q4W group and the donidalorsen Q8W group, respectively, compared with 18.2% in the placebo group.⁷⁶ These differences were statistically significant (p < 0.001 and p = 0.004, respectively).⁷⁶

The percentage of patients with a $\geq 90\%$ reduction from Baseline in investigator-confirmed HAE attacks from Week 5 and Week 25 was 62.2% and 47.8% for the donidalorsen Q4W group and the donidalorsen Q8W group, respectively, compared with 9.1% in the placebo group.⁷⁶ These differences were nominally significant (p [REDACTED] and p [REDACTED], respectively).⁷⁶

Table 13: Patients with $\geq 50\%$, $\geq 70\%$, or $\geq 90\%$ reduction from Baseline in investigator-confirmed HAE attacks (per 4 weeks) from Week 5 and Week 25 (FAS)

Response Rate Analyses on Threshold-Based Reduction Between Week 5 to Week 25 ^{a, b}	Placebo (N=22)	Donidalorsen 80 mg Q4W (N=45)	Donidalorsen 80 mg Q8W (N=23)
Patients with HAE Attack Rate Reductions $\geq 50\%$			
Reduction $\geq 50\%$, n (%)	6 (27.3)	42 (93.3)	19 (82.6)
Reduction < 50%, n (%)	16 (72.7)	3 (6.7)	4 (17.4)
Odds Ratio (95% CI) ^c	-	310.35 (11.63, 8279.94)	14.80 (3.15, 69.41)
Nominal P-value	-	[REDACTED]	[REDACTED]
Patients with HAE Attack Rate Reductions $\geq 70\%$			
Reduction $\geq 70\%$, n (%)	4 (18.2)	37 (82.2)	15 (65.2)
Reduction < 70%, n (%)	18 (81.8)	8 (17.8)	8 (34.8)
Odds Ratio (95% CI) ^c	-	34.74 (7.32, 164.87)	9.17 (2.05, 41.09)
Nominal P-value	-	< 0.001	0.004
Patients with HAE Attack Rate Reductions $\geq 90\%$			
Reduction $\geq 90\%$, n (%)	2 (9.1)	28 (62.2)	11 (47.8)
Reduction < 90%, n (%)	20 (90.9)	17 (37.8)	12 (52.2)
Odds Ratio (95% CI) ^c	-	17.04 (3.36, 86.42)	8.70 (1.56, 48.52)
Nominal P-value	-	[REDACTED]	[REDACTED]

Abbreviations: CI – Confidence interval; FAS – Full analysis set; HAE – Hereditary angioedema; mg – milligrams; Q4W – Once every four weeks; Q8W – Once every eight weeks

^a Baseline was the run-in HAE attack rate which was calculated for each patient as number of HAE attacks occurring during the run-in period divided by the number of days the patient contributed to the run-in period multiplied by 28.

^b The HAE attack rate between Week 5 to Week 25 for each patient was calculated as number of HAE attacks occurring from Week 5 to Week 25 divided by the number of days the patient contributed to the period multiplied by 28.

^c The odds ratio, its 95% confidence interval and p-value were calculated based on a logistic regression with baseline (the time-normalised run-in period attack rate) and the Treatment-by-Baseline interaction as covariates. Source: Riedl et al. 2024¹²; OASIS-HAE CSR⁷⁶.

2.6.2.5 Health related quality of life

In the OASIS-HAE study, the AE-QoL and AECT scores were used to estimate the impact of donidalorsen on QoL. The results from each of these assessments were used to determine the overall improvements on the QoL of patients treated with donidalorsen and placebo.

Change in AE-QoL Questionnaire Total Score at Week 25

Overall, the change from Baseline in AE-QoL questionnaire total score at Week 25 showed a clinically meaningful (≥ 6 points) improvement in QoL for patients treated with donidalorsen compared with patients treated with placebo.^{76,84}

The LSM reduction (improvement) from Baseline in the AE-QoL total score at Week 25 was 24.8 points (95% CI: -29.86, -19.65) for patients in the donidalorsen Q4W group and 19.9 points (95% CI: -26.96, -12.73) for patients in the donidalorsen Q8W group, compared with 6.2 points (95% CI: -13.74, 1.35) in the placebo group.⁷⁶

The LSM difference from the placebo group was 18.6 points (95% CI: -27.67, -9.45), ($p < 0.001$) for the donidalorsen Q4W group and 13.7 points (95% CI: -24.02, -3.29), ($p = 0.010$) for the donidalorsen Q8W group.⁷⁶

Table 14: Analysis of AE-QoL questionnaire total score during the treatment period to Week 25, (FAS)

Visit statistics	Placebo (N=22)	Donidalorsen 80 mg Q4W (N=45)	Donidalorsen 80 mg Q8W (N=23)
Change from Week 1 to Week 25			
n	18	42	22
Mean (SD)	██████████	██████████	██████████
LSM (95% CI) ^a	██████████	-24.76 ██████████	-19.85 ██████████
Treatment different in LSM (95% CI)	-	-18.56 (-27.67, -9.45)	-13.65 (-24.02, -3.29)
Nominal p-value	-	<0.001	0.010

Abbreviations: AE-QoL – Angioedema quality of life; CI – Confidence interval; FAS – Full analysis set; LSM – Least squares mean; mg – milligrams; Q4W – Once every four weeks; Q8W – Once every eight weeks; SD – Standard deviation

Notes: Each item of AE-QoL scored as Never = 0, Rarely = 1, Occasionally = 2, Often = 3, Very often = 4. The AE-QoL domain scores and total score were calculated by using the following formula: (Sum score of all completed items)/(maximum sum score of all possible items)*100.

^a Based on a mixed effect model with repeated measures with fixed effects of treatment (donidalorsen or placebo), time (categorical), treatment-by-time interaction, Baseline and Treatment-by-Baseline interaction. Source: Riedl et al. 2024¹²; OASIS-HAE CSR⁷⁶

Percentage of well-controlled patients on the AECT at Week 25

Based on the last observation, 41 of 45 (91.1%) patients in the donidalorsen Q4W group and ██████████ patients in the donidalorsen Q8W group had well-controlled angioedema activity, compared with 9 of 22 (40.9%) patients in the placebo group, per an AECT score ≥10 at Week 25.^{76,81} The odds ratios were 14.81 (95% CI: 3.90, 56.14) for the donidalorsen Q4W group (p-value < 0.001); and ██████████ ██████████ for the donidalorsen Q8W group (p-value = ██████████).⁷⁶

2.6.3 OASISplus

The results from OASISplus present an interim analysis of both study cohorts.

2.6.3.1 OASISplus OLE cohort

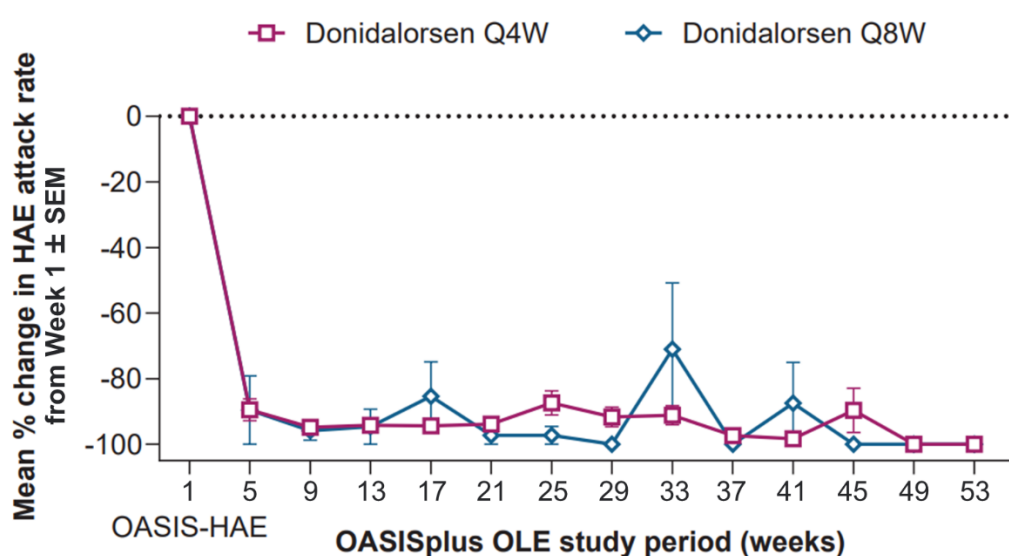
Interim data (data cut-off February 28, 2024) from the OASISplus OLE cohort is presented for patients who completed through Week 53. Patient-reported outcomes were reported up to Week 25 due to the limited number of patients who have

completed later timepoints in the ongoing study. The number of HAE attacks are reported up to Week 53.³⁶

Time-normalised number of investigator-confirmed HAE attacks (per month) from Week 1 to 53

The OASISplus OLE cohort maintained a low HAE attack rate across the study period. In OASIS-HAE, the mean baseline attack rates for patients receiving Q4W and Q8W donidalorsen were 3.61 and 3.18 and reduced to a LSM of 0.44 and 1.02 at the end of the trial in the Q4W and Q8W donidalorsen groups, respectively.⁷⁶ In the OASISplus OLE cohort, a reduction in HAE attack rate from baseline of 93% and 92% was observed for patients receiving donidalorsen Q4W and donidalorsen Q8W, respectively (shown in Figure 14).³⁶

Figure 14: Investigator-confirmed OASISplus OLE cohort HAE attack rate (per month) from Week 1 to Week 53



Donidalorsen Q4W, n =	69	69	69	68	68	57	50	43	38	26	16	13	8	5
Donidalorsen Q8W, n =	14	14	14	14	14	11	9	9	8	6	4	3	2	2

Abbreviations: HAE - Hereditary angioedema; OLE - Open-label extension; Q4W - Once every four weeks; Q8W - Once every eight weeks; SEM - Standard error of the mean

Source: Tachdjian et al. 2024³⁶

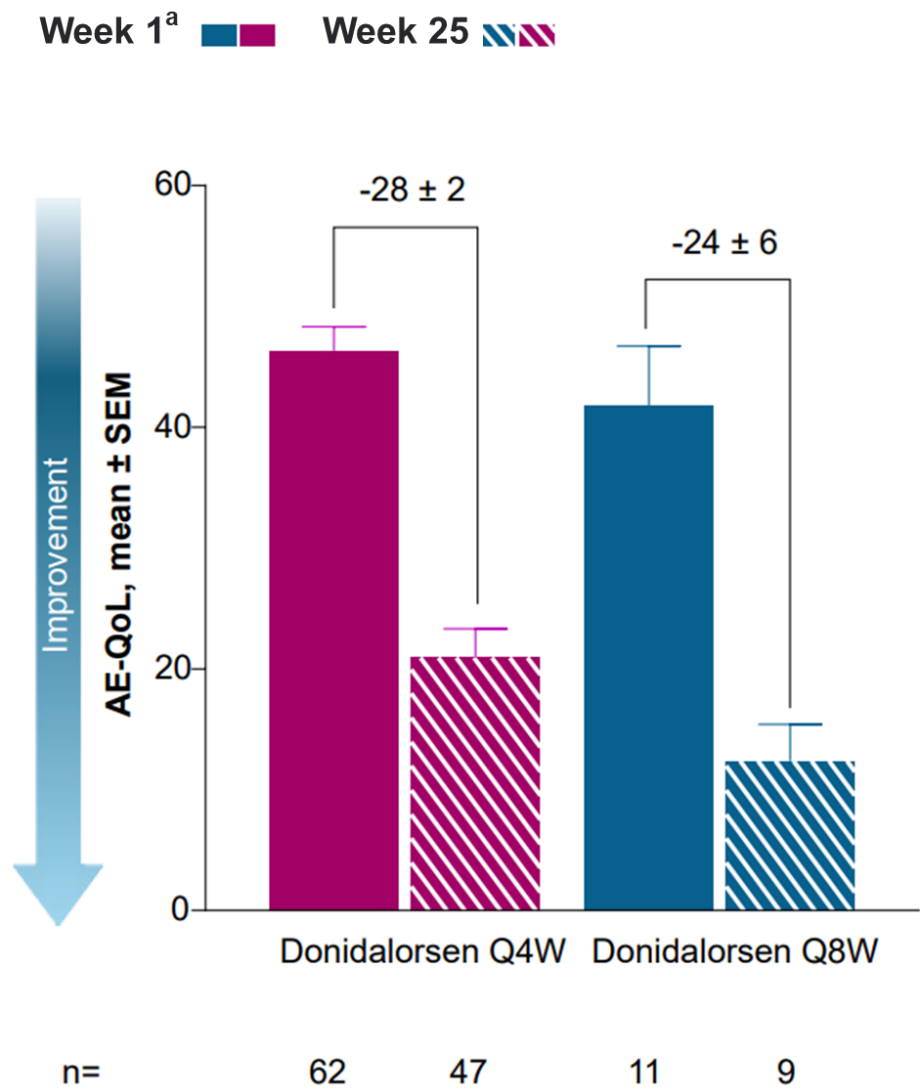
Patient-reported outcomes at Week 25

Patients in both donidalorsen dosing groups reported clinically meaningful improvements in AE-QoL total score, with a reduction of ≥ 6 points, and $\geq 90\%$ of

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patients reported well-controlled disease based on AECT scores, shown in Figure 15 and Figure 16, respectively.³⁶ All 14 patients who had received placebo in OASIS-HAE and initiated donidalorsen Q4W in OASISplus (the index placebo group) experienced an improvement in HAE Quality of Life Questionnaire (HAE-QoL) total scores by 22 points from baseline, as shown in Figure 17.³⁶

Figure 15: AE-QoL at Week 1 and Week 25 of OASISplus OLE cohort

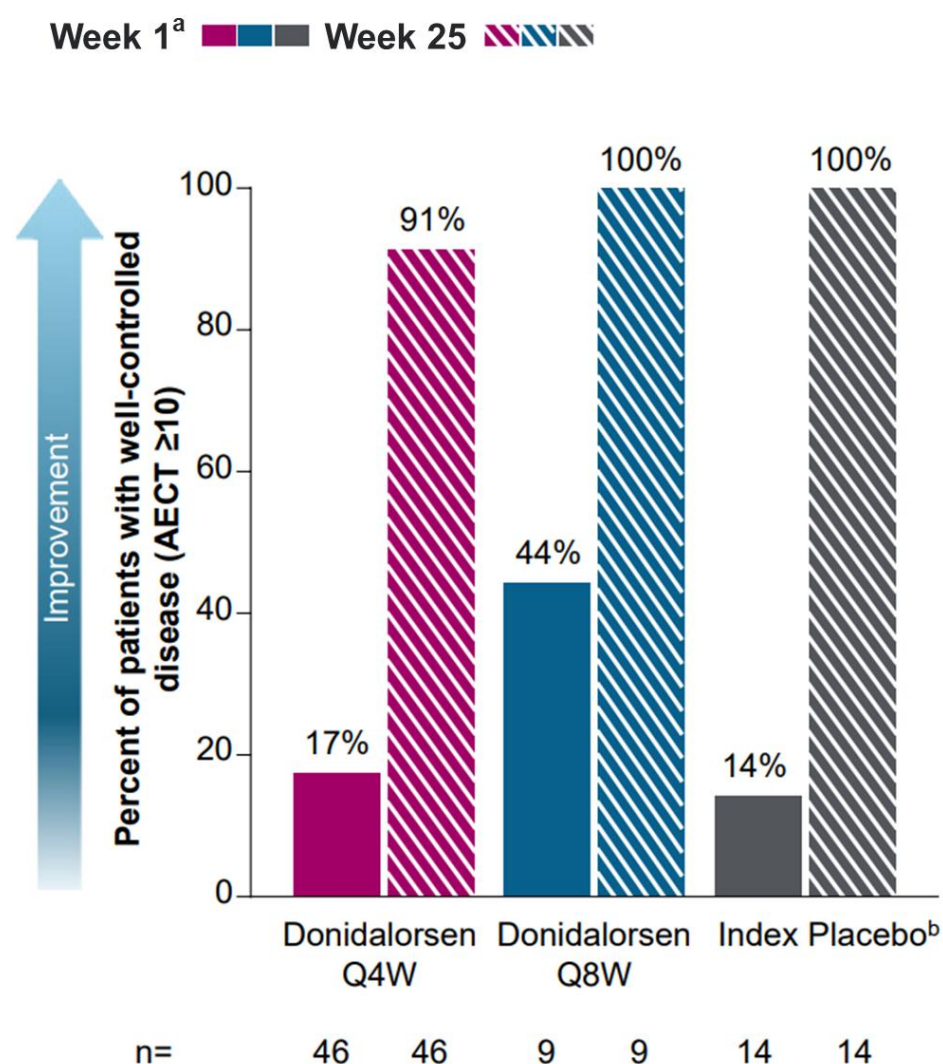


Abbreviations: AE-QoL - Angioedema Quality of Life Questionnaire; Q4W - Once every four weeks; Q8W - Once every eight weeks

^aWeek 1 in the OASIS-HAE study.

Source: Tachdjian et al. 2024³⁶

Figure 16: AECT at Week 1 and Week 25 of OASISplus OLE cohort



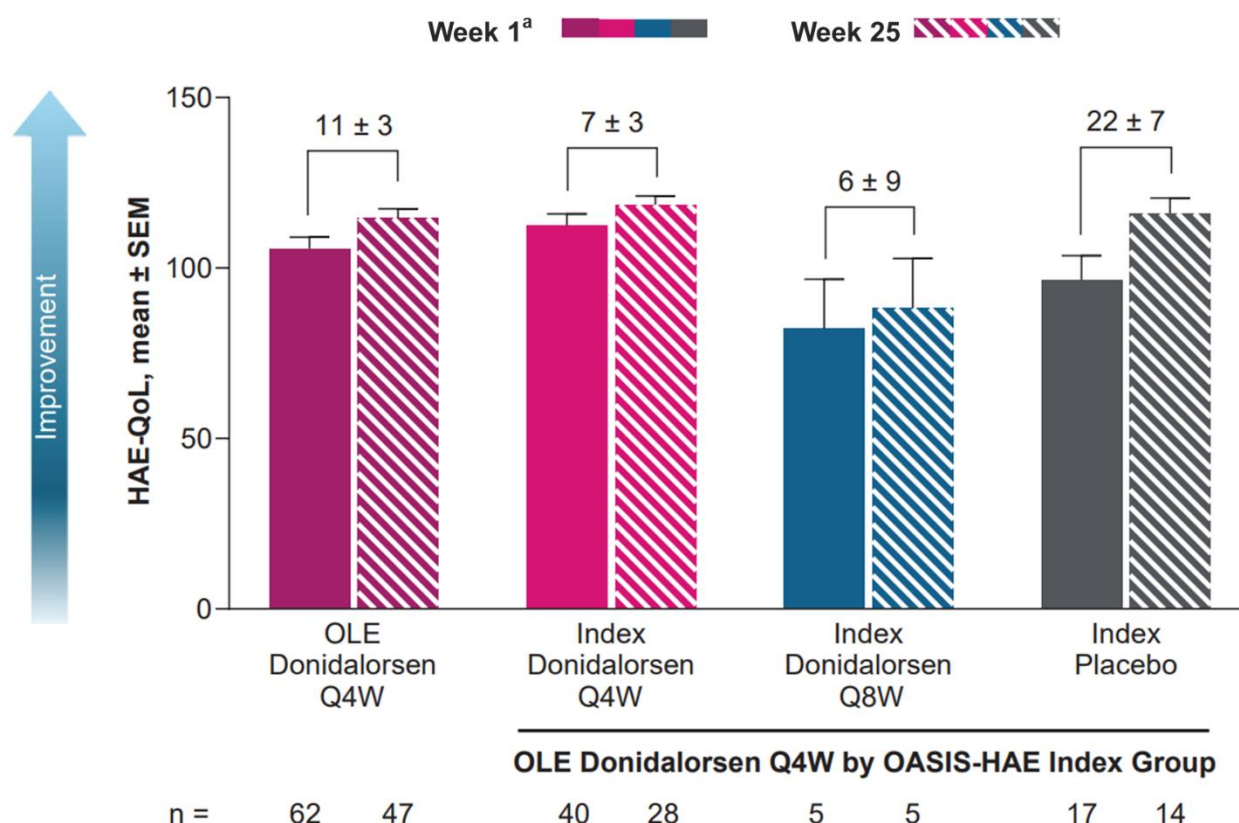
Abbreviations: AECT – Angioedema Control Test; Q4W - Once every four weeks; Q8W - Once every eight weeks

^aWeek 1 in the OASIS-HAE study.

^bIndex placebo is a subgroup of patients in the OASISplus donidalorsen Q4W group (i.e. these patients received placebo in OASIS-HAE and initiated donidalorsen Q4W in OASISplus).

Source: Tachdjian et al. 2024³⁶

Figure 17: AE-QoL at Week 1 and Week 25 of OASISplus OLE cohort, by OASIS-HAE index group



Abbreviations: HAE – Hereditary angioedema; HAE-QoL – HAE Quality of Life Questionnaire; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

^aWeek 1 in the OASIS-HAE study.

Source: Tachdjian et al. 2024³⁶

2.6.3.2 OASISplus switch cohort

Interim data (data cut-off February 28, 2024) from the OASISplus switch cohort is presented for patients who completed through Week 17, due to the limited number of patients who have completed later timepoints in the ongoing study.⁷⁷

Time-normalised number of investigator-confirmed HAE attacks (per month) from Week 1 to Week 17

Overall, patients with HAE receiving donidalorsen Q4W after treatment with other LTPs had a mean reduction in attack rate from baseline of 62%, as shown in Figure 18 and Figure 19. Mean reductions in attack rate from baseline of 73%, 65%, and 41% were observed for patients who had previously received treatment with berotralstat, lanadelumab, and C1-INHs, respectively.⁷⁷

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Figure 18: OASISplus switch cohort, monthly HAE attack rate from Week 1 to Week 17

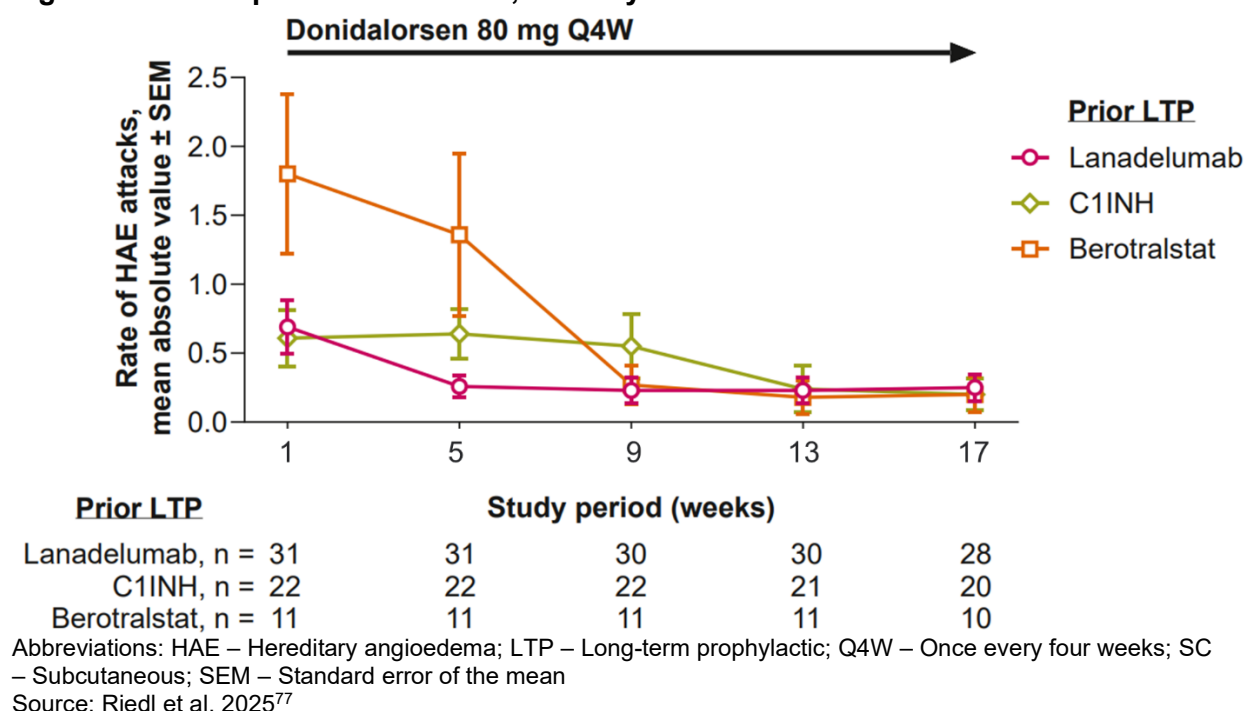
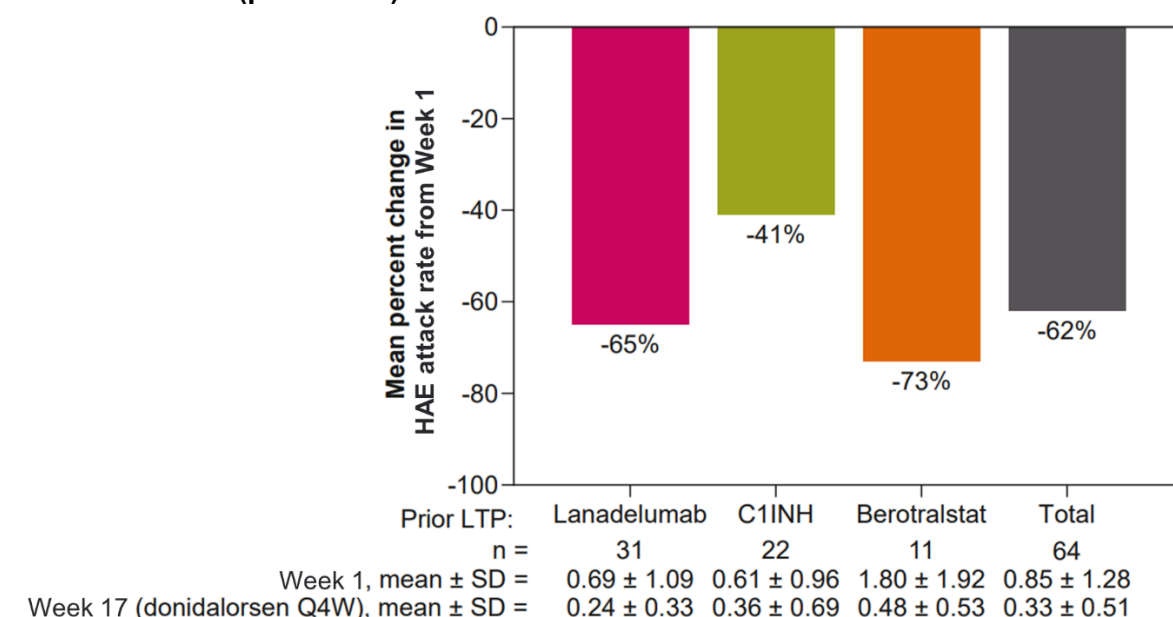


Figure 19: OASISplus switch cohort, mean percentage change in time-normalised HAE attack rate (per month) from Week 1



Abbreviations: C1-INH – C1-esterase inhibitor; HAE – Hereditary angioedema; LTP – Long-term prophylactic
Source: Riedl et al. 2025⁷⁷

Patient-reported outcomes

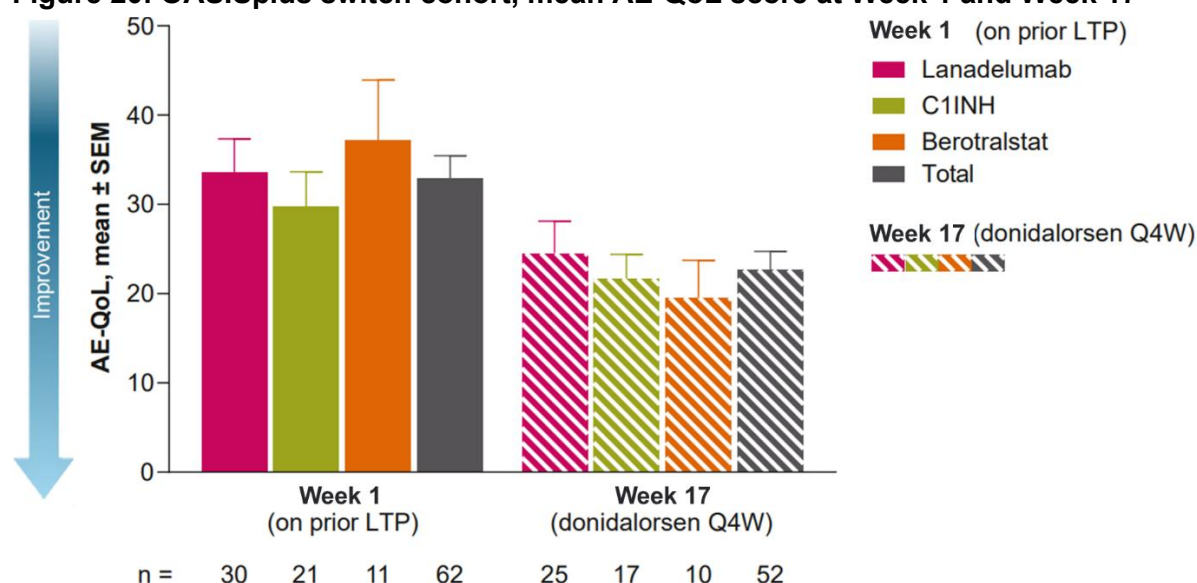
Patient treated with any prior LTP reported a total mean (SD) change of -10.4 (12.6) in AE-QoL scores from Week 1 to Week 17, as shown in Figure 20, exceeding the

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clinically meaningful change threshold of six points.⁷⁷ The number of patients with well-controlled disease based on AECT scores, increased from 67% at baseline to 93% after donidalorsen treatment for 16 weeks, as shown in Figure 20 and Figure 21, respectively.⁷⁷

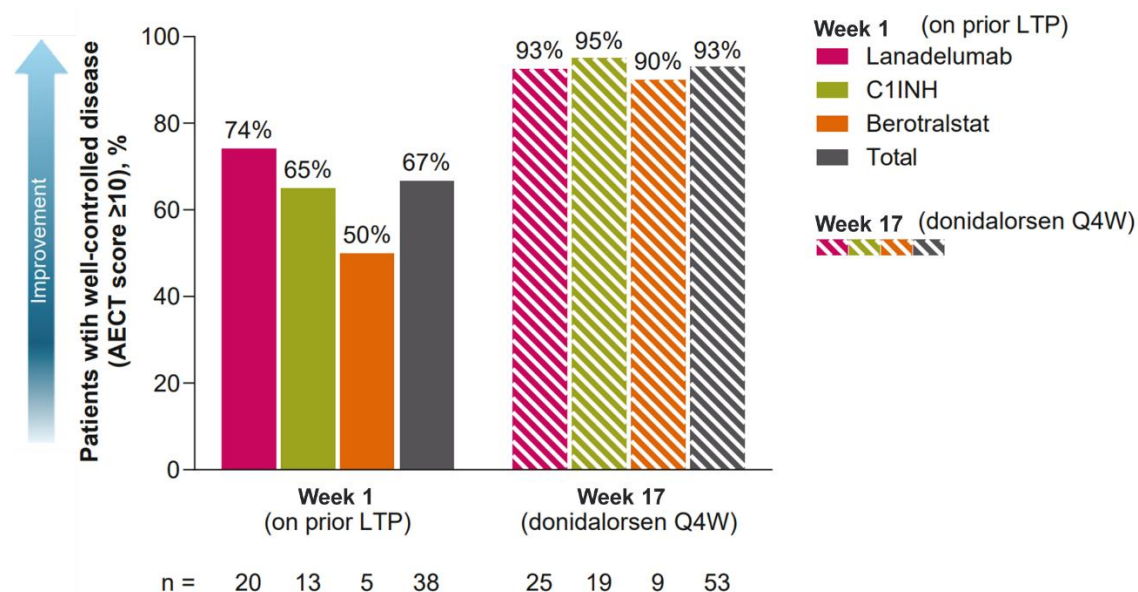
Most patients preferred treatment with donidalorsen compared to treatment with previous LTPs, as shown in Figure 22 and Figure 23.⁷⁷ Among those who preferred donidalorsen, reasons reported included better disease control, less time for administration, and less injection site pain or reactions.⁷⁷ The most common reasons for preference differed according to patients' prior LTP. Patients who switched from lanadelumab most frequently cited less injection-site pain or reactions, whereas patients who switched from C1-INH commonly reported less time for administrations, and patients who switched from berotralstat most frequently cited better disease control as the most common reason for the preference for donidalorsen.⁷⁷

Figure 20: OASISplus switch cohort, mean AE-QoL score at Week 1 and Week 17



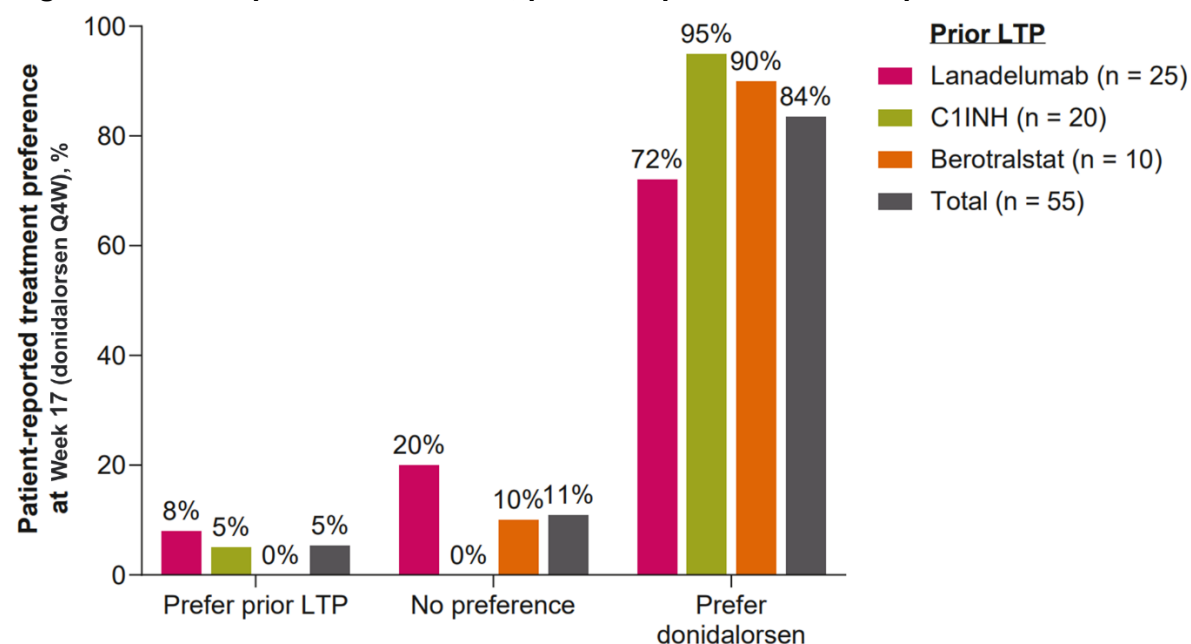
Abbreviations: AE-QoL - Angioedema Quality of Life Questionnaire; C1-INH - C1-esterase inhibitor; LTP - Long-term prophylactic; Q4W - Once every four weeks; SEM - Standard error of the mean
Source: Riedl et al. 2025⁷⁷

Figure 21: OASISplus switch cohort, proportion of patients with well-controlled disease at Week 1 and Week 17



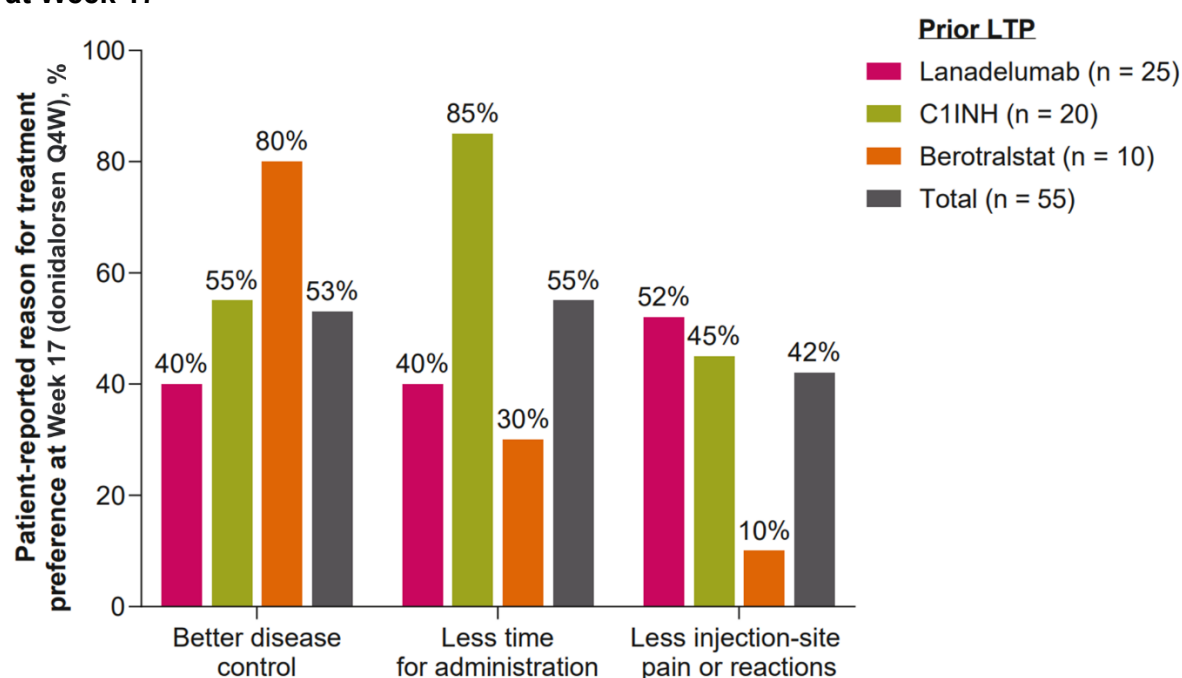
Abbreviations: AECT – Angioedema Control Test; C1-INH – C1-esterase inhibitor; LTP – Long-term prophylactic; Q4W – Once every four weeks
Source: Riedl et al. 2025⁷⁷

Figure 22: OASISplus switch cohort, patient-reported treatment preference at Week 17



Abbreviations: C1-INH – C1-esterase inhibitor; LTP – Long-term prophylactic; Q4W – Once every four weeks
Source: Riedl et al. 2025⁷⁷

Figure 23: OASISplus switch cohort, patient-reported reason for treatment preference at Week 17



Abbreviations: C1-INH – C1-esterase inhibitor; LTP – Long-term prophylactic; Q4W – Once every four weeks
Source: Riedl et al. 2025⁷⁷

2.6.4 Conclusions of the clinical effectiveness

OASIS-HAE is the phase III pivotal trial evaluating the efficacy and safety of donidalorsen (80 mg administered subcutaneously Q4W or Q8W) versus placebo in patients with HAE.⁷⁶ UK clinical experts consulted in clinical validation meetings in September 2025 considered the characteristics of the patient population of OASIS-HAE to be generalisable to the HAE patient population treated in the UK and stated that “[REDACTED]”.¹⁹ OASIS-HAE also follows a similar methodology to the lanadelumab HELP trial, therefore demonstrating that OASIS-HAE follows a robust design which has been accepted previously, and is suitable for informing UK decision-making.

In the OASIS-HAE trial, donidalorsen administered every four weeks at a dose of 80 mg demonstrated statistically significant superiority compared with placebo on all HAE attack primary and secondary endpoints.⁷⁶ Donidalorsen Q4W met its primary endpoint of HAE attack rate over Week 1 to Week 25, with a reduction in mean HAE attack rate compared to placebo of 81% over Week 1 to Week 25 ($p < 0.001$), and of 87% over Week 5 to Week 25 ($p < 0.001$).⁷⁶ Donidalorsen Q4W treatment also led to

an 89% ($p < 0.001$) reduction in the moderate or severe HAE attack rate relative to placebo over Week 5 to Week 25, demonstrating a substantial reduction in disease burden for HAE patients.⁷⁶

Donidalorsen administered every eight weeks also demonstrated efficacy in reducing HAE attack rate across the secondary endpoints.⁷⁶ Donidalorsen Q8W treatment reduced the mean HAE attack rate compared to placebo by 55% over Week 1 to Week 25 ($p=0.004$), and by 60% over Week 5 to Week 25 ($p=0.004$).⁷⁶ The substantial and maintained reduction in attack rates for the less frequent Q8W dosing regimen demonstrates that donidalorsen is a less burdensome but equally effective treatment option for patients with HAE. The option to reduce to a less frequent dosing, while maintaining efficacy, is key for minimising the impact HAE treatment has on patients' daily lives, maximising the benefits to patient QoL.

The reduction in HAE attack rates was maintained in the OASISplus OLE cohort, which demonstrated that both donidalorsen Q4W and Q8W reduced HAE attacks, at week 53 of the OASISplus study, compared with the OASIS-HAE baseline, by 93% and 92%, respectively.³⁶ These results show that the efficacy of donidalorsen is sustained and even improves over long-term treatment, for both Q4W and Q8W dosing regimens, and that that the Q8W dosing regimen is associated with a similar efficacy compared with the Q4W dosing regimen.³⁶ In the OASISplus switch cohort, patients who switched from prior LTPs to donidalorsen had a mean reduction in attack rate of 62%, demonstrating further the efficacy of donidalorsen and the potential for patients to have improved outcomes when switching from prior LTPs to donidalorsen.⁷⁷

The unique mechanism of action of donidalorsen, which uses ligand-conjugated antisense (LICA) technology, allows donidalorsen to be used in lower doses with less frequent administrations than its comparators.³¹ In line with the anticipated marketing authorisation for donidalorsen, explained in Section 2.3.1, [REDACTED]

[REDACTED].¹⁶ A post-hoc analysis of OASIS-HAE was conducted to assess what proportion of patients achieved [REDACTED]

in the donidalorsen Q4W group (see Section 3.5.1.3). The results of the analysis demonstrate that ██████% of patients remained attack-free for ██████ during the OASIS-HAE trial. It is therefore estimated that ██████% of patients in the OASIS-HAE trial would have been eligible for a dose reduction from donidalorsen Q4W to donidalorsen Q8W.⁸⁵

Overall, the efficacy data from OASIS-HAE and OASISplus across a range of clinically meaningful outcomes confirm the substantial efficacy benefit of donidalorsen Q4W and Q8W compared with placebo.^{36,76} The sustained efficacy of both Q4W and Q8W dosing regimens in the long-term, complemented by donidalorsen's mechanism of action enabling lower dosing frequency, demonstrates the substantial clinical and QoL benefit provided by donidalorsen for patients with HAE.

2.7 Subsequent treatments used in the relevant studies

No subsequent treatments were recorded as part of the OASIS-HAE trial or OASISplus OLE.

2.8 Subgroup analysis

Subgroup analyses were conducted on the primary efficacy endpoint of time-normalised number of investigator-confirmed HAE attacks per four weeks from Week 1 to Week 25, as presented in Table 15. Overall, subgroup analyses were consistent with the primary endpoint, with patients treated with donidalorsen Q4W experiencing a reduction in HAE attack rate from baseline, although some minor differences in magnitude of response were observed across some subgroups.⁷⁶

A summary of the full results for the subgroups can be found in Appendix C.

Table 15: Subgroup analysis of time-normalised HAE attack rate from Week 1 to Week 25

Subgroup	Placebo (N=22)	Donidalorsen 80 mg Q4W (N=45)	Donidalorsen 80 mg Q8W (N=23)
Run-in Period HAE Attack Rate			
Mean (SD)	██████████	██████████	██████████

Subgroup	Placebo (N=22)	Donidalorsen 80 mg Q4W (N=45)	Donidalorsen 80 mg Q8W (N=23)
Time-normalised HAE attack rate from Week 1 to Week 25, mean (SD)			
Age			
12-17 years			
18-39 years			
40-64 years			
≥65 years			
Sex			
Male			
Female			
Race			
Caucasian			
Other or Multiple			
Region			
North America			
Europe			
Middle East			
Predefined prophylactic therapy			

Abbreviations: HAE – Hereditary angioedema; mg – milligrams; NA – not applicable; NC – Not calculated; SD – Standard deviation

Source: OASIS-HAE CSR⁷⁶

2.9 Meta-analysis

A meta-analysis is not required because the key efficacy and safety data for donidalorsen are provided by one pivotal phase III study (OASIS-HAE).

2.10 Indirect and mixed treatment comparisons

In the absence of head-to-head studies comparing donidalorsen with other LTPs, an NMA was conducted to estimate the comparative efficacy and effect on quality of life of donidalorsen against berotralstat, lanadelumab, and plasma-derived IV C1-INHs.

2.10.1 Identification of relevant studies

As discussed in Section 2.1, an SLR was conducted in April 2025 to identify any published clinical trial data on the efficacy and safety of LTPs in patients 12 years and older with HAE. See Appendix B for full details of the clinical SLR methodology

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and results. The SLR identified 243 clinical references, of which 65 were full-text publications. 18 studies related to RCTs that evaluated LTPs were identified, including one key study, a phase III, placebo-controlled RCT (OASIS-HAE) investigating donidalorsen, which is presented in Section 2.2.^{12,76} Of the 18 RCT studies extracted in this SLR, six investigated C1-INH; three investigated berotralstat; two for each of the following treatments: donidalorsen, lanadelumab, garadacimab; and one for epsilon aminocaproic acid (an antifibrinolytic), and for avoralstat and danazol (androgens).

For inclusion in the indirect treatment comparison (ITC), additional criteria were applied to restrict the studies included to full-text, phase III RCTs with an intervention that is commissioned by NHSE or recommended by NICE as an LTP in HAE. In total, two studies met the inclusion criteria for the ITC in addition to OASIS-HAE: APeX-2 (berotralstat), and HELP (lanadelumab).^{12,71,86} Of the six studies identified from the SLR that investigated C1-INH, none investigated plasma-derived IV C1-INH. The only plasma-derived IV C1-INH with RCT data available was Cinryze (CHANGE), which is also used as a proxy for IV Berinert in the economic analysis; this study was not captured in the SLR as it includes patients aged six years and over, beyond the standard 12 years and over inclusion criteria of the SLR.⁸⁷

A rigorous feasibility assessment concluded these studies were appropriate data sources to inform an ITC. Additionally, the feasibility assessment included the CHANGE study to incorporate Cinryze as a comparator. Although the CHANGE study was not identified in the SLR, it was included in the feasibility assessment to ensure the relevant comparators for donidalorsen were assessed. Therefore, four unique phase III RCTs investigating the relevant LTPs for this appraisal were identified for inclusion in the ITC:

- Donidalorsen: OASIS-HAE¹²
- Berotralstat: APeX-2⁷¹
- Lanadelumab: HELP⁸⁶
- Plasma-derived IV C1-INH: CHANGE⁸⁷

Key features of the identified studies are presented in Table 16. A summary of the studies identified for the ITC, as well as the interventions evaluated, is presented in the SLR report. Please refer to Appendix B, E, F and G for further details on the SLR.

Table 16: Summary of studies included in the ITC

	OASIS-HAE¹²	HELP⁸⁶	APeX-2⁷¹	CHANGE⁸⁷
Intervention/comparators	Donidalorsen Q4W Donidalorsen Q8W Placebo	Lanadelumab Q2W Lanadelumab Q4W Placebo	Berotrastat: 110 mg Berotrastat: 150 mg Placebo	C1INH-nf (Cinryze) IV: 1000 IU Placebo
Study design	Phase III Randomised Placebo-controlled	Phase III Randomised Placebo-controlled Parallel group	Phase III Randomised Placebo-controlled trial Parallel group	Phase III Randomised Placebo-controlled Crossover
Country/region	21 sites in European Union countries, 11 in North America, 5 in the Middle East and 2 in the UK.	41 sites in Canada, Europe, Jordan, and the United States	United States, Canada, Europe	United States, Israel
Randomisation	2:1 to either Q4W or Q8W interval; then within each dosing interval group, patients were randomly assigned again 3:1 to receive donidalorsen or placebo	2:1 to receive lanadelumab or placebo, patients assigned to lanadelumab were further randomised 1:1:1 to one of the three dose regimens	1:1:1 to receive 110 mg or 150 mg berotrastat, or placebo	Each subject will be randomised either to receive 12 weeks of C1INH-nf followed by 12 weeks of placebo, or 12 weeks of placebo followed by 12 weeks of C1INH-nf
Masking/ Blinding	Double-blind	Double-blind	Double-blind	Double-blind
Loss to follow-up	0 patients	1 patient	NR	2 patients
Study duration	24-week treatment period	26-weeks treatment period	24-week placebo-controlled treatment period	24-week treatment period (Two 12-week treatment periods)

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Key eligibility criteria	Participants must be aged 12 years or over at the time of informed consent and have a documented diagnosis of hereditary angioedema Type I or Type II Participants must: • Experience a minimum of 2 HAE attacks (confirmed by the Investigator) during the Screening Period • Be willing to complete the participant reported outcomes assessments throughout the study • Have access to, and the ability to use acute medication(s) to treat angioedema attacks. Patients were excluded from the study if: • Concurrent diagnosis of any other type of recurrent angioedema, including acquired, idiopathic angioedema or HAE with normal C1-INH (also known as HAE Type III) • Exposure to ACE inhibitors or any oestrogen containing	Patients must be aged 12 years or over of age at the time of screening, with a documented diagnosis of hereditary angioedema (Type I or Type II) based upon a documented clinical history consistent with hereditary angioedema and diagnostic testing results obtained during screening that confirmed hereditary angioedema Type I or Type II. Patients must also have at least one of the following: ≤30 years of age at reported onset of first angioedema symptoms, a family history consistent with hereditary angioedema Type I or Type II, or complement component 1q within the normal range. Patients must experience a baseline rate of ≥1 investigator-confirmed hereditary angioedema attack per 4 weeks as confirmed during the run-in period. Males and females who were fertile and sexually active must have adhered to contraception requirements for the duration of the study.	Patients with HAE–C1-INH were eligible if aged 12 years or older if living in the United States and Canada and 18 years or older if living in Europe. The diagnosis of HAE–C1-INH was confirmed by C1-INH functional level. Patients were excluded if they had used androgen or tranexamic acid prophylaxis within 28 days of screening or C1-INH prophylaxis within 14 days of screening.	Patients must be age ≥ 6 years Patients must have documented HAE based on: • Evidence of a low C4 level plus either a low C1-INH antigenic level or a normal C1-INH antigenic level and a low C1-INH functional level, or; • evidence of a low C4 level plus a known HAE-causing C1-INH mutation • Normal C1 level Patients were excluded from the study if: • Low C1 level • B-cell malignancy • Presence of an anti-C1-INH autoantibody • History of allergic reaction to C1-INH or other blood products. • Participation in a C1 esterase inhibitor trial, received blood or received a blood product in the past 90 days

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	medications with systemic absorption within four weeks prior to Screening Exposure to chronic prophylaxis with lanadelumab, SC-C1-INH, IV C1-INH and conestat alfa or berotralstat within five half-lives prior to screening	Patients were excluded from the study if: - Concomitant diagnosis of another form of chronic recurrent angioedema, such as acquired angioedema, hereditary angioedema with normal C1-esterase inhibitor, idiopathic angioedema, or recurrent angioedema associated with urticaria. - Dosed with an investigational drug or exposure to an investigational device within four weeks of screening. - Exposed to ACE inhibitors or any oestrogen-containing medications with systemic absorption within four weeks of screening. - Used long-term prophylactic therapy for hereditary angioedema (C1-esterase inhibitor, attenuated androgens, or antifibrinolytics) within two weeks of entering the run-in period.		

	OASIS-HAE ¹²	HELP ⁸⁶	APeX-2 ⁷¹	CHANGE ⁸⁷
		Used short-term prophylactic therapy for hereditary angioedema within seven days of entering the run-in period.		
Key outcomes	- Time-normalised number of investigator-confirmed HAE attacks - Number of moderate or severe attacks - Number of acute HAE attacks requiring acute treatment - Percentage reduction in HAE attacks from baseline - Percentage of participants who are well-controlled on the AECT - Change in AE-QoL questionnaire total score - Safety	- Number of investigator-confirmed attacks of hereditary angioedema - Number of attacks requiring acute treatment - Number of moderate or severe attacks - Percentage reduction in HAE attacks from baseline - Change from baseline in AE-QoL total scores - Safety	- Confirmed HAE attacks during the 24-week double-blind treatment period - Number of attacks requiring acute treatment - Percentage reduction in HAE attacks from baseline - Change from baseline in AE-QoL total scores - Safety	- Time-normalised number of HAE attacks during the treatment period - Number of moderate or severe attacks - Number of attacks requiring acute treatment - Safety

Abbreviations: ACE – Angiotensin-converting enzyme; AECT – Angioedema Control Test; AE-QoL – Angioedema Quality of Life Questionnaire; C1-INH – C1-esterase inhibitor; HAE – Hereditary angioedema; IU – International units; IV – Intravenous; mg – milligrams; Nf – Nano filtered; Q2W – Once every two weeks; Q4W – Once every four weeks; Q8W – Once every eight weeks; SC – Subcutaneous; UK – United Kingdom

2.10.2 NMA feasibility assessment

As no head-to-head studies for donidalorsen and the relevant comparators of this appraisal are available, an indirect comparison is required. NMAs allow for the comparison of multiple treatments by combining data from different clinical trials, provided the trials are sufficiently similar and form a connected network. Based on the assumption that donidalorsen is linked to relevant comparators through such a network, a rigorous feasibility assessment was carried out to determine whether the available trials were appropriate for inclusion in an NMA. Trials were assessed to understand whether they can be considered sufficiently homogenous. Heterogeneity between studies was considered, accounting for key features of the studies, including assessment of study design, patient population, treatment arms, and outcomes. The availability of data from each trial was also reviewed to ensure that sufficient data are available to perform an NMA.

Based on these assessments, it was deemed feasible to conduct NMAs for the following outcomes of interest:

- mean monthly attack rate;
- percentage of patients who achieved a specified proportional reduction in attacks from baseline;
- mean monthly moderate or severe attack rate;
- mean monthly attack rate of attacks that require on-demand medication;
- change in total AE-QoL scores.

Based on the results of the feasibility assessment, an NMA was conducted to compare donidalorsen and the relevant comparators of this appraisal.

2.10.3 NMA methodology

2.10.3.1 Model specifications

NMAs were conducted for all outcomes of interest using a Bayesian framework as described in the NICE Evidence Synthesis Decision Support Unit (DSU) Technical Support Document (TSD) series.⁸⁸ All analyses were conducted in R, using the 'multinma' R package, which estimates parameters in a Bayesian framework using Stan.⁸⁹

The analysis included three types of endpoints: count, binary, and continuous outcomes. All analyses are presented relative to donidalorsen Q4W, such that the treatment effect estimates correspond to each comparator versus donidalorsen Q4W.

Count data endpoints included the mean number of HAE attacks per month, mean number of moderate or severe HAE attacks per month, and mean number of attacks per month requiring on-demand medication. These endpoints were analysed to generate rate ratios and credible intervals (CrIs), assuming a Poisson distribution for the total number of attacks reported within each study.

Binary outcomes included the proportion of patients experiencing $\geq 50\%$, $\geq 70\%$, and $\geq 90\%$ reduction in attacks from baseline. These endpoints were analysed to generate odds ratios, assuming a binomial distribution for the numbers of patients achieving the appropriate percentage reduction reported within each study.

The continuous endpoint, mean change from baseline in AE-QoL score, was analysed to generate the mean change from baseline in this score and CrIs, assuming a normal distribution for the change from baseline in AE-QoL reported within each study.

2.10.3.2 Prior distribution

Non-informative priors

As the networks in the current analyses were limited, with only one study informing each treatment comparison, there were not enough data to reliably assess the between-study heterogeneity parameter in treatment effects using non-informative

priors. Therefore, non-informative priors were only considered for the mean treatment effects and the trial-specific baseline treatment effect.

Informative priors

For the between-study variance, informative priors were used due to the limited data in the network meaning this parameter is more difficult to estimate through the NMA.

The informative priors for between-study variance, proposed by Turner et al. (2015) were used throughout.⁹⁰ These were derived from an empirical study of nearly 15,000 meta-analyses. Since all studies being considered were pharmacological interventions versus placebo, the prior specified for the comparison of pharmacological versus placebo/control was used.

2.10.3.3 Assumptions

In instances where exposure time was not reported, the total number of attacks per arm were calculated from the mean attack rate per month and the total number of attacks reported over the study follow-up period. The exposure time, measured in months, was derived as follows:

$$\text{Exposure time} = \frac{\text{total number of attacks}}{\text{mean attack rate per month}}$$

If the total number of attacks was also not reported, then exposure time was assumed equal to the sample size in a given arm multiplied by the follow-up time for the trial.

2.10.3.4 Model selection

The feasibility assessment for this NMA demonstrated that there is heterogeneity across the included studies. For example, the administration method in HELP is consistent with OASIS-HAE (subcutaneous), except for APeX-2 and CHANGE, which used oral and intravenous administrations, respectively.^{12,71,86,87} Similarly, the length of trials (24 weeks versus 26 weeks in some instances) and the difference in the timing of administration may introduce subtle differences in treatment exposure

and efficacy between the trials, introducing bias. Although the trials included in the network of evidence were considered generally similar, the effects of these differences on the analyses were addressed and mitigated through the choice of an appropriate analytical model, the random effects (RE) model.

An RE model assumes that, in addition to sampling error, observed difference in effect size considers the variation of true effect size across studies (between-study variation), otherwise called heterogeneity, attributed to severity of disease, age of patients, dose of drugs, follow-up period, among others. This model was selected for this analysis in line with recommendations by the Multi-parameter Evidence Synthesis Research Group and NICE preferred methods (NICE DSU Unit 2) as it accounts for potential unmeasured heterogeneity and therefore better captures between-study variability.⁸⁸ In addition, the primary estimates of this assessment are intended to generalise beyond the specific trials included in the network (i.e. to the wider HAE patient population). For inference of that kind, an RE model is the appropriate framework because it explicitly models between-study variation in relative effects.

In contrast, a fixed effects (FE) model assumes that, in a network of evidence, all studies have the same underlying treatment effect and any difference between estimates from different studies is attributable to sampling error only (within-study variation). A FE model was therefore considered inappropriate for this analysis as the key between-study heterogeneity highlighted above could not be fully accounted for and the validity of the results would be at a greater risk of being compromised.

Please see Section 3.3.1.2 for further justification of the selection of the RE model.

2.10.4 NMA results

The NMA results for the intervention and comparators of interest for this appraisal are presented in the following section.

As detailed above, the CHANGE study evaluated patients from six years and above, beyond the standard 12 years and over inclusion criteria of the SLR. The study also did not include a washout period between the treatment and placebo phases for

patients who crossover treatment. Outcomes for the proportion of patients achieving a defined percentage reduction in HAE attacks and mean change in AE-QoL were not reported in CHANGE, and methods of reporting for the use of on-demand treatment and severity of attacks were not comparable with the other studies. Therefore, mean monthly attack rate was the only outcome considered feasible for the inclusion of CHANGE (Cinryze) in the NMA analyses. In addition, berotralstat is not included in the NMA analysis for mean monthly rate of moderate or severe HAE attacks and mean number of HAE attacks requiring on-demand medication, as attack severity was not an endpoint in APeX-2 and results for the number of attacks requiring on-demand medication were not reported.⁷¹ The network diagrams for each outcome are presented in Appendix J.

2.10.4.1 Mean number of HAE attacks per month

Median rate ratios for the mean number of HAE attacks per month and 95% CrIs are shown in Table 17 and the forest plot in Figure 24. No statistically significant differences were observed between the mean number of HAE attacks per month, as informed by the median rate ratios, in treatment with donidalorsen Q4W, and donidalorsen Q8W, lanadelumab Q2W, lanadelumab Q4W, C1-INHs, and berotralstat. Treatment with donidalorsen Q4W was associated with [REDACTED]. The results for donidalorsen Q4W showed a [REDACTED], however, as stated above, this difference was not statistically significant. The wide and overlapping CrIs observed in the forest plot presented in Figure 24, demonstrate that there is no statistically significant difference between the median rate ratios of donidalorsen Q4W and comparators. These results were validated by UK clinical experts in September 2025, in validation meetings conducted by the company.¹⁹

A [REDACTED].

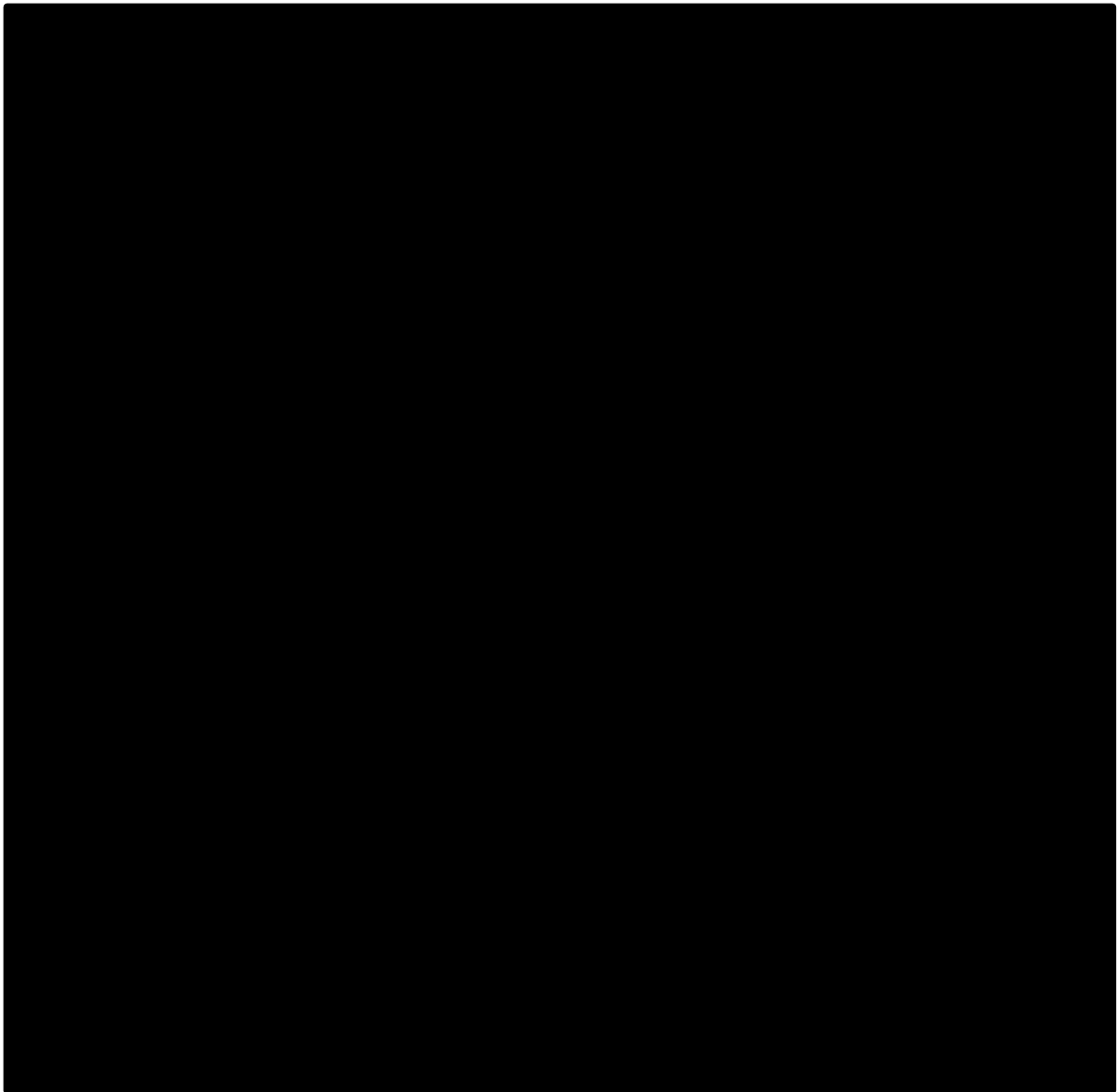
Table 17: Median rate ratios and 95% CrIs from the NMA for mean number of HAE attacks per month

Treatment	Median rate ratio (95% CrI)
Berotrastat	
C1-INH (Cinryze)	
Donidalorsen_Q8W	
Lanadelumab_Q2W	
Lanadelumab_Q4W	
Placebo	

*95% CrI does not include 1 and is therefore considered statistically significant

Abbreviations: C1-INH – C1 inhibitor; CrI – Credible interval; HAE – Hereditary angioedema; NMA – Network meta-analysis; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks

Figure 24: Forest plot of median rate ratios and 95% Crls for mean number of HAE attacks per month



Abbreviations: C1-INH – C1 inhibitor; nf – Nanofiltered; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks

2.10.4.2 Mean number moderate or severe HAE attacks per month

Median rate ratios for the mean number of moderate and severe HAE attacks and 95% Crls are shown in Table 18 and the forest plot in Figure 25. No statistically significant differences were observed between the median rate ratios for mean number of moderate or severe attacks per month in treatment with donidalorsen Q4W, and donidalorsen Q8W, lanadelumab Q2W and lanadelumab Q4W. The

results for donidalorsen Q4W show a [REDACTED].

[REDACTED]. The results for donidalorsen Q4W demonstrate a [REDACTED].

[REDACTED]. However, as stated above, this difference was not considered statistically significant. The wide and overlapping CrIs observed in the forest plot presented in Figure 25, demonstrate that there is no statistically significant difference between the median rate ratios of donidalorsen Q4W and comparators.

A [REDACTED]

[REDACTED], as indicated by the CrIs for the rate ratio, which do not include 1.

Table 18: Median rate ratios and 95% CrIs from the NMA for mean number of moderate or severe HAE attacks per month

Treatment	Median rate ratio (95% CrI)
Donidalorsen_Q8W	[REDACTED]
Lanadelumab_Q2W	[REDACTED]
Lanadelumab_Q4W	[REDACTED]
Placebo	[REDACTED]

*95% CrI does not include 1 and is therefore considered statistically significant

Abbreviations: CrI – Credible interval; HAE – Hereditary angioedema; NMA – Network meta-analysis; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks

Figure 25: Forest plot of median rate ratios and 95% CIs for mean number of moderate or severe HAE attacks per month



Abbreviations: Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks

2.10.4.3 Proportion of patients achieving $\geq 50\%$ reduction in HAE attacks from baseline

Median odds ratios for the proportion of patients achieving $\geq 50\%$ reduction in HAE attacks from baseline and 95% CIs are shown in Table 19 and the forest plot in Figure 26 (plotted on a logarithmic odds ratio scale to accurately illustrate treatment effects). No statistically significant differences were observed between the median odds ratios for the proportion of patients achieving a $\geq 50\%$ reduction in attacks from

baseline in treatment with donidalorsen Q4W, and berotralstat and donidalorsen Q8W. The results for donidalorsen Q4W show a [REDACTED]

The NMA results for donidalorsen Q4W demonstrate a [REDACTED] median odds ratio for the proportion of patients achieving a $\geq 50\%$ reduction in attacks compared with placebo. Conversely, a [REDACTED]

[REDACTED]. Due to [REDACTED], Figure 26 shows treatment effects plotted on a logarithmic odds ratio scale to more accurately illustrate the relative treatment effects for all comparators simultaneously.

As all patients on lanadelumab achieved at least a 50% reduction in HAE attacks from baseline, the associated CrIs for these treatments are much wider than the comparator treatments, as depicted by the forest plot in Figure 26. This reflects the greater statistical uncertainty around estimating the likelihood of *not* reaching the $\geq 50\%$ reduction threshold, when no such events were observed in the trial.

Table 19: Median odds ratio and 95% CrIs from the NMA for proportion of patients achieving a $\geq 50\%$ reduction in HAE attacks from baseline

Treatment	Median odds ratio (95% CrI)
Berotralstat	[REDACTED]
Donidalorsen_Q8W	[REDACTED]
Lanadelumab_Q2W	[REDACTED]
Lanadelumab_Q4W	[REDACTED]
Placebo	[REDACTED]

*95% CrI does not include 1 and is therefore considered statistically significant

Abbreviations: CrI – Credible interval; HAE – Hereditary angioedema; NMA – Network meta-analysis; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks

Figure 26: Logarithmic odds ratio scale forest plot of median odds ratios and 95% CrIs for the proportion of patients achieving a $\geq 50\%$ reduction in HAE attacks from baseline treatment effects



Abbreviations: Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks

2.10.4.4 Proportion of patients achieving $\geq 70\%$ reduction in HAE attacks from baseline

Median odds ratios for the proportion of patients achieving $\geq 70\%$ reduction in HAE attacks from baseline and 95% CrIs are shown in Table 20 and the forest plot in Figure 27. No statistically significant differences were observed between the proportion of patients achieving a $\geq 70\%$ reduction in attacks, informed by the median odds ratios, in the results of donidalorsen Q4W, and berotralstat, donidalorsen Q8W,

lanadelumab Q2W, and lanadelumab Q4W. The treatment of donidalorsen Q4W was associated with a [REDACTED]

[REDACTED]. The results for donidalorsen Q4W show a [REDACTED]

[REDACTED]. However, as stated above, this difference was not considered statistically significant. The wide and overlapping CrIs observed in the forest plot presented in Figure 27, demonstrate that there is no statistically significant difference between donidalorsen and its comparators.

A [REDACTED]

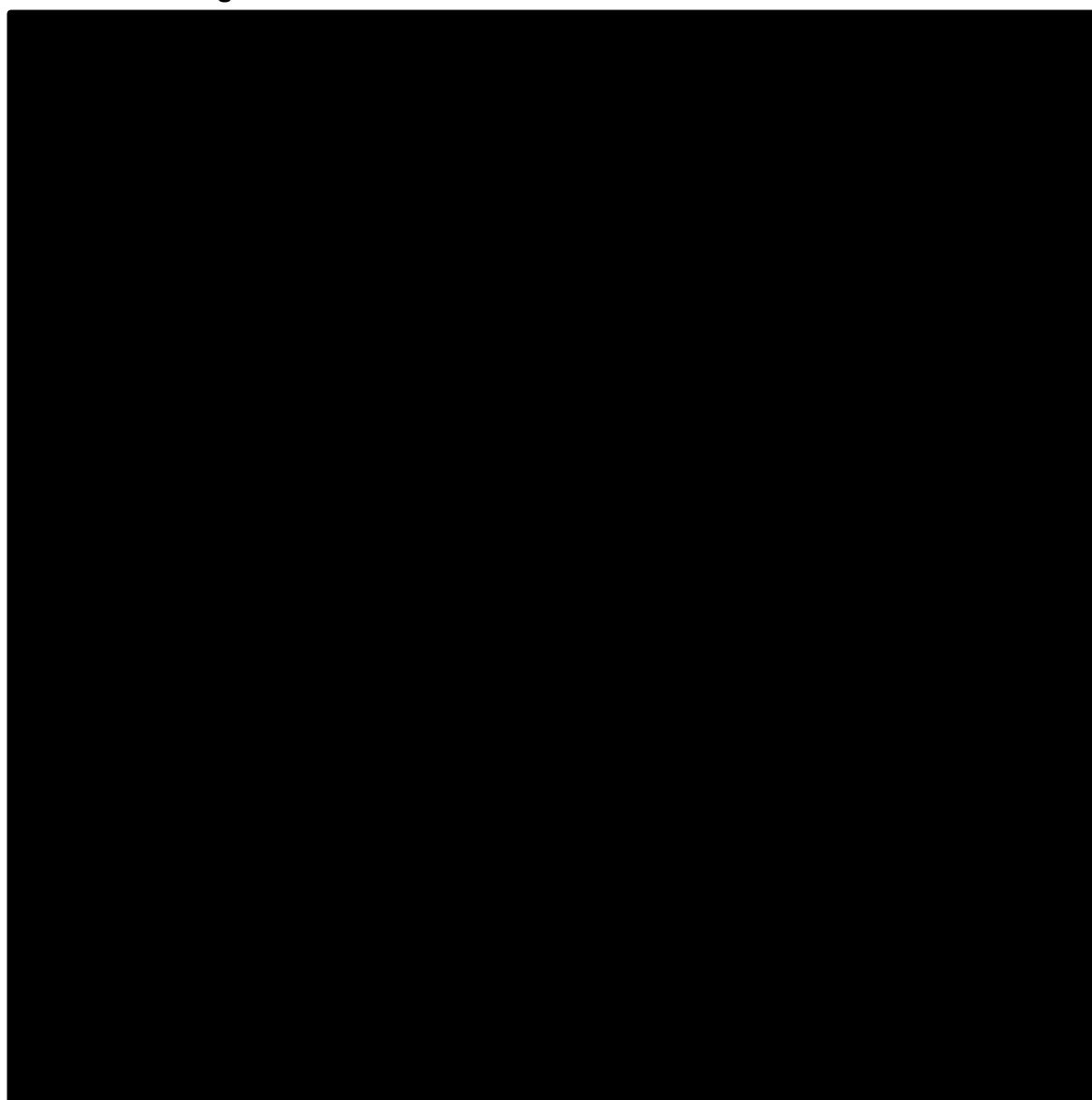
Table 20: Median odds ratio and 95% CrIs from the NMA for proportion of patients achieving a $\geq 70\%$ reduction in HAE attacks from baseline

Treatment	Median odds ratio (95% CrI)
Berotrastat	[REDACTED]
Donidalorsen_Q8W	[REDACTED]
Lanadelumab_Q2W	[REDACTED]
Lanadelumab_Q4W	[REDACTED]
Placebo	[REDACTED]

*95% CrI does not include 1 and is therefore considered statistically significant

Abbreviations: CrI – Credible interval; HAE – Hereditary angioedema; NMA – Network meta-analysis; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks

Figure 27: Forest plot of median odds ratios and 95% Crls for the proportion of patients achieving a $\geq 70\%$ reduction in HAE attacks from baseline treatment effects



Abbreviations: Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks

2.10.4.5 Proportion of patients achieving $\geq 90\%$ reduction in HAE attacks from baseline

Median odds ratios for the proportion of patients achieving $\geq 90\%$ reduction in HAE attacks from baseline and 95% Crls are shown in Table 21 and the forest plot in Figure 28. No statistically significant differences were observed between the median odds ratios for the proportion of patients achieving a $\geq 90\%$ reduction in attacks in treatment with donidalorsen Q4W, and berotralstat, donidalorsen Q8W, lanadelumab

Q2W, and lanadelumab Q4W. The results for donidalorsen Q4W showed a

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]. However, as stated above, this

difference was not statistically significant. The wide and overlapping CrIs observed in the forest plot presented in Figure 28, demonstrate that there is no statistically significant difference between donidalorsen and its comparators.

A [REDACTED]

[REDACTED]

[REDACTED].

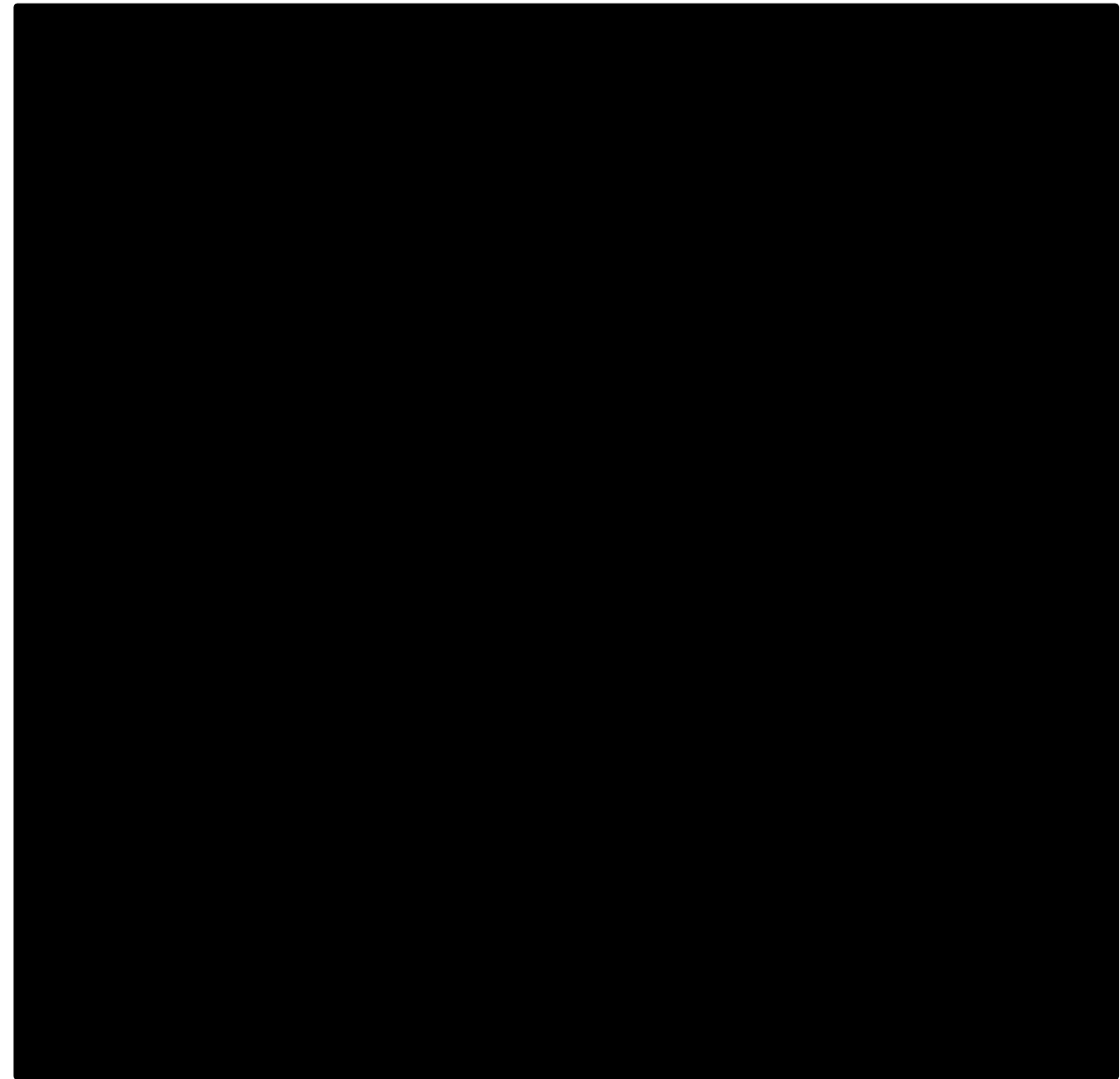
Table 21: Median odds ratio and 95% CrIs from the NMA for proportion of patients achieving a $\geq 90\%$ reduction in HAE attacks from baseline

Treatment	Median odds ratio (95% CrI)
Berotralstat	[REDACTED]
Donidalorsen_Q8W	[REDACTED]
Lanadelumab_Q2W	[REDACTED]
Lanadelumab_Q4W	[REDACTED]
Placebo	[REDACTED]

*95% CrI does not include 1 and is therefore considered statistically significant

Abbreviations: CrI – Credible interval; HAE – Hereditary angioedema; NMA – Network meta-analysis; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks

Figure 28: Forest plot of median odds ratios and 95% CrIs for the proportion of patients achieving a $\geq 90\%$ reduction in HAE attacks from baseline treatment effects



Abbreviations: Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks

2.10.4.6 Mean number of HAE attacks requiring on-demand medication

Median rate ratios for the mean number of HAE attacks requiring on-demand medication and 95% CrIs are shown in Table 22 and the forest plot in Figure 29. No statistically significant differences were observed between the mean number of attacks requiring on-demand medication per month, informed by the median rate ratios, for the results of donidalorsen Q4W and all comparator treatments. The results demonstrated a [REDACTED]

[REDACTED]

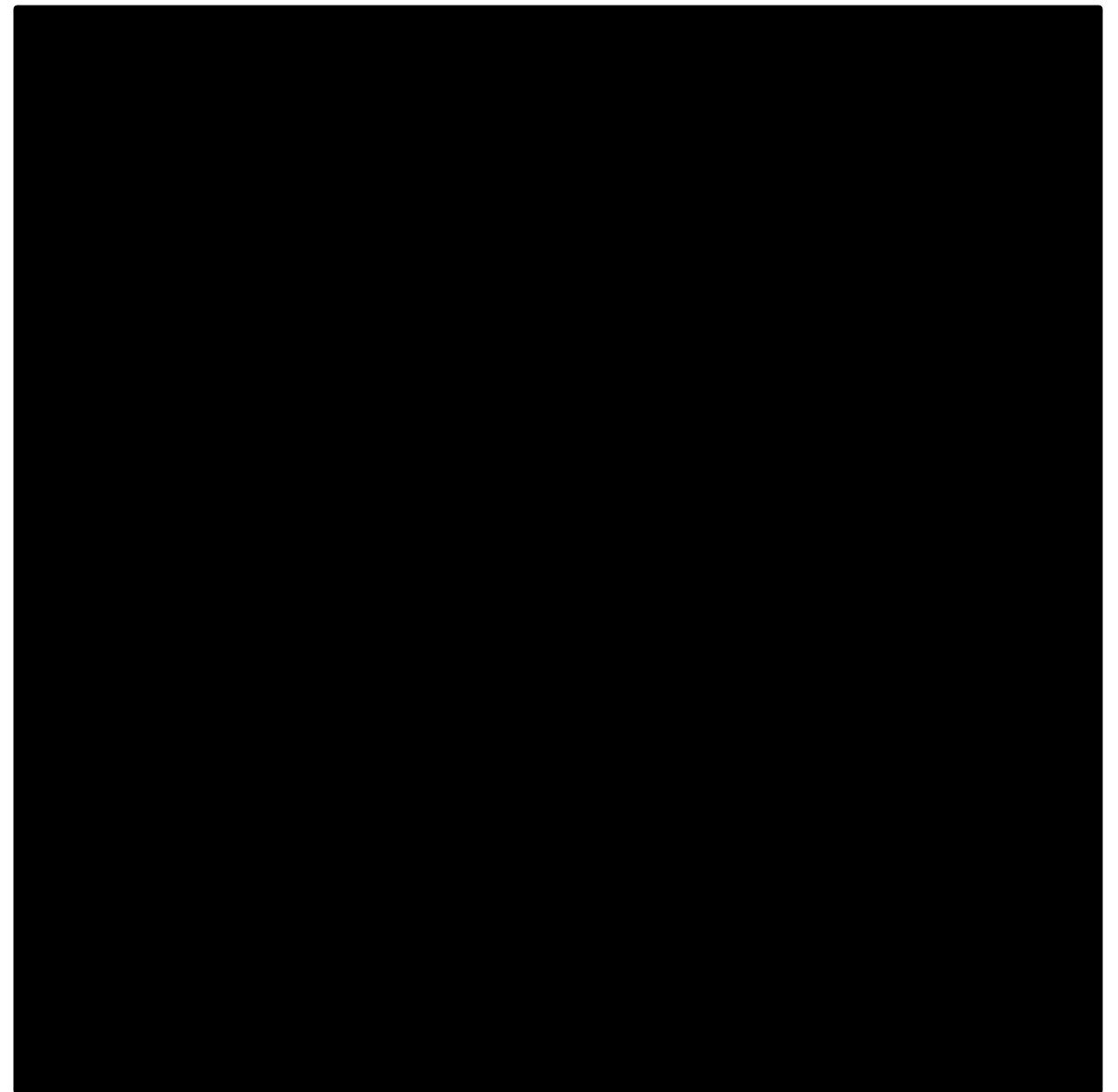
[REDACTED]. Treatment with donidalorsen Q4W was associated with a [REDACTED]
 [REDACTED]
 [REDACTED]. However, as stated above, this difference was not statistically significant. The wide and overlapping CrIs observed in the forest plot presented in Figure 29, demonstrate that there is no statistically significant difference between donidalorsen and its comparators.

Table 22: Median rate ratios and 95% CrIs from the NMA for mean number of HAE attacks that require on-demand medication

Treatment	Median rate ratio (95% CrI)
Donidalorsen_Q8W	[REDACTED]
Lanadelumab_Q2W	[REDACTED]
Lanadelumab_Q4W	[REDACTED]
Placebo	[REDACTED]

Abbreviations: CrI – Credible interval; HAE – Hereditary angioedema; NMA – Network meta-analysis; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks

Figure 29: Forest plot of median rate ratios and 95% Crls for the mean number of HAE attacks requiring on-demand medication treatment effects



Abbreviations: Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks

2.10.4.7 Mean change from baseline in AE-QoL score

Mean differences for the mean change in AE-QoL score from baseline and 95% Crls are shown in Table 23 and the forest plot in Figure 30. No statistically significant differences were observed between the mean difference from baseline in AE-QoL score for treatment with donidalorsen Q4W, and donidalorsen Q8W, lanadelumab Q2W, and lanadelumab Q4W. The results for donidalorsen Q4W show a [REDACTED]

[REDACTED]. The wide and overlapping CrIs observed in the forest plot presented in Figure 30, demonstrate that there is no statistically significant difference between donidalorsen and lanadelumab Q2W and lanadelumab Q4W.

A [REDACTED], as [REDACTED], as indicated by the CrIs of the mean difference which do not include 0.

Table 23: Mean difference and 95% CrIs from the NMA from baseline in AE-QoL score

Treatment	Mean difference (95% CrI)
Berotrastat	[REDACTED]
Donidalorsen_Q8W	[REDACTED]
Lanadelumab_Q2W	[REDACTED]
Lanadelumab_Q4W	[REDACTED]
Placebo	[REDACTED]

*95% CrI does not include 0 and is therefore considered statistically significant

Abbreviations: AE-QoL - Angioedema Quality of Life Questionnaire; CrI – Credible interval; NMA – Network meta-analysis; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks

Figure 30: Forest plot of mean differences and 95% CrIs for the mean change from baseline in AE-QoL score



Abbreviations: Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks

2.10.5 Uncertainties in the indirect and mixed treatment comparisons

The NMA was conducted in a robust manner, ensuring that both the data and outcomes used were appropriate for making valid comparisons between all treatments. The analysis was undertaken in line with best practice for conducting and reporting NMA, aligned with NICE reference case methods.²⁸ A comprehensive SLR was conducted to identify all relevant evidence, and each included study

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underwent rigorous risk-of-bias assessment to ensure that only data of sufficient quality informed the model. Potential sources of heterogeneity were evaluated through a feasibility assessment to highlight sources of across-study heterogeneity, and sensitivity and face-validity checks were performed on the results. The company therefore posits that despite the acknowledged limitations of certain datasets, this NMA is the most robust analysis possible for the comparative efficacy and effect on quality of life of donidalorsen and its comparator LTPs based on the data available. All results are presented with a 95% CrIs, to demonstrate the range of plausible values for that parameter, based on the observed data and prior beliefs.

A limitation of the analyses was the inevitable heterogeneity between studies, which included differences in the administration method (subcutaneous versus oral and intravenous), the length of trials (24 weeks versus 26 weeks) and the difference in the timing of administration. The Cinryze study, CHANGE, introduced some other potential uncertainty due to differences in study design and population. The absence of a washout period in the CHANGE trial prior to randomisation could have introduced bias into the analysis because residual effects from previous prophylactic treatments may have influenced baseline attack rates and treatment responses. This key design difference reduced the comparability of the CHANGE population with that of the other trials and therefore it was deemed inappropriate to include in the analysis. However, this study was incorporated to facilitate the comparison of all key trials.

Although this heterogeneity from the Cinryze study, CHANGE, and the residual heterogeneity between the other studies in the analysis exists and may reduce the validity of some analyses, the robustness of the NMA methodology and use of an RE model over a FE model, as discussed in Section 2.10.3.4, demonstrates that this does not have substantial impact on the validity of the NMA results. On the contrary, the RE model was selected as this better captured potential variability between studies.

Due to the small number of studies and limited appropriately comparable data, the evidence networks were sparse; most treatment comparisons were supported by

only a single trial, with no head-to-head comparisons available. Consequently, the network structure was simplified, which amplified the model dependence on individual studies and therefore increased the potential for biased treatment-effect estimates.

2.10.6 Conclusions from the NMA results

The results of the NMA were generally consistent across all reported outcomes. No statistically significant difference was observed between donidalorsen and comparator LTPs, in the mean number of attacks per month as well as other outcomes. Donidalorsen Q4W demonstrated [REDACTED]
[REDACTED]
[REDACTED]. However, as stated above, these differences were not statistically significant, therefore indicating donidalorsen Q4W provides similar efficacy and QoL benefits compared to existing treatments. This is also indicated by the wide and overlapping Crls for each of the rate ratios which do not include 1. This suggests that an assumption of equal efficacy of donidalorsen Q4W to donidalorsen Q8W, berotralstat, lanadelumab Q2W, lanadelumab Q8W and C1-INH is clinically appropriate. This was further validated by clinical experts in September 2025, who concluded that as the results do not demonstrate a statistically significant difference, it is reasonable to assume all treatments can demonstrate equal efficacy.¹⁹

2.11 Adverse reactions

2.11.1 Treatment exposure

In OASIS-HAE, the mean duration of exposure was [REDACTED] days in the donidalorsen Q4W group and [REDACTED] days in the donidalorsen Q8W group. A full summary of the drug exposure is provided in Table 24. Patients in the OASISplus study could receive treatment for up to 157 weeks, with the mean (SD) study treatment exposure for the OASISplus OLE cohort as 227.2 (80.3) days for the donidalorsen Q4W group, 232.4 (92.3) days for the donidalorsen Q8W group, and 228.1 (81.9) days in total.³⁶

Table 24: Summary of treatment exposure in OASIS-HAE

Parameter	Placebo (N=22)	Donidalorsen 80 mg Q4W (N=45)	Donidalorsen 80 mg Q8W (N=23)
Duration of donidalorsen exposure (days)^a			
Mean (SD)	-		
Median (P25, P75)	-		
Min, Max	-		
Mean 95% CI	-		

Abbreviations: CI – Confidence interval; Max – Maximum; Min – Minimum; mg - milligrams; P25 – 25th percentile; P75 – 75th percentile; SD – Standard deviation

Notes: ^a Treatment duration was derived as min (the date/time of the last dose of study drug + 28 days for Q4W dosing, +56 days for Q8W dosing, last contact date) - the date/time of the first dose + 1.

Source: OASIS-HAE CSR⁷⁶

2.11.2 Adverse events

2.11.2.1 OASIS-HAE safety data

A summary of safety data is presented in Table 25.

The proportion of patients who experienced at least one TEAE was higher in the placebo group compared to the donidalorsen Q4W and donidalorsen Q8W groups.⁷⁶ Overall, the majority of TEAEs were mild or moderate in severity. The proportion of patients experiencing a TEAE related to the study drug was higher in the donidalorsen Q4W group compared to the donidalorsen Q8W and placebo groups.⁷⁶ No deaths were reported during this study. One patient in the donidalorsen Q8W group permanently discontinued the drug due to a TEAE of increased levels of ALT.⁷⁶

Table 25: Overview of adverse events, Safety set, OASIS-HAE

Parameter	Placebo (N=22)	Donidalorsen 80 mg Q4W (N=45)	Donidalorsen 80 mg Q8W (N=23)
Patients with any adverse event, n (%)			
Patients with any TEAE^a, n (%)			
Patients with any TEAE related to study drug^b, n (%)			
Patients with any TEAE by maximum severity			
Mild, n (%)			
Moderate, n (%)			

Parameter	Placebo (N=22)	Donidalorsen 80 mg Q4W (N=45)	Donidalorsen 80 mg Q8W (N=23)
Severe ^c , n (%)	██████	██████	██████
Patients with any TEAE related to study drug by maximum severity			
Mild, n (%)	██████	██████	██████
Moderate, n (%)	██████	██████	██████
Severe, n (%)	█	██████	█
Patient with any serious AE, n (%)	██████	█	█
Patients with any serious AE related to study drug, n (%)	█	█	█
Patients with any TEAE leading to permanent discontinuation, n (%)	█	█	██████
Patients with any TEAE leading to permanent treatment discontinuation related to study drug, n (%)	█	█	██████

Abbreviations: AE – Adverse event; mg – milligrams; TEAE – Treatment-emergent adverse event

Notes:

^a TEAE was defined as any AE starting or getting worse on or after the first dose of the study drug. At each level of summation (overall, preferred term), patients reporting at least one relevant event were counted only once for the total incidence and for each treatment. At each level of patient summarisation, a patient was classified according to the highest severity even if the patient reported one or more events.

^b Related was defined as "Related", "Possible", or missing relationship to study drug (donidalorsen or placebo).

^c One patient in the donidalorsen Q4W group experienced a headache which was deemed to be related to the study drug. The severe TEAEs in the placebo (headache and limb injury) and donidalorsen Q8W (epicondylitis and blood creative phosphokinase increased) were not related to the study drug.

^d One patient in the placebo group experienced a SAE of limb injury that was considered not related to study drug per the Investigator and Sponsor.

Source: OASIS-HAE CSR⁷⁶

The most common TEAEs experienced by >5% of patients in any treatment group of are summarised in Table 26. The most common events were erythema at the injection site ██████, headache ██████, and nasopharyngitis ██████ in the Q4W group, influenza ██████, nasopharyngitis ██████ in the Q8W group and nasopharyngitis ██████, limb injury ██████, and headache ██████ in the placebo group.⁷⁶ A greater proportion of patients in the donidalorsen Q4W group ██████ experienced at least one treatment-emergent injection-site reaction compared with the donidalorsen Q8W group ██████ and placebo group ██████.⁷⁶ All injection site reactions were nonserious, mild in severity, and did not result in any action taken.

The majority of injection site reactions resolved spontaneously without any complications or any additional treatment.⁷⁶

Table 26: Most common TEAEs (>5% of patients in any treatment group), Safety set, OASIS-HAE

Preferred term ^a	Placebo (N=22) n (%)	Donidalorsen 80 mg Q4W (N=45) n (%)	Donidalorsen 80 mg Q8W (N=23) n (%)
Patients with any TEAE^b, n (%)	██████████	██████████	██████████
Headache	██████████	██████████	██████████
Nasopharyngitis	██████████	██████████	██████████
Urinary tract infection	█	██████████	██████████
Upper respiratory tract infection	██████████	██████████	██████████
Patients with at least 1 treatment emergent injection-site reaction	██████████	██████████	██████████
Injection site erythema	█	██████████	██████████
Injection site discolouration	█	██████████	██████████
Injection site pruritus	█	██████████	█
Injection site pain	█	██████████	█
Abdominal discomfort	█	██████████	█
Influenza	██████████	██████████	██████████
Abdominal pain	██████████	██████████	█
Covid-19	██████████	██████████	█
Gastroenteritis	██████████	██████████	██████████
Dyspepsia	██████████	█	█
Limb injury	██████████	█	██████████
Oral herpes	█	█	██████████
Sinusitis	██████████	█	█
Vomiting	██████████	█	██████████

Abbreviations: AE – Adverse event; mg – milligrams; TEAE – Treatment-emergent adverse event

^a At each level of summation (overall, preferred term), patients reporting at least 1 relevant event were counted only once for the total incidence and for each treatment.

^b A TEAE was defined as any AE starting or getting worse on or after the first dose of the study drug

Source: OASIS-HAE CSR⁷⁶

AEs of special interest were defined prior to the completion of the study, in the protocol.⁷⁶ These include:

- Severe reduction in platelet count < 50,000/mm³ accompanied by a major bleeding event or a clinically relevant non-major bleeding event; or

- Platelet count of $< 25,000/\text{mm}^3$ independent of a major bleeding event or clinically relevant non-major bleeding event.

No patient in any treatment group experienced these AEs during the study.⁷⁶

2.11.2.2 OASISplus OLE cohort safety data

The incidence and severity of TEAEs are shown in Table 27. No patients discontinued donidalorsen due to TEAEs, and no serious TEAEs were reported as related to the study drug. Furthermore, most TEAEs were mild or moderate, and therefore no new safety signals were identified in the OLE data. Fewer patients experienced any TEAEs and TEAEs related to the study drug in the Q8W compared to the Q4W group.

Table 27: Overview of TEAEs, Safety set, OLE cohort at Week 53 (data cut off February 2024)

	Donidalorsen 80 mg every 4 weeks (n=69)	Donidalorsen 80 mg every 8 weeks (n=14)	All patients (n=83)
Any TEAE ^a , n (%)	56 (81.2)	10 (71.4)	66 (79.5)
Any TEAE related to study drug, n (%)	16 (23.2)	2 (14.3)	18 (21.7)
Any TEAE leading to discontinuation, n (%)	0	0	0
Severity of TEAEs, n (%)			
Mild	28 (40.6)	5 (35.7)	33 (39.8)
Moderate	26 (37.7)	4 (28.6)	30 (36.1)
Severe	2 (2.9)	1 (7.1)	3 (3.6)
Any serious TEAE, n (%)	4 (5.8)	0	4 (4.8)
Any serious TEAE related to study drug, n (%)	0	0	0

	Donidalorsen 80 mg every 4 weeks (n=69)	Donidalorsen 80 mg every 8 weeks (n=14)	All patients (n=83)
Any serious TEAE leading to discontinuation, n (%)	0	0	0

^aTreatment-emergent adverse events (TEAEs) are defined as AEs that either start or worsen in severity on or after the date/time of first dose of study drug in the current study. Related is defined as “related”, “possible” or missing relationship to study drug (donidalorsen or placebo).

Abbreviations: mg – milligram; OLE – Open-label extension; TEAE – Treatment-emergent adverse events

Source: Tachdjian et al. 2024³⁶

2.11.2.3 OASISplus switch cohort safety data

The incidence and severity of TEAEs are shown in Table 28. Only one TEAE led to discontinuation, however this was not related to the study drug, and no serious TEAEs relating to the study drug were reported. Furthermore, most TEAEs were mild or moderate in severity.

Table 28: Overview of TEAEs, Safety set, switch cohort at Week 17 (data cut off February 2024)

	Donidalorsen 80mg every 4 weeks (N = 64)
Any TEAE^a, n (%)	45 (70.3)
Any TEAE related to study drug^b, n (%)	17 (26.6)
Any TEAE leading to discontinuation, n (%)	1 (1.6) ^c
Any serious TEAE, n (%)	1 (1.6) ^c
Any serious TEAE related to study drug, n (%)	0
Severity of TEAEs related to study drug, n (%)	
Mild	17 (26.6)
Moderate	5 (39.1)
Severe	3 (4.7)

^aTreatment-emergent adverse events (TEAEs) are defined as AEs that either start or worsen in severity on or after the date/time of first dose of study drug in the current study. Related is defined as “related”, “possible” or missing relationship to study drug (donidalorsen or placebo).

^bPotentially related is defined as related, possible, or missing relationship to study drug.

^cPatient discontinued owing to complications associated with ongoing congestive heart failure that were considered unrelated to the study drug.

Abbreviations: mg – milligram; OLE – Open-label extension; TEAE - Treatment-emergent adverse events

Source: Riedl et al. 2025⁷⁷

2.12 Ongoing studies

The OASISplus study is ongoing, with an expected completion date in 2027. The latest available efficacy and safety data are presented in Section 2.6.3 and Section 2.11.2, respectively.

2.13 Interpretation of clinical effectiveness and safety evidence

The clinical benefits of donidalorsen were comprehensively evaluated through a 24-week treatment period in a RCT (OASIS-HAE) with a long-term extension providing data up to 157 weeks in total (OASISplus).^{12,75}

Donidalorsen is highly effective for the routine prevention of HAE attacks

Ultimately, achieving total control of HAE and normalising patients' lives can only currently be achieved by LTP, and donidalorsen provides long-term HAE control without compromising lifestyle, providing patients the convenience and stability they need to take back control of their lives. In the OASIS-HAE phase III trial, donidalorsen at a dose of 80 mg (Q4W or Q8W) significantly reduced the mean HAE attack rate during Week 1 to Week 25 compared to placebo, demonstrating a relative reduction of 81% ($p < 0.001$) and 55% ($p = 0.004$) in the Q4W and Q8W groups, respectively.⁷⁶ In addition, a reduction in the mean HAE attack rate from Week 5 to Week 25, compared to baseline, of 87% ($p < 0.001$) and 60% ($p = 0.004$), for the donidalorsen Q4W and Q8W groups, respectively, demonstrates that early observed reductions in HAE attack rate due to donidalorsen were sustained throughout the treatment period.

Donidalorsen sustains continued HAE attack rate reductions in long-term treatment, including when patients switch from other LTPs

The reduction in HAE attack rates observed in OASIS-HAE in patients treated with donidalorsen was maintained in the OASISplus OLE cohort, which showed that both Q4W and Q8W donidalorsen groups had a 92-93% reduction in HAE attacks compared with the OASIS-HAE baseline.³⁶ These results demonstrate that the

efficacy of donidalorsen is sustained in long-term treatment, for both Q4W and Q8W dosing regimens. Furthermore, patients in the OASISplus switch cohort receiving donidalorsen Q4W after treatment with other LTPs had a mean reduction in attack rate from baseline of 62%, demonstrating that donidalorsen can allow patients to maintain reduced attack rates and achieve further reductions in attack rates after treatment with other LTPs.⁷⁷

A robust NMA demonstrated donidalorsen provides similar efficacy and quality of life benefits compared to existing treatments

An NMA was conducted to estimate the clinical effectiveness of donidalorsen Q4W compared with donidalorsen Q8W, placebo and the comparators of interest for this appraisal: lanadelumab, berotralstat, and IV C1-INHs. The NMA results were broadly consistent across all outcomes analyses. The wide and overlapping CrIs indicate that there is no statistically significant difference between donidalorsen Q4W and comparator LTPs; [REDACTED]

[REDACTED]. The absence of statistically significant differences between LTPs demonstrates donidalorsen provides similar efficacy compared to existing treatment, as validated by UK clinical experts in September 2025, and is an effective treatment option for patients to manage their disease effectively and improve their QoL.¹⁹

Donidalorsen offers less frequent dosing than comparators and a convenient method of administration

Donidalorsen is administered subcutaneously via an auto-injector pen, which gives patients the ability to self-administer at home, removes the need for hospital visits to receive LTP and minimise the burden of treatment on their daily lives. Driven by its unique mechanism of action using LICA conjugation technology, donidalorsen has a once monthly dosing frequency, with the option to reduce this further to every two months [REDACTED], offering a reduced dosing regimen compared to its comparators, lanadelumab, and

berotralstat and C1-INH.¹⁶ Based on a post-hoc analysis of OASIS-HAE, it is estimated that [REDACTED] % of patients will be eligible for a dose reduction from donidalorsen Q1M to donidalorsen Q2M after a six-month treatment period. Furthermore, results from the OASISplus OLE cohort demonstrate a sustained and similar efficacy with Q8W dosing of donidalorsen compared to the Q4W group in the long-term. This demonstrates the significant opportunity that patients treated with donidalorsen will have to use an LTP with the least frequent dosing regimen of all available LTPs, thus reducing their overall treatment administration burden.

Donidalorsen demonstrates significant benefits to the quality of patients' lives and a favourable safety profile

As discussed above, a post-hoc analysis of OASIS-HAE demonstrated that a substantial proportion of patients treated with donidalorsen were able to remain attack-free for a sustained period during the trial. The results of the analysis demonstrate that [REDACTED] % of patients remained attack-free for [REDACTED] [REDACTED] within six months after treatment initiation with donidalorsen. Having extended periods of attack freedom is crucial to alleviating the physical and mental burden which repeated attacks impose on patients, allowing patients to feel that they have achieved disease control and the burden of HAE on their daily life has been significantly reduced.

Furthermore, a reduced mean number of moderate or severe HAE attacks was demonstrated with donidalorsen, compared to placebo; reductions of 89% ($p < 0.001$) and 41% ($p = [REDACTED]$) were demonstrated with donidalorsen Q4W and Q8W groups, respectively, compared to placebo. Such reductions in attack severity are key to alleviating the significant physical burden which HAE patients suffer, making symptoms more manageable, and minimising the potential impact HAE attacks have on patients' ability to carry out their normal activities.

In OASIS-HAE there were clinically meaningful improvements in patient AE-QoL scores. These results indicate that donidalorsen treatment allows patients to preserve their overall well-being, emotional and physical functioning, as well as daily activities while receiving treatment.⁷⁶ This is a meaningful benefit to patients, as it

demonstrates that their QoL is maintained during treatment, allowing them to manage their condition with minimal disruption to their everyday life. This was further supported by patient-reported outcomes from OASISplus, demonstrating sustained improvement of HRQoL and disease control, and patient preference for treatment with donidalorsen compared to other LTPs.^{36,77}

Donidalorsen also demonstrated a favourable safety profile, and was well tolerated, with an absence of serious AEs and discontinuations related to the study drug over the course of the study.^{8,74} This is key to ensuring there is minimal impact on patients' HRQoL due to treatment – a key factor for patient satisfaction.⁷⁰

Overall, donidalorsen offers an effective, well-tolerated, alternative treatment option for patients with HAE. The clinical study results have shown donidalorsen can significantly improve patients' lives by reducing their attack rate and increasing their attack-free periods, allowing them to continue with work, school, and normal daily living and reducing the psychological burden associated with this disease.

3 Cost effectiveness

- An SLR was conducted in April 2025 to identify published cost-effectiveness studies conducted in HAE. The SLR identified 16 publications relating to cost-effectiveness, including eight abstracts, two full-text studies and six HTA reports.
- A *de novo* economic model was developed to compare donidalorsen to berotralstat, in patients experiencing ≥ 2 attacks per month, and to lanadelumab and C1-INHs, in patients experiencing ≥ 8 attacks per month. The model was developed in Microsoft Excel® and adopted a cohort-based Markov model, as aligned with four out of eight economic models reviewed as part of the SLR.
- Following the NICE reference case, the analysis is conducted from the perspective of the NHS and Personal Social Services (PSS) with a lifetime horizon, and costs are discounted at a rate of 3.5% discount rate per annum.²⁸
- Clinical effectiveness data for donidalorsen were derived from the phase III OASIS-HAE trial.⁷⁶ In the absence of head-to-head studies comparing donidalorsen with other LTPs, an NMA was conducted to compare the comparative efficacy of donidalorsen against berotralstat, lanadelumab, and plasma-derived IV C1-INHs in patients with HAE (see Section 2.10).
 - The outcomes from the NMA demonstrated that there is no statistically significant difference between donidalorsen and comparator LTPs, indicating donidalorsen provides similar efficacy and QoL benefits compared to existing treatments. The assumption of equal efficacy across the LTPs was validated by UK clinical experts in September 2025.¹⁹ Therefore, the company base case analysis is a cost-comparison with a cost-utility analysis (CUA) scenario presented in Appendix K.
- The base case economic evaluation, with the inclusion of a simple PAS discount of [REDACTED]%, demonstrates that treatment with donidalorsen in patients with HAE experiencing ≥ 2 attacks per month is associated with a cost-saving of £[REDACTED] versus berotralstat. In patients experiencing ≥ 8 attacks per month, treatment with donidalorsen is associated with a cost saving of £[REDACTED] versus lanadelumab and £[REDACTED] versus C1-INH.

- The results of the economic analysis were tested through deterministic and probabilistic sensitivity analyses. The mean probabilistic results lie close to the deterministic results, indicating that the model is robust to parameter uncertainty. Scenario analyses were also performed in order to test key structural and inputs assumptions.
- The results of the company's economic analysis demonstrate that donidalorsen is a cost-saving alternative treatment option, offering similar efficacy and a reduced administration frequency compared to existing LTP options.

3.1 Published cost-effectiveness studies

An SLR was conducted in April 2025 to identify all relevant cost-effectiveness studies for the treatment of patients aged 12 years or older with HAE. Full details of the process and methods used to identify and select the economic evidence relevant to the technology being evaluated are presented in the SLR report – attached in Appendix E.

The SLR identified 16 publications relating to cost-effectiveness, including eight abstracts, two full-text studies and six HTA reports. The two full-text publications reported on the cost-effectiveness of on-demand treatment, and of the six HTA reports, four reported on the cost-effectiveness of LTP treatment. A summary of the cost-effectiveness studies identified in the SLR (excluding abstracts) is presented in Table 29.

Table 29: Summary list of published cost-effectiveness studies identified through the SLR

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Bernstein <i>et al.</i> ⁹¹	2020	Decision tree model. From the acute attack node, there are 4 treatment paths with the same structure for each.	HAE (NR)	Mean QALYs per year: rhC1-INH: 0.825 Icatibant: 0.816 Ecallantide: 0.822 pdC1-INH: 0.817	Mean cost per year (USD): rhC1-INH: \$347,145 Icatibant: \$398,281 Ecallantide: \$566,729 pdC1-INH: \$395,107 Cost per attack (USD): rhC1-INH: \$12,905 Icatibant: \$14,806 Ecallantide: \$21,068 pdC1-INH: \$14,668	NR
Federici, C. <i>et al.</i> ⁹²	2018	Logistic regression was used to estimate the probability of seeking treatment, followed by conditional regression to determine the effect of variables on attack cost, using both Bayesian and frequentist approaches.	C1-INH-HAE (NR)	Improvements in QALYs gained of C1-INH vs icatibant: 1.42 vs 1.40	Costs of C1-INH vs icatibant (Euro): €11,874 vs €12,496	NR
NICE ⁹	2021	Cohort-level Markov model with 2 health states: (i) Alive (ii) Dead The alive health state was split into 2 sub-states: (i) Attack-free	People aged 12 years or older with HAE Type I or II who: (i) Experience ≥2 clinically significant attacks per month and are unsuitable for, or refractory to, androgens; (ii) Experience ≥2 clinically significant attacks per week	NR	NR	Cost per QALY gained (GBP): £20,707 per QALY gained

Company evidence submission template for donidalorsen for preventing hereditary angioedema attacks in people 12 years and over [ID6457]

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		(ii) Attack	and are unsuitable for regular injectable prophylaxis with lanadelumab or C1-INHs.			
NICE ¹⁸	2019	Cohort-level model with two health states: (i) Alive with HAE; patients within the alive state are either in an 'attack-free period' or in an 'attack period' (average number of attacks estimates from HELP data) (ii) Dead	People aged 12 years and older with HAE Type I or II who have at least one angioedema attack every 4 weeks.	NR	NR	ICER (GBP): Dominant and lower than £20,000
SMC	2012	Decision-analytic model 2 health states: (i) During an attack (ii) After recovery	Adult patients with C1-INH deficiency treated for moderate to severe attacks of HAE Type I or II.	QALY gain per attack: 0.0000852 in favour of icatibant	NR	NR
SMC ⁹⁴	2018	Cost-minimisation analysis	Adults and adolescents with HAE due to C1-INH deficiency.	NR	Incremental cost (GBP): £685.59 of conestat alfa (Ruconest®)	NR
SMC ⁹⁵	2019	Cohort-level Markov model comprised of 2 health states: (i) Alive (with HAE) (ii) Dead The alive health state was split into 2 sub-states: (i) Attack-free	Patients aged 12 years and older with HAE, with a restriction to patients who would otherwise be considered for LTP treatment with C1-INH.	NR	NR	ICER: Dominant

Company evidence submission template for donidalorsen for preventing hereditary angioedema attacks in people 12 years and over [ID6457]

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		(ii) Attack				
SMC ⁹⁶	2022	Markov model with 2 health states: (i) Alive (ii) Dead The alive health state was split into 2 sub-states: (i) Attack-free (ii) Attack	Adult and adolescent populations aged 12 years and older with HAE.	NR	NR	ICER Berotralstat versus SoC (GBP): £743,158

Abbreviations: C1-INH – C1 Inhibitor; GBP – Great British Pound; HAE – Hereditary angioedema; ICER – Incremental cost-effectiveness ratio; LTP – Long-term prophylaxis; NICE – National Institute for Health and Care Excellence; NR – Not reported; pdC1-INH – Plasma-derived C1 Inhibitor; QALY – Quality adjusted life year; rhC1-INH – Recombinant human C1 Inhibitor; SMC – Scottish Medicines Consortium; SoC – Standard of care; USD – United States Dollar.

3.2 Economic analysis

As described in Section 3.1, the SLR identified eight relevant full-text publications reporting cost-effectiveness evidence for the treatment of HAE.

The SLR did not identify any existing cost-effectiveness analyses directly comparing donidalorsen to berotralstat, lanadelumab, or C1-INH in patients with HAE.

Therefore, a *de novo* economic model was developed in Microsoft Excel® using a cohort-based Markov model. The model contains two health states: alive (comprised of patients who are either experiencing an attack or are attack-free), or dead. This model structure was selected based on the following reasons:

- This structure captures the disease progression of patients with HAE over a lifetime horizon, capturing the cost differences and clinical outcomes associated with the relevant comparators, such as differences in HAE attacks and the associated health care resource use (HCRU). This allows the model to reflect both the clinical and economic burden of HAE in a comprehensive way that reflects real world clinical practice.
- A cohort-level model was selected as the most appropriate based on consideration of the data available for donidalorsen, and the relevant comparators. HAE is a rare disease, resulting in limited data being available in published literature as well as small patient numbers within the clinical trials. Hence, a patient-level model was considered inappropriate due to the limited data available to inform the parameters.
- This structure is in line those used in previous NICE appraisals in HAE (TA606 [lanadelumab] and TA738 [berotralstat]), which were accepted as appropriate for decision making by the respective committees.^{9,18}

The objective of the economic analysis is to assess the cost-savings of donidalorsen compared with current clinical management of HAE in England for patients [REDACTED]

[REDACTED]

[REDACTED]

The model structure was validated by clinical experts in validation meetings held in September 2025 and is further discussed in Sections 3.2.2 and 3.2.5.¹⁹

The base-case economic analysis adopts a cost-comparison approach, as the NMA results demonstrated no statistically significant differences in the efficacy of donidalorsen Q4W compared with donidalorsen Q8W, berotralstat, lanadelumab Q2W, lanadelumab Q4W and C1-INH (Section 2.10). Specifically, when using donidalorsen Q4W as the reference treatment, the median rate ratios for the mean number of HAE attacks per month showed overlapping credible intervals across all assessed comparators, indicating a lack of meaningful differences in outcomes. In validation meetings with UK clinical experts held in September 2025, experts confirmed it is reasonable to assume no clinically meaningful difference in efficacy between donidalorsen, berotralstat, lanadelumab and C1-INH.¹⁹ Given this evidence, a CUA was not considered appropriate. Further details on the justification of a cost-comparison approach and details regarding the NMA can be found in Section 3.3.1.3. Appendix K presents a scenario analysis evaluating donidalorsen compared to current clinical management using a cost-utility approach.

3.2.1 Patient population

In line with the anticipated marketing authorisation, the cost-comparison analysis evaluated donidalorsen in patients [REDACTED]. The [REDACTED]. The patient population is consistent with that of the OASIS-HAE clinical trial for donidalorsen and represents those with the greatest unmet need within current clinical practice. Within NHSE, the only licensed LTP for patients experiencing ≥ 2 attacks per month is berotralstat, associated with demanding administration regimens and tolerability concerns, demonstrating the unmet need for LTP options in this patient population (see Section 1.3.3.3 for more detail).^{9,10,17} For patients who experience ≥ 8 attacks per month, lanadelumab and C1-INH are the LTPs used in standard clinical practice. Donidalorsen has demonstrated to be an effective and well-tolerated LTP (see Section 2.6) that aims to provide an alternative treatment option, offering greater convenience for patients because of the option to reduce to a dosing frequency of Q2M, which is less frequent than all alternative LTPs.

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Evidence from the OASIS-HAE trial is used to inform this cost-comparison.⁷⁶ The baseline characteristics of patients in the OASIS-HAE trial are presented in Section 2.3. The baseline characteristics of patients in the OASIS-HAE trial were considered generalisable to the general HAE population in the NHS, which was confirmed by UK clinical experts (September 2025).¹⁹

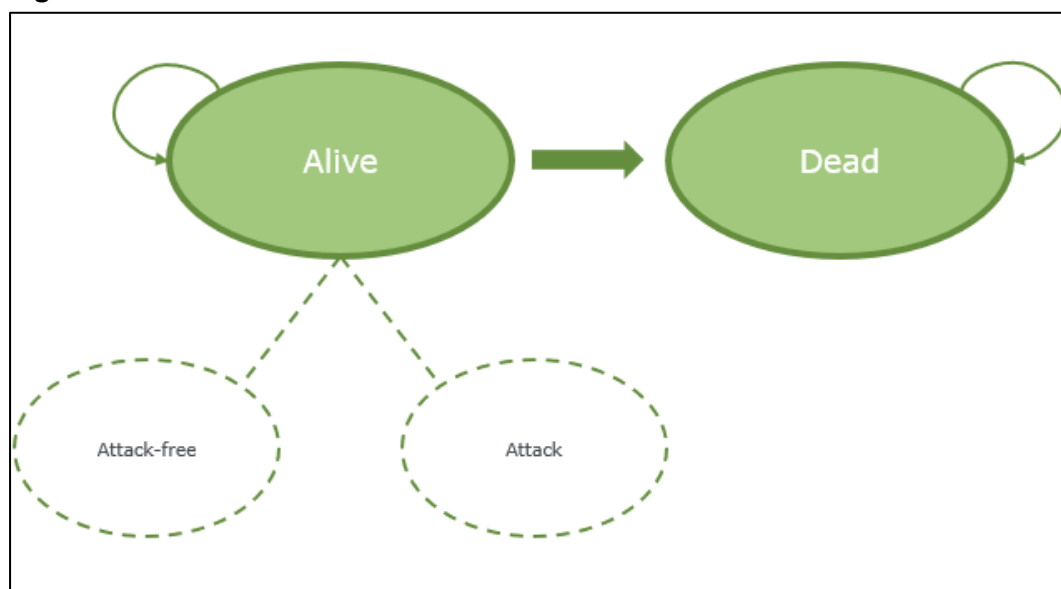
3.2.2 Model structure

The economic model utilises a Markov-model structure with two mutually exclusive and collectively exhaustive health states:

- **Alive:** Patients in this health state are alive and can accumulate costs. The alive health state is comprised of patients who are:
 - Currently experiencing an HAE attack
 - Currently attack-free
- **Dead:** Patients in this state are dead and cannot accumulate costs.

Patients enter the model in the alive health state and receive treatment with either donidalorsen Q1M, berotralstat, lanadelumab Q2W or C1-INH. Within the alive health state, patients may experience HAE attacks over time or remain attack-free during a given cycle. The frequency and duration of these attacks is captured within the model to reflect the cost and resource use associated with HAE attacks per cycle, rather than patients moving between separate 'attack' or 'attack-free' sub-states. As part of the cost-comparison base-case, the frequency and duration of each attack is considered equal across all treatments. The death health state is an absorbing health state. A schematic of the model structure is presented in Figure 31.

Figure 31: Model structure



3.2.3 Cycle length

The cycle length used within the economic model is four weeks (28 days). A 28-day cycle length was chosen as it aligns with timepoints at which data were collected in the OASIS-HAE trial and with previous NICE appraisals in HAE.^{9,18} A 28-day cycle length was also considered suitable to capture the change in costs and outcomes associated with the disease progression of HAE.

The model base case applies a half-cycle correction to account for the fact that attacks HAE attacks may occur at any timepoint within the cycle period.

3.2.4 Time horizon

A lifetime horizon (60.4 years [100 years – mean age at baseline]), from the age of starting treatment upon entering the model, is used in the base case as per the NICE reference case.²⁸ This covers the period over which all important differences in costs between donidalorsen and relevant comparators would be observed.

3.2.5 Discount rate and perspective

As per the NICE reference case, the analysis is conducted from the perspective of the NHS and PSS for costs and health outcomes. A 3.5% discount rate per annum is used for costs.²⁸

3.2.6 Features of the economic analysis

Table 30 presents the key features of the economic analysis in comparison to previous NICE appraisals of treatments for patients with HAE with ≥ 2 attacks per month. These include:

- NICE TA606: lanadelumab for the routine prevention of recurrent attacks in patients who experience eight or more clinically significant attacks per month (defined as ≥ 2 attacks per **week**).¹⁸
- NICE TA738: berotralstat for the routine prevention of recurrent attacks in patients who experience ≥ 2 attacks per **month**.⁹

Table 30: Features of the economic analysis

Factor	Previous evaluation, TA606 (lanadelumab) ¹⁸	Previous evaluation, TA738 (berotralstat) ⁹	Current evaluation, chosen values	Current evaluation, justification
Model structure	Markov model with 2 health states; alive and dead. Within the alive health state patients can experience an attack-free or attack period.	Markov model with 2 health states; alive and dead. Within the alive health state there are 2 sub-states: patients who are currently experiencing an HAE attack, and patients who are currently attack-free.	Markov model with 2 health states; alive and dead. Within alive health state patients are either currently experiencing an HAE attack or currently attack-free.	This structure is in line with previous NICE appraisals in HAE, which have been accepted as appropriate for decision making by the respective committees.
Time horizon	Lifetime (60 years)	Lifetime (56 years)	Lifetime (63 years)	In line with the NICE reference case. ²⁸
Cycle length	28 days	28 days	28 days	This cycle length aligns with the data collection points in the OASIS-HAE trial and previous NICE appraisals. UK clinical experts consulted by the company in September 2025 validated the model settings including the cycle length. ¹⁹
Discount for utilities and costs	3.5%	3.5%	3.5%	In line with the NICE reference case. ²⁸
Perspective (NHS/PSS)	UK NHS/PSS	UK NHS/PSS	UK NHS/PSS	In line with the NICE reference case. ²⁸
Population	Patient with HAE who experience ≥ 2 attacks per week	Patient with HAE who experience ≥ 2 attacks per month	Patient with HAE who experience ≥ 2 attacks per month	This population is aligned with TA378 and reflects the population with the greatest unmet need.
Intervention	Lanadelumab	Berotralstat	Donidalorsen	In line with the final scope. ⁶⁴

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Factor	Previous evaluation, TA606 (lanadelumab)¹⁸	Previous evaluation, TA738 (berotralstat)⁹	Current evaluation, chosen values	Current evaluation, justification
Comparators	SoC	SoC	Berotralstat, lanadelumab and C1-INH	In line with NICE technology appraisal guidance and NHSE clinical commissioning policies, and consistent with the final scope. ⁶⁴ They are also considered establish SoC. Further details on current treatment landscape can be found in Section 1.3.3.
Treatment waning	Lifetime	Lifetime	Lifetime	In line with previous NICE appraisals.
Economic evaluation	Cost-effectiveness	Cost-effectiveness	Cost-comparison	NMA results demonstrated no statistically significant differences in the efficacy of donidalorsen, berotralstat, lanadelumab and C1-INH, indicating that all treatments have similar clinical effectiveness. The outcome used in the economic model was mean number of attacks per month, as aligned to the primary endpoint of each clinical trial; no statistically significant difference was observed between donidalorsen and comparator LTPs for this endpoint. The assumption of equal efficacy amongst the LTPs in the economic model

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Factor	Previous evaluation, TA606 (lanadelumab) ¹⁸	Previous evaluation, TA738 (berotralstat) ⁹	Current evaluation, chosen values	Current evaluation, justification
				was validated by clinical experts, consulted by the company in September 2025. ¹⁹
Source of utilities	Base case; patient utilities Attack utility values were based on EQ-5D-5L data from Nordenfelt (2014).⁹⁷ Treatment administration utilities were based on data from Jørgensen (2017).⁹⁸ Base case; carer disutilities Caregiver disutilities were not considered.	Base case; patient utilities ‘Attack’ and ‘attack-free’ utilities were based on EQ-5D-5L data from Nordenfelt (2014).⁹⁷ Base case; carer disutilities Caregiver disutilities were informed by a TTO study commissioned by BioCryst Pharmaceuticals. Scenario analyses ‘Attack’ and ‘attack-free’ utilities informed by a TTO study commissioned by BioCryst. Treatment administration utilities based on data from Holko (2018).⁹⁹	Base case No utilities were applied in our cost-comparison base case. Cost-utility scenario; patient utilities (please refer to Appendix K for more details) ‘Attack’ and ‘attack-free’ utilities were based on EQ-5D-5L data from Nordenfelt et al (2014).⁹⁷ Cost-utility scenario; carer disutilities Carer disutilities were included and derived using a carer utility decrement from Pennington et al (2025)¹⁰⁰, applied to the attack utilities from Nordenfelt et al (2014).⁹⁷	In line with previous NICE appraisals.

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Factor	Previous evaluation, TA606 (lanadelumab)¹⁸	Previous evaluation, TA738 (berotralstat)⁹	Current evaluation, chosen values	Current evaluation, justification
Source of costs	NHS reference costs, and literature.	BNF costs, NHS reference costs, PSSRU costs.	BNF costs, NHS reference costs, PSSRU costs.	In line with the NICE reference case. ²⁸

Abbreviations: BNF – British National Formulary; C1-INH – C1 Inhibitor; EQ-5D-5L – EuroQol 5 Dimensions-5 Levels; HAE – Hereditary angioedema; NHS – National Health Service; NICE – National Institute of Health and Care Excellence; NMA – Network meta-analysis; PSS – Personal Social Services; PSSRU – Personal Social Services Research Unit; SoC – Standard of care; TA – Technology appraisal; TTO – Time trade-off; UK – United Kingdom

3.2.7 Intervention technology and comparators

As stated in Section 1.2, donidalorsen is an RNA-targeted PKK inhibitor, intended for the [REDACTED]

[REDACTED].¹⁶ Donidalorsen is administered subcutaneously via an auto-injector pen, giving patients the ability to self-administer at home. In the phase III OASIS-HAE trial, donidalorsen demonstrated a favourable safety profile and was well tolerated, enabling minimal impact to patients' HRQoL due to treatment.^{12,76}

Two dosing regimens of donidalorsen were evaluated in the OASIS-HAE trial:^{12,76}

- Donidalorsen 80 mg Q4W
- Donidalorsen 80 mg Q8W

In line with the anticipated marketing authorisation for donidalorsen, patients should initiate treatment at a dose of [REDACTED].¹⁶ [REDACTED]

[REDACTED].¹⁶ The trial data are presented as donidalorsen Q4W and donidalorsen Q8W; however, no differences in outcomes are expected between Q4W and Q1M dosing, or between Q8W and Q2M dosing.^{12,76}

In the UK, eligibility for specific LTPs is determined by patients' attack frequency. Therefore, in the economic model, the comparators are different for patients who experience ≥ 2 attacks per month and patients who experience ≥ 8 attacks per month. The comparator in the economic model for patients with HAE experiencing ≥ 2 attacks per month is berotralstat; the comparators for patients with HAE experiencing ≥ 8 attacks per month are lanadelumab and C1-INH. The comparators are aligned with NICE technology appraisal guidance, NHSE clinical commissioning policies, which recommend these therapies as preferred "first-line" LTP options, and is consistent with established standard of care and the final scope.^{9,18,23} An overview of the current treatment landscape can be found in Section 1.3.3.

3.2.7.1 Two or more attacks per month

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Berotrastat is the only standard of care LTP recommended for use in patients with ≥ 2 attacks per month. While berotrastat is reimbursed for patients who experience ≥ 2 attacks per month, in practice it is not established care for patients who experience ≥ 8 attacks.⁹ This was confirmed by input from a UK clinical expert who said that berotrastat is not used at all in their clinical practice in patients who experience ≥ 8 per month.¹⁹ Berotrastat is administered at a dose of 150 mg once daily, as per the licensed dosing in the SmPC.¹⁷

3.2.7.2 Eight or more attacks per month

Lanadelumab is recommended by NICE for use in patients experiencing ≥ 8 attacks per month.¹⁸ The recommended starting dose of lanadelumab is 300 mg Q2W, as per the licensed dosing in the SmPC.¹⁵ In patients with a body weight less than 40 kg, a starting dose of 150 mg lanadelumab every 2 weeks may also be considered; however, a dose of 300 mg is assumed in the model.¹⁵ In patients who are stably attack-free on treatment, a dose reduction to 300 mg lanadelumab Q4W may be considered. This has been implemented in the economic analysis (see Section 3.5.1.3 for further details).^{15,101}

C1-INHs (IV Cinryze and off-label IV Berinert) are also considered established standard of care in patients with ≥ 8 attacks per month, based on NHSE commissioning policies.²¹ C1-INH is presented as a singular comparator in the model, but the inputs reflect two C1-INHs: IV Cinryze and off-label use of IV Berinert. A distribution of patients receiving IV Cinryze (27%) and IV Berinert (73%) is applied to calculate the costs of C1-INH treatment. The data for the distribution of patients are sourced from the lanadelumab NICE appraisal (TA606); as part of TA606, the manufacturer consulted with an NHSE commissioning expert and sourced data from NHSE.^{18,21} Cinryze is administered at a dose of 1,000 international units (IU) every three or four days in accordance with the SmPC.¹³ Due to it being used off-label, the dosing of IV Berinert is associated with uncertainty, but clinical experts consulted as part of TA606 (lanadelumab) concluded that IV Berinert, used as LTP, is most commonly dosed according to weight. However, during consultation as part of this appraisal, clinical experts stated they typically use a fixed dose of 1,500 IU of Berinert, with adjustments made for patients with weight at the upper and lower ends

of the spectrum. As such, a distribution of patients prescribed 1,000 or 1,500 IU of Berinert was implemented, assuming [REDACTED] of patients are on 1,000 IU and [REDACTED] of patients receive a dose of 1,500 IU, informed by insights provided by clinical experts to the company in June 2025.¹⁹

3.3 Clinical parameters and variables

The clinical parameters included in the economic analysis are attack rate, attack duration and severity, mortality (general population), and treatment discontinuation.

3.3.1 Attack rate

3.3.1.1 Baseline attack rate

The baseline HAE attack rate (assumed upon entering the model) is equal for all patients, irrespective of treatment received. While there may be some variation in baseline attack rate between patients in clinical practice, an equal baseline attack rate per month ensures that there is no bias towards donidalorsen or comparator treatments. The baseline HAE attack rate is defined by the run-in period HAE attack rate in the placebo arm of the OASIS-HAE trial: the baseline attack rate for the ≥ 2 attacks per month population in the model is 0.725 attacks per week, which is equivalent to the mean run-in period HAE attack rate in the placebo arm of the OASIS-HAE of 2.90 per 4-weeks.⁷⁶ For the population of patients experiencing ≥ 8 attacks per month, the baseline attack rate is 2 attacks per week, equivalent to 8 attacks per 4 weeks in line with the lanadelumab reimbursement criteria.¹⁸ The baseline attack rates for both populations were validated by clinical experts in meetings held in September 2025.¹⁹

3.3.1.2 NMA model specification

In the absence of head-to-head studies comparing donidalorsen with other LTPs, an NMA was conducted to directly compare the treatment effects of donidalorsen against berotralstat, lanadelumab, and plasma-derived IV C1-INHs for patients with HAE. The NMA results from the RE model were considered most appropriate to inform the assumptions in the economic analysis.

A RE model assumes that, in addition to sampling error, observed difference in treatment effect is attributed to some variation of true underlying treatment effect across studies (known as between-study heterogeneity). This is often influenced by several factors e.g. severity of disease, age of patients, dose of drugs, follow-up period.

Although the trials included in the network of evidence were considered generally similar, the feasibility assessment for the NMA demonstrated that there is some heterogeneity across the studies included in the analyses. For example, the administration method in all trials is consistent with OASIS-HAE (subcutaneous), except for APeX-2 and CHANGE, which used oral and intravenous administrations, respectively. Similarly, the difference in the timing of administration may introduce subtle differences in treatment exposure and efficacy between the trials. Some minor differences in the geographic location of recruitment were also identified. However, as there is only one study per treatment comparison within the network, estimating the between-study heterogeneity parameter is not feasible without incorporating an informative prior.

RE models account for heterogeneity between studies while FE models do not and therefore may be considered less reflective of clinical practice and can lead to artificially narrow CrIs. Although the deviance information criterion was used to assess which model has superior goodness-of-fit, the presence of heterogeneity between the studies used in the analysis means there is some uncertainty, which is better represented by the RE model.

Therefore, the NMA results from the RE model are selected to inform the assumptions in the economic analysis to account for potential unmeasured heterogeneity in study populations and trial designs. The use of the RE model is also in line with the recommendations by the Multi-parameter Evidence Synthesis Research Group, as it better captures the between-study variability.¹⁰² Furthermore, as highlighted in the NICE TSD 2, a RE model is preferred when there is evidence of heterogeneity in treatment effects between studies.⁸⁸ Given the sparse network, informative priors were applied for between-study variance based on Turner et al.'s

meta-analytic distributions.⁹⁰ Please see Section 2.10 for further details on the NMA methodology.

3.3.1.3 Assumption of equal efficacy between comparators

The assumption of equal efficacy between donidalorsen and comparator LTPs, is based primarily on the results of the NMA. In the absence of head-to-head clinical trials, the NMA provides the most robust source of comparative effectiveness evidence. The NMA found no statistically significant differences in efficacy between the median rate ratios of berotralstat, lanadelumab, and IV C1-INHs relative to donidalorsen Q4W. With respect to donidalorsen compared to berotralstat, the assumption of equal efficacy is considered to be reasonable. As discussed below, clinical trial point estimates, the impact of the berotralstat stopping rule, and OASISPlus switch data suggest that donidalorsen is at least as effective as berotralstat, if not more so. The equal efficacy assumption between donidalorsen and comparator LTPs has been validated by UK clinical experts and has been implemented in the cost-effectiveness model to support a pragmatic and evidence-based evaluation of donidalorsen and comparator LTPs.

Evidence from NMA

To estimate the comparative efficacy of donidalorsen against berotralstat, lanadelumab, and plasma-derived IV C1-INHs, a robust NMA was conducted in line with NICE standards.²⁸

As observed in the NMA results relative to donidalorsen Q4W (Section 2.10.4.1; Table 17), there were no statistically significant differences in the efficacy of donidalorsen Q4W compared with donidalorsen Q8W, berotralstat, lanadelumab Q2W, lanadelumab Q4W and C1-INH, as measured by median rate ratio for the mean number of HAE attacks per month. This is indicated by the wide and overlapping CrIs for each of the rate ratios, which cross the null value of 1. This overlap suggests uncertainty around the point estimates and supports interpretation that there is no clear evidence of superiority or inferiority among LTPs. The NMA provides evidence to support the assumption of equal efficacy of donidalorsen Q4W

to donidalorsen Q8W, berotralstat, lanadelumab Q2W, lanadelumab Q8W and C1-INH for the economic analysis.

Specific considerations for berotralstat

While the results of the NMA support an assumption of equal efficacy, below are specific considerations of evidence which suggests that donidalorsen may be at least as effective as berotralstat, if not more so.

Firstly, in a naïve comparison of efficacy outcomes from the OASIS-HAE and APeX-2 trials and the results of the NMA (presented in Table 17), [REDACTED]. These point estimates indicate that donidalorsen may be more efficacious than berotralstat, even though these differences do not reach statistical significance.^{12,71} In OASIS-HAE trial, the mean monthly attack rate ratio compared to placebo from Week 1 to the end of the treatment period was 0.19 ($p < 0.001$) for donidalorsen Q4W.¹² In comparison, the mean monthly attack rate ratio for berotralstat compared to placebo in APeX-2 was 0.56 ($p < 0.001$), demonstrating that donidalorsen is associated with a lower mean number of attacks relative to placebo, compared with berotralstat.⁷¹

Secondly, the reimbursement criteria defined by NICE for berotralstat includes a treatment stopping rule which states that patients should discontinue treatment with berotralstat if they do not achieve at least a 50% reduction in the monthly attack rate from baseline after three months of treatment.⁹ Therefore, this stopping rule allows for treatment discontinuation for patients that do not respond to treatment. In the APeX-2 trial, 42% of patients receiving berotralstat failed to achieve at least a 50% reduction in monthly attacks from baseline, highlighting that a large proportion of patients do not respond sufficiently to berotralstat.⁷¹ The stopping rule likely improves the long-term outcomes associated with berotralstat in UK clinical practice relative to outcomes from the APeX-2 trial, as a significant proportion of patients who start treatment fail to respond to berotralstat and will need to discontinue treatment after three months; consequently only those patients who achieve a sufficient response are reflected in long-term, real-world efficacy data. Based on the clinical trial, a greater proportion of patients would be expected to respond to donidalorsen compared to berotralstat, with 93.3% of the donidalorsen Q4W group achieving at Company evidence submission template for donidalorsen for preventing hereditary angioedema attacks in people 12 years and over [ID6457]

least a 50% reduction in HAE attacks (per 4 weeks) from Week 5 and Week 25 in OASIS-HAE, compared to 58% in APeX-2.^{12,71}

Thirdly, interim data from the OASISplus switch cohort on patients switching from berotralstat to donidalorsen showed improved outcomes post-switch.⁷⁷ Patients treated with berotralstat who switched to donidalorsen achieved a 73% reduction in mean HAE attack rate compared to the attack rate at baseline (i.e. the attack rate when patients were treated with berotralstat) (see Section 2.6.3.2).⁷⁷ This additional clinical evidence supports the assumption that donidalorsen is at least comparable, if not superior, in efficacy to berotralstat.

Validation by UK clinical experts

The appropriateness of the equal efficacy assumption was validated by UK clinical experts in September 2025, who agreed that the assumption aligns with the data, NMA results and their clinical experience.¹⁹ One clinician stated that although the comparative efficacy data between LTPs is sparse, [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED].¹⁹ Another

clinician stated, “[REDACTED]
[REDACTED]”.¹⁹ This validation from UK clinical experts further supports the assumption of equal efficacy between LTPs and its appropriateness for the economic analysis in using a cost-comparison approach.

Implementation into the cost-effectiveness model

For the purpose of the economic analysis, an analysis of the mean number of attacks per month for donidalorsen and comparator LTPs relative to placebo was conducted, such that the treatment effect estimates correspond to each LTP versus placebo (Table 31). Please see Section 2.10 and Appendix J for further details on the methodology of the NMA and full networks.

Table 31: Median rate ratios from the NMA for mean number of HAE attacks per month (RE) with placebo as reference treatment

Treatment	Median rate ratio (95% CrI)
Donidalorsen Q4W	
Donidalorsen Q8W	
Berotrastat	
Lanadelumab Q2W	
Lanadelumab Q4W	
C1-INH (Cinryze)	

Abbreviations: CrI – Credible interval; C1-INH – C1 Inhibitor; HAE – Hereditary angioedema; Q2W – Once every two weeks; Q4W – Once every four weeks; Q8W – Once every eight weeks

For the cost-effectiveness model, the rate ratios, as presented in Table 31, are multiplied with the weekly attack rate observed in the placebo arm of the OASIS-HAE trial to obtain weekly attack rate for donidalorsen, berotrastat, lanadelumab and IV C1-INHs. These weekly attack rates per treatment are calculated for the first 24 weeks of the economic model, in line with the duration of the OASIS-HAE trial.⁷⁶ The attack rate beyond Week 25 is the average attack rate from the timepoint at which the treatment has reached maximum effect, until the end of the trial period (Week 25).⁷⁶ The timepoint at which donidalorsen has taken effect is based on the steady state definition taken from the OASIS-HAE trial, which is at Weeks 5 onwards.¹² In the base case cost-comparison analysis, efficacy of all comparators, reflected by the HAE attack rate per cycle, is set equal to the efficacy of donidalorsen Q4W, referred to as Q1M in the model [REDACTED].

As discussed above, treatment with berotrastat for patients in England and Wales is subject to an efficacy-based stopping rule.⁹ For the purpose of the cost-comparison analysis, and in-line with the assumption of equal efficacy across LTPs, this stopping rule has been excluded. It is assumed that all patients treated with berotrastat respond to treatment. As such, patients receiving berotrastat are modelled to discontinue at the same rate as those receiving donidalorsen and other LTPs. This assumption is likely favourable to berotrastat, as it implies a better clinical profile for berotrastat than is typically observed in clinical practice.¹⁹ While excluding the efficacy-based stopping rule for berotrastat is a limitation in this analysis, the company considers that applying a consistent assumption of efficacy and discontinuation across all LTPs is the most appropriate and pragmatic approach in this instance.

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3.3.2 Attack duration and attack severity

In the absence of data from OASIS-HAE to calculate attack duration, the duration of attack in the model is based on data presented in a paper by Lumry et al (2010); Lumry et al. (2010) reports reduced productivity and missed opportunities for patients each time they experience an HAE attack.¹⁰³ The study presents the mean number of missed work, school and leisure days due to HAE attacks by severity.¹⁰³ The attack duration used in the model is based on a weighted average of the missed work and leisure days, to calculate a mean duration of 2.9 days per HAE attack. Given the assumption of equal efficacy, the attack duration and severity are assumed equal across all treatments.

The incidence of moderate or severe attacks in OASIS-HAE, which is a secondary endpoint in the OASIS-HAE trial, informs the distribution of severity of attacks. In the OASIS-HAE trial, moderate attacks are defined as mild to moderate limitation in activity requiring some assistance and severe attacks are defined as marked limitation in activity requiring assistance.⁷⁶ OASIS-HAE reports the LSM HAE attack rate for all attacks, moderate/severe attacks, as well as laryngeal attacks, for Weeks 1 to 25.⁷⁶ The proportion of attacks classified as moderate/severe was estimated by dividing the number of moderate/severe attacks per month by the total number of attacks per month. This method was applied to estimate the proportion of laryngeal attacks. It is assumed that all attacks that are not moderate/severe are mild and that laryngeal attacks are a proportion of moderate/severe attacks. As laryngeal attacks occur in the larynx and can lead to suffocation, it is reasonable to assume that these are moderate or severe in nature. As such, the percentage of moderate/severe attacks and the percentage of mild attacks, as a proportion of all attacks, can be estimated. In the economic model, the proportion of attacks by severity is the same for all comparators and is informed by attack rate data from the donidalorsen Q4W in OASIS-HAE which is used to calculate the proportion of moderate/severe and laryngeal attacks, as presented in Table 32.

Table 32: Proportion of attacks by severity

Attack classification	Proportion of all attacks	Source
All	-	OASIS-HAE, donidalorsen Q4W all attacks Weeks 1-25 LSM ⁷⁶

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Attack classification	Proportion of all attacks	Source
Laryngeal	■	OASIS-HAE, donidalorsen Q4W laryngeal attacks Weeks 1-25 LSM ⁷⁶
Moderate/severe (excluding laryngeal attacks)	■	OASIS-HAE, donidalorsen Q4W moderate/severe Weeks 1-25 LSM ⁷⁶
Mild	■	Assumed to be 1 minus moderate/severe proportion

Abbreviations: HAE – Hereditary angioedema; Q4W – Once every four weeks

3.3.3 Mortality

Laryngeal HAE attacks are associated with increased mortality, particularly in undiagnosed patients.⁴⁸ Due to the rarity of the disease, there is limited evidence to calculate the percentage of laryngeal attacks resulting in death due to asphyxiation as a proportion of all laryngeal HAE attacks for patients on LTP. As such, no disease-specific mortality is considered in the economic model; this is considered a conservative assumption because it is expected that with an increasing number of HAE attacks, there is a higher risk of death due to asphyxiation during a laryngeal attack. This assumption is in line with other NICE TAs in HAE.^{9,18}

General population mortality in the economic model was informed by life tables sourced from the UK Office for National Statistics matched for age and sex of the model cohort.¹⁰⁴ General population mortality was applied as a risk of death per cycle which transitions a proportion of patients from the 'alive' to 'dead' health state each cycle.

3.3.4 Treatment discontinuation

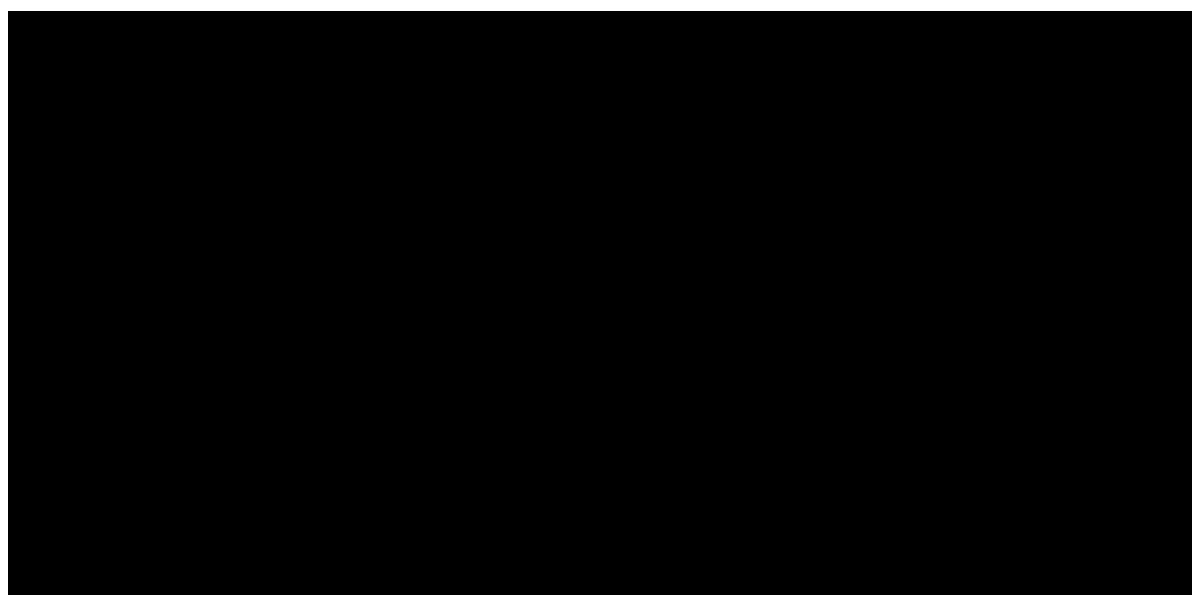
Of the 69 patients who initiated treatment with donidalorsen in the OASIS-HAE trial, four (5.8%) discontinued treatment for any reason.⁷⁶ Comparator discontinuation was assessed relative to donidalorsen discontinuation. Of the 84 patients enrolled onto one of the three lanadelumab dosing regimens in HELP-03, five patients withdrew from treatment (6.0%).⁸⁶ Additionally, of the 24 patients enrolled in the CHANGE trial, two patients discontinued treatment while receiving C1-INH (8.3%).¹⁰⁵ Given the small number of events observed across OASIS-HAE, OASISplus, HELP-03 and CHANGE, and the safety profile for donidalorsen, lanadelumab and C1-INH reported in the trials, discontinuation was assumed to be the same across these treatments.

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Discontinuation for donidalorsen was informed by a time to discontinuation (TTD) curve derived from Kaplan-Meier (KM) analysis of the OASIS-HAE trial. The KM curve captures all-cause discontinuation throughout the OASIS-HAE trial period, including discontinuation due to AEs, lack of efficacy and voluntary withdrawals. The TTD curve provides a long-term extrapolation of all-cause discontinuation throughout the time horizon. It is assumed that patients discontinue donidalorsen Q1M and Q2M at the same rate, and at the same time point in the model.

To apply a lifetime horizon in the analysis, extrapolation beyond the OASIS-HAE follow-up period is required. Survival curves for donidalorsen were fitted to the time-to-event patient-level data, based on DSU 14 guidance from NICE.¹⁰⁶ Treatment discontinuation curves were fitted using individually modelled standard parametric curves: exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised Gamma. Time on treatment curves were modelled for the full model time horizon; the first 10 years of treatment are presented in Figure 32.

Figure 32: Independent parametric curves fitted to OASIS-HAE TTD for donidalorsen Q1M and all comparator treatments, over a 10 year time horizon



Abbreviations: KM – Kaplan-Meier; Q1M – once per month; TTD – time to treatment discontinuation

Source: Data on file. Otsuka survival analysis.¹⁰⁷

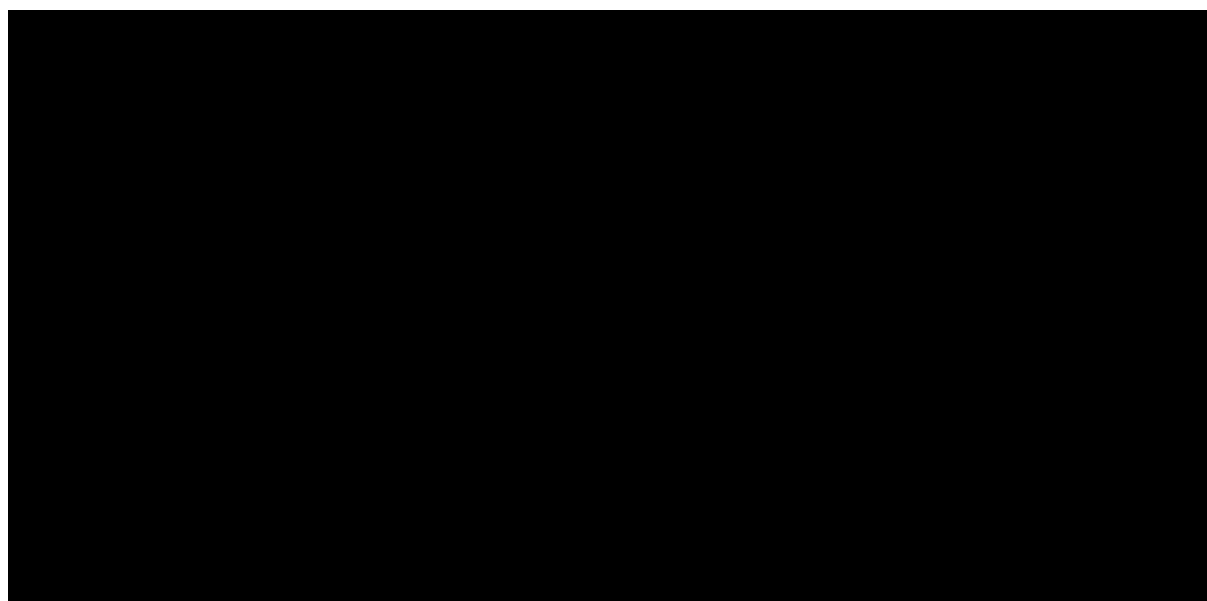
The exponential curve was chosen to extrapolate TTD in the base case as it provides the best statistical fit to the observed KM data, determined by assessing the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics.

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The AIC and BIC statistics for the exponential curve were the lowest by at least 2 and 3 points, respectively, in comparison to the other curves. A summary of the goodness-of-fit statistics for the TTD extrapolations is presented in Table 33.

At 5 years, █% of patients treated with donidalorsen, berotralstat, lanadelumab and C1-INH are estimated to remain on treatment when the exponential curve is selected, and this decreases to █% at 10 years, as presented in Figure 33. As stated in Section 3.3.1.3, patients receiving berotralstat are modelled to discontinue at the same rate as those receiving donidalorsen and other LTPs, which is an assumption that is likely favourable to berotralstat, as it implies a better clinical profile for berotralstat than is typically observed in clinical practice. UK clinical experts consulted as part of the validation meetings held in September 2025 agreed with the use of the exponential curve to model TTD, with one expert stating it provided good median estimates for the expected discontinuation rates of lanadelumab and berotralstat in clinical practice.¹⁹

Figure 33: Exponential parametric curve fitted to OASIS-HAE TTD data for donidalorsen Q1M and all other comparators, over a 10 year time horizon



Source: Data on file. Otsuka survival analysis.¹⁰⁷

To account for the uncertainty in the selection of the exponential curve, the next best-fitting curve, log-normal, has been presented as a scenario in Section 3.11.

Table 33: Goodness-of-fit statistics for OASIS-HAE TTD for donidalorsen Q1M

Distribution	Donidalorsen	
	AIC	BIC
Exponential		
Weibull		
Gompertz		
Log-logistic		
Log-normal		
Generalised Gamma		

Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; Q1M – once per month; TTD – time to treatment discontinuation

Exponential curve is assessed as the best fitting curve as it has the lowest AIC and BIC.

In the base case cost-comparison analysis, equal efficacy is assumed across all treatments, including berotralstat. Therefore, as discussed in Section 3.3.1.3, the stopping rule is not applied for patients receiving berotralstat and discontinuation is modelled in the same way as all other LTPs, with patients treated with berotralstat discontinuing at the same rate as donidalorsen.

Once patients discontinue their current LTP in the model they go on to receive ‘no LTP’ treatment (i.e. on-demand treatment only) as per the treatment pathway presented in Figure 9 (Section 1.3.4). In the base case cost-comparison analysis, it is assumed that patients who receive ‘no LTP’ experience an attack rate informed by the placebo arm of the OASIS-HAE trial.

3.4 Measurement and valuation of health effects

In the base case cost-comparison analysis, no HRQoL data (patient utility, administration disutility and carer disutility) is included as the efficacy of all treatments is assumed to be equal and only costs associated with each treatment are modelled. To fulfil the scope of this appraisal and to emphasise the burden that HAE has on a patients’ QoL, details relating to the measurement and valuation of health effects of the CUA are presented in Appendix K.

3.4.1 Adverse reactions

Full details regarding the AE data in the OASIS-HAE clinical trial are presented in Section 2.11.2. It is standard methodology to only include in the model Grade 3+ AEs that occur in ≥5% of patients in either treatment arm. As described in Section 2.11.2.1, the proportion of patients experiencing a TEAE is similar across the Company evidence submission template for donidalorsen for preventing hereditary angioedema attacks in people 12 years and over [ID6457]

treatment arms in the OASIS-HAE trial, and overall, the majority of patients experiencing TEAEs were experiencing those of mild (■%) or moderate (■%) severity.¹² None of the patients in the donidalorsen treatment arms experienced serious TEAEs in OASIS-HAE.¹² Only one patient (4.5%) in the placebo group experienced a serious TEAE, which was considered unrelated to the drug by the investigator.¹² Therefore, no AEs of any grade were included for donidalorsen.

In the HELP study for lanadelumab, SAEs were reported in three patients in the 300 mg Q4W lanadelumab arm, and in one patient in the 300 mg Q2W lanadelumab arm.⁸⁶ None of the SAEs were considered to be related to the study drug.⁸⁶ In the APeX-2 trial for berotralstat, the investigators reported all serious TEAEs as unrelated to the study drug.⁷¹ The COMPACT trial for C1-INHs reported one AE that was classified by an investigator as related to the study drug, however, this was reported in the placebo arm of the trial.¹⁰⁸

Overall, there were no serious TEAEs assessed by an investigator to be related to any of the study drugs. A UK clinical expert consulted in a validation meeting held in September 2025 agreed that it is reasonable to exclude AEs in the economic model.¹⁹ Therefore, AE rates and AE-related costs were not included in this cost-comparison analysis. Additionally, there are no reported AEs in any of the primary RCTs that have significant cost or HRQoL impact. As such, the impact of AEs on cost and QoL is assumed to be negligible, providing further rationale for omitting AEs from the model.

3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted in April 2025, to identify all relevant cost and resource use studies for the treatment of patients aged 12 years or older with HAE. Full details of the process and methods used to identify and select the economic evidence relevant to the technology being evaluated are presented in the SLR report – attached in Appendix G.

The SLR identified 81 records that met the cost and resource use analysis selection criteria. Of these, 51 were abstracts, 19 were full-text journal articles and 11 were HTA appraisals; a summary of included studies is presented in Appendix G. None of the full-text articles identified reported on costing in England or the UK, and two of the HTA appraisals were NICE appraisals which were used as a reference point to inform the cost and healthcare resource used in the economic model.

Consistent with the studies identified in the SLR and other relevant NICE appraisals, the following cost categories were included in the model: intervention and comparators' drug acquisition costs, drug administration costs, and resource use costs associated with HAE attacks.

3.5.1 Intervention and comparators' costs and resource use

Costs included in the base case cost-comparison analysis are drug acquisition costs, drug administration costs, and resource use costs associated with HAE attacks for the most recent cost year (2023/2024).

3.5.1.1 Drug acquisition costs of intervention and comparator

In line with the anticipated marketing authorisation for donidalorsen, patients should initiate treatment at a dose of [REDACTED].¹⁶ [REDACTED]

[REDACTED]¹⁶ The trial data are presented as donidalorsen Q4W and donidalorsen Q8W; however, no differences in outcomes are expected between Q4W and Q1M dosing or between Q8W and Q2M dosing.

Donidalorsen is available as an 80 mg pre-filled pen which has a list price of £[REDACTED] per pre-filled pen. A simple PAS of [REDACTED] has been applied to the list price which equates to a PAS price of [REDACTED] per pre-filled pen used in the economic model.

The dosing regimens for the treatments being evaluated are presented in Table 34. Drug posology and pack prices for donidalorsen and comparator LTPs are summarised in Table 35. List prices for berotralstat, lanadelumab and IV Cinryze and IV Berinert were obtained from the British National Formulary (BNF), in accordance with the NICE reference case guidelines.^{28,109}

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To calculate the cost per cycle for C1-INHs, a dose of 1,000 IU twice per week was assumed for IV Cinryze, consistent with its licence.¹³ The dosing for IV Berinert was based on inputs gathered from clinical experts in June 2025 who stated that they expect [REDACTED] of patients to receive a fixed dose of 1,000 IU and [REDACTED] of patients receive a fixed dose of 1,500 IU.¹⁹

Table 34: Summary of dosing regimens

Treatment	Dosing regimen
Donidalorsen	The anticipated recommended starting dose in adult and adolescent patients [REDACTED] [REDACTED] [REDACTED] ¹⁶
Berotrastat	150 mg once daily ¹⁷
Lanadelumab	The recommended starting dose is 300 mg lanadelumab Q2W. In patients who are stably attack-free on treatment, a dose reduction to 300 mg lanadelumab Q4W may be considered, especially in patients with low weight. ¹⁵ In patients with a body weight of less than 40 kg, a dose of 150 mg instead of 300 mg may be considered. However, as the unit price is the same for 300 mg and 150 mg this dose reduction for patients with a low weight is not modelled.
C1-INH	IV Cinryze: 1,000 IU every 3 or 4 days ¹³
	IV Berinert is not licensed for routine prevention of HAE attacks, but an average dose of [REDACTED] IU is assumed based on insights from clinical experts obtained in June 2025. ¹⁴

Abbreviations: C1-INH – C1 Inhibitor; HAE – Hereditary angioedema; IU – International unit; IV – Intravenous; kg – kilogram; mg – milligram; Q1M – Once every month; Q2M – Once every two months; Q2W – Once every two weeks; Q4W – Once every four weeks

Table 35: Drug posology, form, administration, unit size, pack size and costs

Treatment	Posology			Cost per pack	Acquisition cost per model cycle (28 days)
	Unit size	Units per pack	Admin frequency used in the economic model		
Donidalorsen	80 mg	1	80 mg Q1M with █████% of patients transferring to Q2M at month 6 (see Section 3.5.1.3).	█████ (with PAS discount)	Assuming a █████%/█████% Q1M/Q2M split: £█████ (with PAS discount)
Berotrastat	150 mg	28	150 mg once daily	£10,205.00	£10,205.00
Lanadelumab	300 mg	1	300 mg Q2W with 45% of patients transferring to 300 mg Q4W after year 1 (see Section 3.5.1.3).	£12,420.00	Assuming a 55%/45% Q2W/Q4W split: £19,251.00
C1-INH	Cinryze: 500 IU	Cinryze: 2	Cinryze: 1,000 IU twice per week	Cinryze: £1,336.00	Assuming a 27%/73% Cinryze/ Berinert split: £█████
	Berinert: 500 IU	Berinert: 1	Berinert: █████ of patients receiving 1,000 IU and █████ of patients receiving 1,500 IU of IV Berinert twice per week.	Berinert: £670.00	

Abbreviations: HAE – Hereditary angioedema; IU – International unit; IV – Intravenous; mg – milligram; PAS – Patient access scheme; Q1M – Once every month; Q2M – Once every two months; Q2W – Once every two weeks; Q4W – Once every four weeks; SmPC – Summary of Product Characteristics

3.5.1.2 Administration costs

No administration costs were assumed for oral treatments (berotralstat), as per standard practice.

Based on clinical validation meetings held in June 2025, for IV treatments (C1-INH) it is assumed that █% of patients self-administer their treatment and these patients incur a one-off 45-minute training session with a band 6 hospital nurse, sourced from Unit Costs of Health and Social Care (PSSRU).^{19,110} The cost per hour for a band 6 hospital nurse is £62.00, and therefore the cost per 45-minute training session is £46.50. Using the proportion of patients who self-administer intravenous injections (█%), the weighted one-off training cost per patient treated with IV therapy is therefore £█.

Based on clinical validation meetings held in June 2025, for subcutaneous treatments (donidalorsen and lanadelumab) it is assumed that █% of patients self-administer their treatment and these patients incur a one-off 30-minute training session with a band 6 hospital nurse, sourced from PSSRU.^{19,110} The cost per 30-minute training session for subcutaneous injections is therefore £31.00 (£62.00 / 2), and the weighted one-off training cost per patient treated with subcutaneous therapy is £█ (£31.00 * █). The percentage of patients who self-administer IV or SC treatments were validated by UK clinical experts in June 2025. For all patients who do not self-administer, a 45-minute appointment with a hospital specialist nurse was assumed at every treatment administration.

3.5.1.3 Donidalorsen and lanadelumab dose frequency reduction

In line with the anticipated marketing authorisation for donidalorsen, █
█. ¹⁶ █
█
█. ¹⁶

The timepoint at which donidalorsen is anticipated to achieve maximum effect is based on the steady state definition taken from the OASIS-HAE trial, defined as Week 5 onwards (see Section 3.3.1.3), meaning that while patients are anticipated to

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achieve improvement in the reduction of HAE attacks in the initial five weeks of treatment, the maximum therapeutic effect is reached from Week 5 onwards.¹² Clinical experts noted that patients are expected to be reviewed in clinic approximately three months after treatment initiation with donidalorsen, consistent with follow-up upon initiation of any LTP.¹⁹ As a result, some patients may therefore not have had sufficient opportunity to achieve [REDACTED] by the time of their first clinic assessment following treatment initiation with donidalorsen Q1M. Patients' second clinic assessment, six months following treatment initiation, is therefore considered a more appropriate timepoint to assess their eligibility to transfer to donidalorsen Q2M. This assumption was validated by UK clinical experts in June 2025, supporting the clinical relevance of this timepoint and dose adjustment threshold.¹⁹

Based on data from the full population of the OASIS-HAE trial, [REDACTED]% of patients remained attack-free for [REDACTED] during the trial.⁸⁵ Therefore, the model assumes that after month 6, in line with the 24-week treatment period, [REDACTED]% of patients treated with donidalorsen Q1M transfer to the Q2M dosing frequency in the base case of the economic analysis. Within a subgroup analysis of European patients in the OASIS-HAE trial, [REDACTED]% of patients remained attack-free for [REDACTED] during the trial.⁸⁵ Therefore, a scenario has also been explored assuming [REDACTED]% of patients treated with donidalorsen Q1M transfer to the Q2M dosing frequency at month 6 (Section 3.11.3).

For lanadelumab, the SmPC states patients should receive a dose of 300mg Q2W and in patients who are stably attack-free on treatment, a dose reduction to 300mg Q4W may be considered, especially in patients with low weight.¹⁵ A real-world evidence study by Dorr et al. (2022) examines the use of lanadelumab based on UK data examining 62 patients across 16 centres in the UK.¹⁰¹ As this study is based on UK real-world evidence, and therefore most likely to be reflective of NHS clinical practice, this is considered the most appropriate data source to estimate the proportion of patients who receive lanadelumab Q4W in the base case of the economic analysis. The study reports that 45% of patients receive lanadelumab Q4W, based on data from 60 patients (with dosing data) included in the audit.¹⁰¹ UK clinical experts consulted in validation meetings in June 2025 agreed that

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approximately 45% of patients would transfer to lanadelumab Q4W in their clinical practice. UK clinical experts noted that in clinical practice, the timepoint at which patients move to the less frequent dosing schedule of lanadelumab varies between six to 12 months, often at the 12-month timepoint; this is consistent with the 12-month timepoint accepted by the committee as part of the NICE appraisal of lanadelumab (TA606).¹⁹ In the base case of the economic analysis, it is assumed that 45% of patients treated with lanadelumab transfer to the Q4W dosing regimen at Month 12, in line with clinical expert feedback and TA606.^{18,19}

3.5.1.4 HAE on-demand attack management and drug acquisition costs

In accordance with TA738 (berotralstat) and TA606 (lanadelumab), patients receive on-demand treatment at the onset of HAE attacks.^{9,18} Currently, four on-demand therapies are approved for use in the UK and 'no treatment' is also included as an option to reflect that some (mild) attacks may not require on-demand treatments:

- C1-INH (IV Berinert)
- C1-INH (IV Cinryze)
- Icatibant (Firazyr)
- Ruconest (a recombinant analogue of the human C1-INH)
- No treatment

In line with TA738 (berotralstat), C1-INH (Berinert, Cinryze) and icatibant (Firazyr) injections are administered at home and therefore no administration costs are applied.⁹ In addition, despite Ruconest (a recombinant analogue of the human C1-INH) not being licensed for self-administration, UK clinical experts consulted as part of TA738 (berotralstat) confirmed that Ruconest is administered at home and thus no additional administrative costs are assumed.⁹

The cost of on-demand treatments were calculated based on their cost per pack sourced from the BNF and their dosing regimens sourced from the SmPC, shown in Table 36.^{14,20,111} Berinert and Ruconest use weight-based dosing therefore the dose per attack was calculated using the mean weight of the ITT population in the OASIS-HAE trial. For patients receiving Ruconest, there are two separate doses depending

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on the weight of the patient: for patients weighing less than 84 kg the dose is 50 U/kg, and for patients weighing at least 84 kg a fixed dose of 4,200 U is used. The proportion of patients in each weight category was estimated using a normal distribution using the mean weight and standard deviation from the ITT population in the OASIS-HAE trial, [REDACTED].⁷⁶

Table 36: On-demand medication dosing regimen

On-demand treatment	Labelled dose regimen per attack	Total dose per attack	Source
All cycles – Cinryze	1,000 IU	1,000.00 IU	SmPC ¹³
All cycles – Berinert	20 IU/kg	[REDACTED] IU	SmPC ¹⁴
All cycles – Ruconest (weight <84 kg)	50 U/kg	[REDACTED] U	SmPC ²⁰
All cycles – Ruconest (weight ≥84 kg)	4,200 U	4,200.00 U	SmPC ²⁰
All cycles – Firazyr	30 mg	30.00 mg	SmPC ⁶⁶

Abbreviations: IU – International unit; kg – kilogram; mg – milligram; SmPC – Summary of Product Characteristics; U – Unit

The distribution of on-demand treatments, assumed to be equal as a simplified approach, as well as the cost of on-demand treatments used to treat mild, moderate/severe and laryngeal attacks, are shown in Table 37.

Table 37: On-demand treatment acquisition costs

Comparator	Unit size	Cost per unit	Treatment distribution per attack: mild	Treatment distribution per attack: moderate/severe
Berinert	500.00 IU	£670.00	20%	20%
Cinryze	500.00 IU	£668.00	20%	20%
Ruconest	2,100.00 IU	£750.00	20%	20%
Firazyr	30.00 mg/3ml	£1,395.00	20%	20%
No treatment	N/A	£0.00	20%	20%

Abbreviations: IU – International unit; mg – milligram; ml – millilitre; N/A – Not applicable

3.5.2 Health-state unit costs and resource use

In addition to drug acquisition costs, patients with HAE may require additional healthcare resources to manage their attacks. However, due to the heterogeneity of HAE, resource use can vary substantially from patient-to-patient i.e. dependent on attack severity, its location and patient preference. In the base case cost-comparison analysis, no HCRU data are included in the model as the efficacy of all treatments is assumed to be equal and therefore HCRU does not differ across LTPs. Hence, HCRU will not be accounted for in the base case cost-comparison. However, the relevant HCRU data have been included in the CUA scenario presented in Appendix K.

3.5.3 Adverse reaction unit costs and resource use

As discussed in Section 2.11.2 and Section 3.4.1, AEs are not considered as part of this economic analysis. Therefore, no costs associated with AEs are included in the cost-comparison analysis.

3.5.4 Subsequent treatment costs

In the economic model it is assumed that all patients who discontinue treatment with their initial LTP go on to receive on-demand treatment only and no patients go on to receive subsequent treatment with another LTP. In the base case cost-comparison analyses on-demand attack management treatment costs, acquisition costs of the on-demand treatment, are incorporated into the model based on the number of attacks a patient experiences which are informed by the placebo arm of the OASIS-HAE-trial. It is assumed there are no additional acquisition or administration costs associated with subsequent treatment costs outside of the on-demand attack management treatment costs associated with HAE attacks.

3.6 Severity

The company does not anticipate that donidalorsen will meet the criteria for the severity weighting modifier.

3.7 Uncertainty

The key uncertainties in the appraisal relate to the comparative effectiveness data and the limited duration of the pivotal clinical trial for donidalorsen, OASIS-HAE, as well as the rarity of HAE and data limitations associated with this.

In the absence of any head-to-head trials comparing donidalorsen to the comparators included in the economic model, an NMA was conducted to estimate the clinical effectiveness of donidalorsen Q4W relative to donidalorsen Q8W, berotralstat, lanadelumab Q2W, lanadelumab Q4W, C1-INHs, and placebo, and to generate comparative efficacy estimates to be used in the economic analysis. The results and methodology of the NMA were validated by clinical experts in September 2025.¹⁹ Any uncertainty around the NMA analysis arises from the variation in how data were presented per comparator, not in the methodology of the NMA. Detailed analysis of how the NMA handles these uncertainties and the conclusions can be found in Sections 2.10.5 and 2.10.6, respectively.

There is limited data to inform the economic analysis because HAE is a rare disease. Therefore, several assumptions have been made to fill in evidence gaps with the aim to streamline the appraisal and ensure faster access to donidalorsen because of the unmet need for well-tolerated and effective alternative LTPs. More specifically, every patient with HAE is different and the disease course varies both from patient to patient, and over time for individual patients, which means there are challenges in quantifying the HRQoL impact and the healthcare costs accrued for patients over a lifetime. Regional differences in clinical management in centres across the UK create further uncertainty in these data inputs as clinical experts provide varying opinions that make it difficult to gather consensus. With HAE being a rare disease and published literature being limited, this results in gaps in the evidence available to populate the economic analysis of this appraisal.

The key sources of variable and parameter uncertainty in the cost-comparison have been extensively explored through deterministic sensitivity analyses, probabilistic sensitivity analyses (PSA) and scenario analyses. Variables and parameters explored in these analyses include the percentage of patients who reduce their dosing frequency for donidalorsen, alongside a value derived from the European

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subgroup of patients, timepoints at which patients reduce their dosing frequency for lanadelumab, the donidalorsen Q1M rate ratio, and treatment discontinuation estimation methodology. The associated outcomes can be found in Section 3.11. To further explore uncertainty in the clinical efficacy of donidalorsen, the company have conducted a CUA between donidalorsen, berotralstat, lanadelumab, and C1-INHs. For further details on this CUA, please see Appendix K.

3.8 Managed access proposal

The company consider the clinical and economic evidence presented within this appraisal to be a suitable basis for a routine commissioning decision.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

A summary of the key parameters used in the cost-comparison analysis is presented in Table 38.

Table 38: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in appraisal)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in appraisal
Model settings			
Population	People with HAE aged ≥12	N/A	Section 3.2.1
Perspective	NHS and PSS	N/A	Section 3.2.5
Time horizon	Lifetime (62.80)	N/A	Section 3.2.4
Proportion males	46.70%	SE: 0.09 (beta)	Section 3.2.1
Starting age (years)	37.20	SE: 7.44 (gamma)	Section 3.2.1
Patient weight (kg)	██████	SE: ██████ (gamma)	Section 3.2.1
Half cycle correction	Yes	Fixed	Section 3.2.3
Discount rate (costs and outcomes)	3.5%	Fixed	Section 3.2.5
Clinical parameters			
Efficacy source LTP treatments	NMA	N/A	Section 3.3
Efficacy source 'no LTP'	OASIS-HAE trial placebo arm	N/A	Section 3.3
Baseline attack rate per week (≥2 attack per month population)	0.73	SE: 0.15 (gamma)	Section 3.3.1
Baseline attack rate per week (≥8 attack per month population)	2.00	SE: 0.40 (gamma)	Section 3.3.1
Cost parameters			
Donidalorsen cost per unit (80 mg) – PAS price	£██████ (Table 35)	Fixed	Section 3.5.1.1
Berotrastat cost per pack	£10,250.00 (Table 35)	Fixed	Section 3.5.1.1
Lanadelumab cost per unit (300 mg)	£12,420.00 (Table 35)	Fixed	Section 3.5.1.1
Cinryze cost per unit (500 IU)	£668.00 (Table 35)	Fixed	Section 3.5.1.1
Berinerst cost per unit (500 IU)	£670.00 (Table 35)	Fixed	Section 3.5.1.1
Subcutaneous administration cost	£46.50	SE: 9.30 (gamma)	Section 3.5.1.2
Intravenous administration cost	£46.50	SE: 9.30 (gamma)	Section 3.5.1.2
Oral administration costs	£0.00	SE: 0.00 (gamma)	Section 3.5.1.2

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Variable	Value (reference to appropriate table or figure in appraisal)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in appraisal
Proportion of donidalorsen patients who reduce to a Q2M dosing frequency	█████%	SE: 0.04 (beta)	Section 3.5.1.3
Timepoint at which donidalorsen patients who reduce to a Q2M dosing frequency (in model cycles)	6.52	SE: 1.30 (gamma)	Section 3.5.1.3
Proportion of lanadelumab patients who reduce to a Q4W dosing frequency	45%	SE: 0.02 (beta)	Section 3.5.1.3
Timepoints at which lanadelumab patients who reduce to a Q4W dosing frequency (in model cycles)	13.04	SE: 2.61 (gamma)	Section 3.5.1.3
Proportion of patients who require SC injection support	█████%	SE: █████ (beta)	Section 3.5.1.2
Proportion of patients who require IV injection support	█████%	SE: █████ (beta)	Section 3.5.1.2
Weighted one-off subcutaneous administration training cost per patient in cycle 1	£█████	SE: █████ (gamma)	Section 3.5.1.2
Weighted one-off intravenous administration training cost per patient in cycle 1	£█████	SE: █████ (gamma)	Section 3.5.1.2
On-demand treatment per HAE attack distribution (proportion)	20% for all on-demand treatments and attack types	SE: 0.04 (beta)	Section 3.5.2
On-demand treatment acquisition costs per HAE attack	£1,382.00	SE: 276.44 (gamma)	Section 3.5.2

Abbreviations: HAE – Hereditary angioedema; HCRU – Healthcare resource use; IU – International unit; IV – Intravenous; mg – milligram; N/A – Not applicable; NHS – National Health Service; NMA – Network meta-analysis; PAS – Patient access scheme; PSS – Personal Social Services; Q2M – Once every two months; Q4W – Once every four weeks; SC - Subcutaneous SE – Standard error

3.9.2 Assumptions

The key assumptions made in the base case analysis are presented in Table 39.

Table 39: Key assumptions in the model

Model input	Assumption	Rationale	Reference in appraisal
Model structure	Markov model	In line with previous NICE appraisals.	Section 3.2.2
Half-cycle correction	Yes	To account for uncertainty in the exact timing of HAE attacks within the cycle period.	Section 3.2.3
Time horizon	Lifetime	In line with the NICE reference case. ²⁸	Section 3.2.4
Intervention and comparators			
Proportion and timepoint of patients who transfer to donidalorsen Q2M	██████% of patients transfer to donidalorsen Q2M in UK clinical practice after 6 months of treatment with donidalorsen Q1M.	Based on data from the OASIS-HAE trial, ██████% of patients remained attack-free for ██████████ during the trial. ⁸⁵ Therefore, the model assumes that, ██████% of patients treated with donidalorsen Q1M transfer to the Q2M dosing frequency in the base case of the economic analysis. The timepoint at which patients transfer to a reduced dosing frequency is set to month 6, based on the expected interval of follow-up visits, as validated by clinical experts. ¹⁹	Section 3.5.1.3
Proportion and timepoint of patients who transfer to lanadelumab Q4W.	45% of patients transfer to lanadelumab Q4W in UK clinical practice after 12 months of treatment with lanadelumab Q4W.	As part of TA606 (lanadelumab), the committee accepted that some patients will reduce to lanadelumab 300 mg Q4W by the end of the first year. ¹⁸ The timepoint at which patients switch to the less frequent dosing schedule of Q4W lanadelumab is aligned to the timepoint used in TA606 of 12-months. Data from a real-world evidence study by Dorr et al (2022), which found that that 45% of patients are treated with Q4W lanadelumab, was used to inform the percentage of patients who receive the less frequent dosing regimen of lanadelumab. As this study is based on UK real-world evidence, and therefore most likely to be reflective of NHS clinical practice, this is	Section 3.5.1.3

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Model input	Assumption	Rationale	Reference in appraisal
		considered the most appropriate data source to estimate the dose reduction percentage in the base case of the economic analysis. ¹⁰¹ This was validated by UK clinical experts in validation meetings held in September 2025. ¹⁹	
Efficacy	Efficacy of all LTP treatments equal to donidalorsen Q1M.	The results of the NMA showed no statistically significant difference in the efficacy of donidalorsen Q4W compared with all other LTPs used as comparators in the model, as measured by the median rate ratio for the mean number of HAE attacks per month, demonstrating that donidalorsen provides similar efficacy and QoL benefits compared to existing treatments. Clinical experts consulted in validation meetings in September 2025 also concluded that as the results do not demonstrate a statistically significant difference, therefore it is considered appropriate to assume all treatments demonstrate equal efficacy. ¹⁹ Therefore, based on the estimated RRs and Crls from the NMA and input from clinical experts, an assumption of equal efficacy between donidalorsen Q1M and comparator LTPs is deemed appropriate for the economic analysis.	Section 3.3.1.3
Treatment discontinuation	Patients discontinue all LTP treatments at an equal rate in line with the exponential parametric TTD curve.	Given the small number of patients who discontinued in the OASIS-HAE and comparators trials, the small number of AEs and the favourable safety profile of donidalorsen and comparators, discontinuation is assumed to be equal amongst comparators. Furthermore, due to the equal efficacy assumption in the base case no treatment stopping rules are applied to any treatments as a conservative assumption.	Section 3.3.4

Abbreviations: HAE – Hereditary angioedema; LTP – Long-term prophylaxis; NICE – National Institute for Health and Care Excellence; NMA – Network meta-analysis; Q1M – Once every month; Q2M – Once every two months; Q4W – Once every four weeks; RR – Rate ratio; TA – Technology appraisal; TTD – Time to treatment discontinuation curve; UK – United Kingdom

3.10 Base-case results

All results below include a PAS discount of [REDACTED]% for donidalorsen with a net price of [REDACTED] per 80 mg pre-filled pen.

3.10.1 Base-case incremental cost-comparison analysis results

The base case results using the list prices of berotralstat, lanadelumab and C1-INH, and a PAS discount of [REDACTED]% with a net price of [REDACTED] per 80 mg pre-filled pen for donidalorsen, are presented in Table 40. Over a lifetime time horizon, treatment with donidalorsen in patients with HAE experiencing ≥ 2 attacks per month was associated with cost savings of £[REDACTED] versus berotralstat.

In patients with HAE experiencing ≥ 8 attacks per month, treatment with donidalorsen was associated with cost savings of £[REDACTED] versus lanadelumab and cost savings of £[REDACTED] versus C1-INH, resulting in donidalorsen providing cost-savings to the NHS versus all comparators. Disaggregated results from the cost-comparison analysis are presented in Appendix H.

The economic evaluation confirms a robust and favourable cost-savings profile for donidalorsen. As such, the company maintains that a cost-comparison analysis is the most appropriate approach to appraise donidalorsen in HAE. Cost-comparison results are presented in Table 40 and Table 41. While the company consider a cost-comparison analysis to be the most appropriate analysis for evaluating the clinical and economic benefit of donidalorsen, a CUA has been conservatively explored in Appendix K.

Table 40: Base-case deterministic results (≥ 2 attacks per month)

Intervention/comparator	Total costs (£)	Incremental costs versus donidalorsen (£)
Donidalorsen	[REDACTED]	-
Berotralstat	[REDACTED]	[REDACTED]

Table 41: Base-case deterministic results (≥8 attacks per month)

Intervention/comparator	Total costs (£)	Incremental costs versus donidalorsen (£)
Donidalorsen	████████	-
Lanadelumab	████████	████████
C1-INH	████████	████████

Abbreviations: C1-INH – C1 Inhibitor

3.11 Exploring uncertainty

Uncertainty in the model results were explored through extensive deterministic sensitivity analysis, PSA and scenario analyses.

3.11.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through PSA where all parameters are assigned probability distributions and varied jointly. The model allowed the beta and gamma distributions to be used dependent on the characteristics of the parameter. This constitutes one ‘simulation’; 1,000 simulations were performed, and a distribution of incremental results, and consequently, an assessment of the robustness of the cost savings results were recorded.

Table 42 presents a summary of the key model inputs and the distributions used to vary each parameter in the PSA.

Table 42: Distribution options by model parameter for PSA

Parameter	Distribution
Age	Gamma distribution
Proportion of male	Beta distribution
Baseline attack rate	Gamma distribution
Time to discontinuation	Exponential distribution
Proportion of patients who transfer to donidalorsen Q2M dosing regimen	Beta distribution
Proportion of patients who transfer to lanadelumab Q4W dosing regimen	Beta distribution
NMA rate ratio for donidalorsen Q1M*	Gamma distribution
Treatment acquisition costs	Gamma distribution
Treatment administration costs	Gamma distribution
HAE attack drug acquisition costs	Gamma distribution
HAE attack use of on-demand treatment proportions	Dirichlet distribution

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Abbreviations: HAE – Hereditary angioedema; HCRU – Healthcare resource utilisation; LTP – Long-term prophylaxis; NMA – Network meta-analysis; PSA – Probabilistic sensitivity analysis; Q2M – Once every two months; Q4W – Once every four weeks
 *The rate ratio for all treatment comparators is set equal to the rate ratio for donidalorsen Q1M, therefore only the rate ratio of donidalorsen Q1M is varied in the PSA.

The results of the base-case PSA are presented in Table 43 and Table 44. The PSA results show consistency with the deterministic results; in patients with HAE experiencing ≥ 2 attacks per month, donidalorsen is associated with incremental savings of £[REDACTED] versus berotralstat.

For patients experiencing ≥ 8 attack per month, the PSA results show treatment with donidalorsen is associated with incremental cost savings of £[REDACTED] and £[REDACTED] versus lanadelumab and C1-INH, respectively.

The mean probabilistic results lie close to the deterministic results, indicating that the model is robust to parameter uncertainty.

Table 43: PSA results for donidalorsen vs. comparators (≥ 2 attacks per month)

Intervention/comparator	Total costs (£)	Incremental costs versus donidalorsen (£)
Donidalorsen	[REDACTED]	-
Berotralstat	[REDACTED]	[REDACTED]

Abbreviations: PSA – Probabilistic sensitivity analysis

Table 44: PSA results for donidalorsen vs. comparators (≥ 8 attacks per month)

Intervention/comparator	Total costs (£)	Incremental costs versus donidalorsen (£)
Donidalorsen	[REDACTED]	-
Lanadelumab	[REDACTED]	[REDACTED]
C1-INH	[REDACTED]	[REDACTED]

Abbreviations: C1-INH – C1 Inhibitor; PSA – Probabilistic sensitivity analysis

3.11.2 Deterministic sensitivity analysis

The deterministic one-way sensitivity analysis (OWSA) was conducted to explore the effect of uncertainty associated with varying individual parameters on the model results. In the OWSA, each variable was systematically increased and decreased based on 95% CIs. In the absence of data, a standard error of $\pm 20\%$ of the mean for each parameter was assumed and the lower and upper bounds were estimated by

applying the appropriate distribution (gamma for parameters that must be greater than or equal to zero or beta for parameters that must be bounded between 0 and 1).

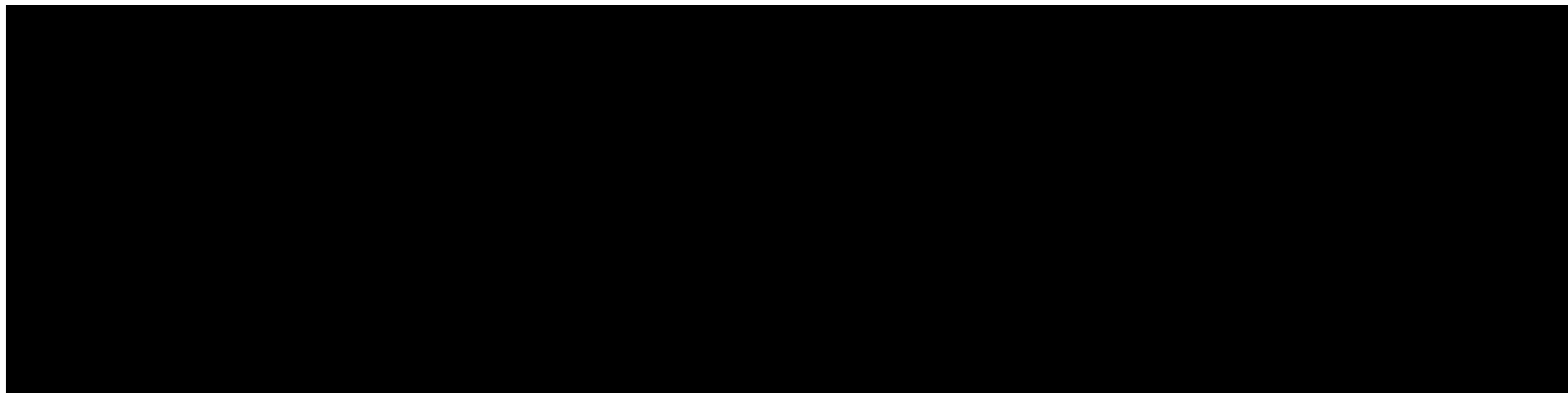
A tornado diagram was developed to graphically present the top 10 parameters which have the greatest impact on cost savings (Figure 34 to Figure 36). The top most sensitive parameters for the cost savings of donidalorsen versus the modelled comparators are summarised in Table 45 to Table 47 and Figure 34 to Figure 36. The model was most sensitive to the percentage of patients who switch from a Q1M to a Q2M dosing regimen and the timepoints as which this occurs.

Table 45: OWSA incremental costs for donidalorsen vs berotralstat (≥ 2 attacks per month subgroup)

Parameter name	Lower bound incremental costs (£)	Upper bound incremental costs (£)
Donidalorsen dose reduction one-off percentage	██████	██████
Donidalorsen dose reduction timepoint (cycles)	██████	██████
Age	██████	██████
Percentage male	██████	██████
Subcutaneous administration cost	██████	██████
Proportion of patients requiring SC injection support	██████	██████
Weighted one-off SC administration training cost per patient in cycle 1 (£)	██████	██████

Abbreviations: OWSA – One-way sensitivity analysis; SC - Subcutaneous

Figure 34: Tornado diagram – incremental costs for donidalorsen vs berotralstat (≥ 2 attacks per month subgroup)



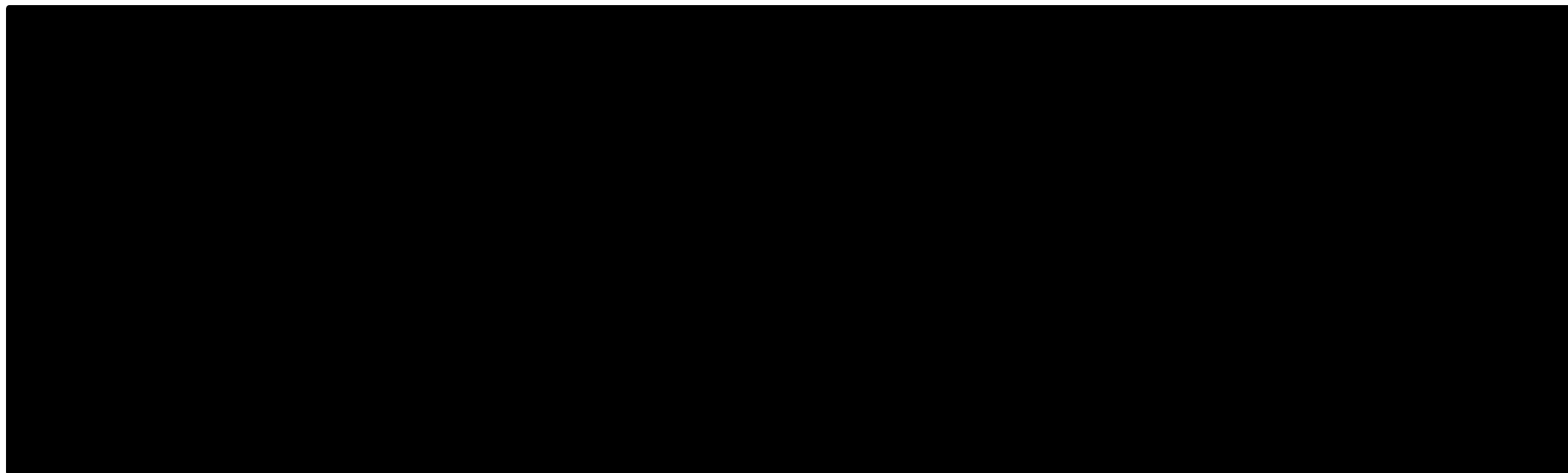
Abbreviations: SC – subcutaneous.

Table 46: OWSA incremental costs for donidalorsen vs lanadelumab (≥ 8 attacks per month subgroup)

Parameter name	Lower bound incremental costs (£)	Upper bound incremental costs (£)
Donidalorsen dose reduction one-off percentage	████████	████████
Lanadelumab dose reduction one-off percentage	████████	████████
Age	████████	████████
Lanadelumab dose reduction timepoint (cycles)	████████	████████
Donidalorsen dose reduction timepoint (cycles)	████████	████████
Percentage male	████████	████████
Subcutaneous administration cost	████████	████████
Proportion of patients requiring SC injection support	████████	████████
Weighted one-off SC administration training cost per patient in cycle 1 (£)	████████	████████

Abbreviations: OWSA – One-way sensitivity analysis; Q2W – Once every two weeks; SC – Subcutaneous.

Figure 35: Tornado diagram – incremental costs for donidalorsen vs lanadelumab (≥ 8 attacks per month subgroup)



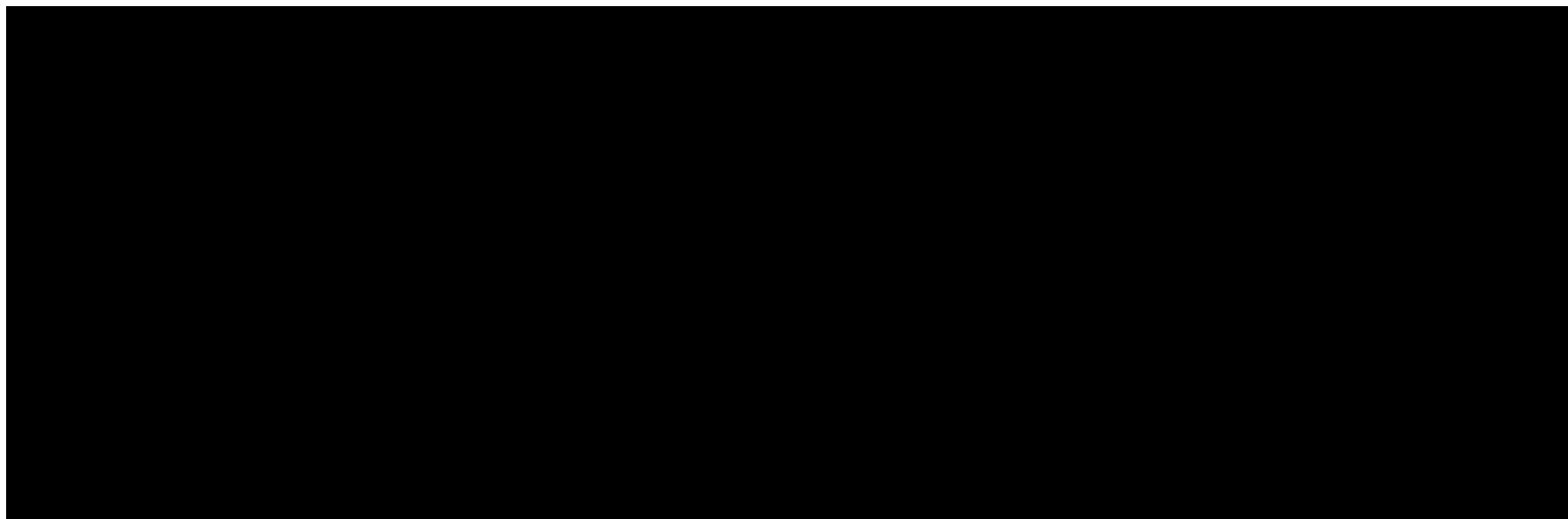
Abbreviations: Q2W – Once every two weeks; SC – Subcutaneous.

Table 47: OWSA incremental costs for donidalorsen vs C1-INH (≥ 8 attacks per month subgroup)

Parameter name	Lower bound incremental costs (£)	Upper bound incremental costs (£)
C1-INH proportion - Cinryze	██████	██████
Donidalorsen dose reduction one-off percentage	██████	██████
Age	██████	██████
Donidalorsen dose reduction timepoint (cycles)	██████	██████
Intravenous administration cost	██████	██████
Proportion of patients requiring IV injection support	██████	██████
Percentage male	██████	██████
Subcutaneous administration cost	██████	██████
Proportion of patients requiring SC injection support	██████	██████
Weighted one-off IV administration training cost per patient in cycle 1 (£)	██████	██████

Abbreviations: C1-INH – C1 Inhibitor; IV – Intravenous; OWSA – One-way sensitivity analysis; SC - Subcutaneous

Figure 36: Tornado diagram - incremental costs for donidalorsen vs C1-INH (≥ 8 attacks per month subgroup)



Abbreviations: C1-INH – C1 Inhibitor; IV – Intravenous; SC – Subcutaneous

3.11.3 Scenario analysis

Scenario analyses were performed to address and alleviate uncertainty within the base case inputs and assumptions. Details of each of the included scenario analyses are presented in Table 48. Deterministic and probabilistic scenario analysis results for donidalorsen versus berotralstat, lanadelumab and C1-INH are presented in Table 49 to Table 54.

The probabilistic results are consistent with the deterministic results, indicating the robustness of the analyses to parameter uncertainty. In all probabilistic, with the exception of a 10 year time horizon versus berotralstat, and deterministic scenarios, donidalorsen demonstrated cost savings compared to berotralstat in the ≥ 2 attacks per month population and compared to lanadelumab and C1-INH in the ≥ 8 attacks per month population.

Table 48: Scenario analyses

Parameter	Scenario number	Base case	Scenario	Rationale for scenario
Proportion of patients who transfer to donidalorsen Q2M	1	█████%	█████%	This is the proportion of patients who are attack-free for three consecutive months in OASIS-HAE within the European subgroup of patients, as per the post-hoc analysis.
Timepoint at which patients transfer to lanadelumab Q4W	2	After month 12	After month 6	Setting this equal to the dose frequency reduction point for donidalorsen. ^{19,85}
Treatment discontinuation	3	TTD from the OASIS-HAE trial using an exponential curve	TTD from the OASIS-HAE trial using a log-normal curve	Based on input from UK clinical experts. ¹⁹
	4		█████% per year	
Time horizon	5	Lifetime (63 years)	10 years	To explore the effect of a range of time horizons.
	6		30 years	
Discount rate for costs	7	3.5%	1.5%	To explore the effect of a range of discount rates on costs.
	8		6%	

Abbreviations: Q2M – Once every two months; Q4W – Once every four weeks

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3.11.3.1 Deterministic scenario analysis results

Table 49: Scenario analysis results - donidalorsen vs berotralstat (≥ 2 attacks per month population)

Parameter	Scenario	Total costs donidalorsen (£)	Total costs berotralstat (£)	Incremental costs versus donidalorsen (£)
Proportion of patients who transfer to donidalorsen Q2M	█████%	██████	██████	██████
Timepoint at which patients transfer to lanadelumab Q4W	After month 6	██████	██████	██████
Treatment discontinuation	TTD from the OASIS-HAE trial using a log-normal curve	██████	██████	██████
	█████% per year	██████	██████	██████
Time horizon	10 years	██████	██████	██████
	30 years	██████	██████	██████
Discount rate for costs	1.5%	██████	██████	██████
	6%	██████	██████	██████

Abbreviations: HAE – Hereditary angioedema; Q2M – Once every two months; Q4W – Once every four weeks; TTD – Time-to-treatment discontinuation

Table 50: Scenario analysis results - donidalorsen vs lanadelumab (≥8 attacks per month population)

Parameter	Scenario	Total costs donidalorsen (£)	Total costs lanadelumab (£)	Incremental costs versus donidalorsen (£)
Proportion of patients who transfer to donidalorsen Q2M	█████%	██████	██████	██████
Timepoint at which patients transfer to lanadelumab Q4W	After month 6	██████	██████	██████
Treatment discontinuation	TTD from the OASIS-HAE trial using a log-normal curve	██████	██████	██████
	█████% per year	██████	██████	██████
Time horizon	10 years	██████	██████	██████
	30 years	██████	██████	██████
Discount rate for costs	1.5%	██████	██████	██████
	6%	██████	██████	██████

Abbreviations: HAE – Hereditary angioedema; Q2M – Once every two months; Q4W – Once every four weeks; TTD – Time-to-treatment discontinuation

Table 51: Scenario analysis results - donidalorsen vs C1-INH (≥ 8 attacks per month population)

Parameter	Scenario	Total costs donidalorsen (£)	Total costs C1-INH (£)	Incremental costs versus donidalorsen (£)
Proportion of patients who transfer to donidalorsen Q2M	█████%	██████████	██████████	██████████
Timepoint at which patients transfer to lanadelumab Q4W	After month 6	██████████	██████████	██████████
Treatment discontinuation	TTD from the OASIS-HAE trial using a log-normal curve	██████████	██████████	██████████
	█████% per year	██████████	██████████	██████████
Time horizon	10 years	██████████	██████████	██████████
	30 years	██████████	██████████	██████████
Discount rate for costs	1.5%	██████████	██████████	██████████
	6%	██████████	██████████	██████████

Abbreviations: C1-INH – C1 esterase inhibitor; HAE – Hereditary angioedema; Q2M – Once every two months; Q4W – Once every four weeks; TTD – Time-to-treatment discontinuation

3.11.3.2 Probabilistic scenario analysis results

Table 52: Scenario analysis results - donidalorsen vs berotralstat (≥ 2 attacks per month population)

Parameter	Scenario	Total costs donidalorsen (£)	Total costs berotralstat (£)	Incremental costs versus donidalorsen (£)
Proportion of patients who transfer to donidalorsen Q2M	█████%	█████	█████	█████
Timepoint at which patients transfer to lanadelumab Q4W	After month 6	█████	█████	█████
Treatment discontinuation	TTD from the OASIS-HAE trial using a log-normal curve	█████	█████	█████
	█████% per year	█████	█████	█████
Time horizon	10 years	█████	█████	█████
	30 years	█████	█████	█████
Discount rate for costs	1.5%	█████	█████	█████
	6%	█████	█████	█████

Abbreviations: HAE – Hereditary angioedema; Q2M – Once every two months; Q4W – Once every four weeks; TTD – Time to treatment discontinuation

Table 53: Scenario analysis results - donidalorsen vs lanadelumab (≥ 8 attacks per month population)

Parameter	Scenario	Total costs donidalorsen (£)	Total costs lanadelumab (£)	Incremental costs versus donidalorsen (£)
Proportion of patients who transfer to donidalorsen Q2M	█████%	█████	█████	█████
Timepoint at which patients transfer to lanadelumab Q4W	After month 6	█████	█████	█████
Treatment discontinuation	TTD from the OASIS-HAE trial	█████	█████	█████

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Parameter	Scenario	Total costs donidalorsen (£)	Total costs lanadelumab (£)	Incremental costs versus donidalorsen (£)
	using a log-normal curve			
	█% per year	█	█	█
Time horizon	10 years	█	█	█
	30 years	█	█	█
Discount rate for costs	1.5%	█	█	█
	6%	█	█	█

Abbreviations: HAE – Hereditary angioedema; Q2M – Once every two months; Q4W – Once every four weeks; TTD – Time to treatment discontinuation

Table 54: Scenario analysis results - donidalorsen vs C1-INH (≥8 attacks per month population)

Parameter	Scenario	Total costs donidalorsen (£)	Total costs lanadelumab (£)	Incremental costs versus donidalorsen (£)
Proportion of patients who transfer to donidalorsen Q2M	█%	█	█	█
Timepoint at which patients transfer to lanadelumab Q4W	After month 6	█	█	█
Treatment discontinuation	TTD from the OASIS-HAE trial using a log-normal curve	█	█	█
	█% per year	█	█	█
Time horizon	10 years	█	█	█
	30 years	█	█	█
Discount rate for costs	1.5%	█	█	█
	6%	█	█	█

Abbreviations: C1-INH – C1 Inhibitor; HAE – Hereditary angioedema; Q2M – Once every two months; Q4W – Once every four weeks; TTD – Time to treatment discontinuation

3.11.3.3 Cost-utility scenario analysis

In addition to the scenarios presented in Table 48 to Table 54, a cost-utility scenario analysis was conducted to capture the QoL burden of HAE. Over a lifetime time horizon, treatment with donidalorsen in patients with HAE experiencing ≥2 attacks per month resulted in a █ incremental cost-effectiveness ratio (ICER)

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versus berotralstat. In patients with HAE experiencing ≥ 8 attacks per month, treatment with donidalorsen resulted in an ICER of £ [REDACTED] and a [REDACTED] ICER versus C1-INH. The ICER versus lanadelumab in the ≥ 8 attacks per month population [REDACTED] meaning that donidalorsen is associated with [REDACTED], and [REDACTED] incremental quality-adjusted life years (QALY) compared with lanadelumab. The [REDACTED] incremental QALY versus lanadelumab is [REDACTED] ([REDACTED]), and this [REDACTED] difference can be attributed to the NMA outcomes that inform efficacy in the model, which demonstrated no statistically significant difference in median rate ratio for the mean number of HAE attacks per month between donidalorsen and lanadelumab. For further detail on this analysis, please refer to Appendix K.

3.12 Subgroup analysis

A consistent treatment effect was observed across all subgroups in OASIS-HAE, as presented in Section 2.8. Therefore, subgroup analyses were not considered relevant for this economic analysis, as per the final scope.

3.13 Benefits not captured in the QALY calculation

The base case cost-comparison analysis does not capture QALYs; this section will discuss benefits not captured in the QALY calculation for the cost-utility scenario which is presented in Appendix K.

Overall, donidalorsen provides an effective, well-tolerated, and convenient alternative LTP for patients with HAE. The clinical study results have shown donidalorsen can significantly improve patients' lives by reducing their attack rate and increasing their attack-free periods, allowing them to continue with work, school, and normal daily living and reducing the psychological burden associated with this disease. To assess all the benefits provided by donidalorsen, a holistic approach is required, which considers the direct impacts of HAE on patients, and the indirect impacts on their carers and family members. These indirect impacts can include reductions in work or leisure time, negative impacts on future planning, and emotional burden. A study by Lumry et al (2010) reported that 50.6% of all full-time or part-time employed HAE patients reported they missed at least 1 day of work

because of their most recent HAE attack, and 44.4% of students missed at least 1 day of school.¹⁰³ However, this analysis still does not account for any societal costs and impacts as the NHS and PSS perspective has been taken. As such, the wider societal benefits produced by the introduction of donidalorsen as an LTP are not fully captured in this analysis.

For patients who can self-administer donidalorsen at home and do not require injection support in clinics, the need for continued hospital visits to receive treatment, following the first administration training appointment, can be minimised or potentially eliminated. As a result, the burden of treatment on their daily lives compared to IV C1-INHs can be reduced.

In addition to the ability to self-administer donidalorsen at home, patients can travel with their injection pen of donidalorsen as it can be left unrefrigerated for up to six weeks in the original carton when stored below 30°C, thereby potentially reducing restrictions on patients' travel, work and leisure plans.¹⁶ As such, donidalorsen provides long-term HAE control with minimal impact on lifestyle, providing patients the convenience and stability they need to take back control of their lives.

Lastly, berotralstat is associated with a higher incidence of GI-related TEAEs compared to the other treatments. In the APeX-2 trial, 50% of patients in the 150mg berotralstat arm experienced GI abdominal TEAEs, most commonly abdominal pain, diarrhoea and vomiting.⁷¹ While these AEs were not considered serious or severe, their frequency highlights a distinct tolerability concern for berotralstat. To remain conservative these AEs were not captured in the economic model and therefore, their impact on QoL, treatment adherence and patient burden are not reflected in the QALY calculations. This omission represents a potential benefit for alternative therapies which are not associated with these AEs, such as donidalorsen, and may therefore, provide a more favourable real-world patient experience than captured in the model.

3.14 Validation

3.14.1 Validation of economic analysis

The model was built to align with the NICE reference case and preferred methods and adopted an NHS and PSS perspective. Upon completion of the model programming, rigorous and comprehensive quality checks of the model were conducted by an internal health economist not involved with the original programming and an external vendor, to ensure the completed model contained no errors and worked as intended. This included validation of the logical structure of the model, verification of all input data with original sources, and programme validation including checks of the expressions and sequences of calculations, model results, cell references, and Visual Basic for Application.

Extreme-value sensitivity analyses were conducted on all applicable model inputs. The direction and magnitude of change for each extreme value tested was noted and confirmed that this aligned with the expected result (e.g. if all drug cost inputs are set to 0, the model should output total drug costs of 0 as well). The validated model was used to generate the results included in this report.

3.14.2 Clinical validation

The model structure, assumptions, inputs and outputs were validated by UK clinical experts in validation meetings held in June and September 2025.¹⁹ Feedback from the experts was incorporated into this appraisal. The clinical experts agreed with the model structure and settings. Inputs from clinical experts were used to inform the HCRU per HAE attack, as well as to validate model assumptions.¹⁹

3.14.3 Validation against trial data and previous TAs

In addition, the outputs of the model were compared to the outputs of relevant clinical trial data for validation purposes. To validate the number of attacks used in the economic model, the attack rates based on the NMA are compared to the attack rates reported in the relevant clinical trials. In the base case analysis, the efficacy of all comparators is assumed to be equal to donidalorsen Q1M, therefore this is

validated using the outcomes from the OASIS-HAE trial. Based on the NMA outputs used in the model the number of HAE attacks per model cycle (4-weeks) is [REDACTED] compared to the number of reported HAE attacks per 4-week of 0.44 from the OASIS-HAE trial.

The outcomes from the NMA, which measure the relative reduction in HAE attacks compared with the placebo arm of the OASIS-HAE trial, were also compared with outcomes of relevant clinical trials. The median rate ratio applied in the model for donidalorsen Q1M relative to placebo, derived from the NMA, is [REDACTED] which aligns with the reduction in HAE attack rates versus placebo reported in the OASIS-HAE trial of 81%.¹² While the other clinical trials do not report a reduction in HAE attacks compared with placebo directly, the rate ratios reported in the APeX-2 (model-based attack rate ratio comparing berotralstat with placebo: 0.56) and HELP-03 (rate ratio for number of attacks per month versus placebo: 0.13) studies are aligned with the rate ratios obtained from the NMA as presented in Table 31.^{71,86} Similarly, the number of reported attacks in the C1-INH arm in the CHANGE study trial (6.12 per 12-week period) was approximately 50% that of the placebo arm (12.73 per 12-week period), which is in line with the rate ratio from the NMA of [REDACTED].⁸⁷ The correlation between outcomes reported in the clinical trials for the comparators and the median rate ratios estimated in the NMA suggests that the NMA accurately predicts the reduction in attacks observed in clinical practice.

A review of treatments for HAE in previous NICE TAs (in particular, NICE TA606 [lanadelumab] and TA738 [berotralstat]) and published literature was carried out further to validate the key model assumptions, inputs and outputs. The pharmacological cost associated with on-demand treatments for every HAE attack are almost the same at those reported in TA606 (lanadelumab), with this appraisal using a total cost per attack of £1,382.20 and TA606 reporting a cost of £1,382.21.¹⁸ Furthermore, in line with previous TAs in HAE, no subsequent treatments are modelled in the economic analysis since on-demand treatments for every HAE attack are modelled.

3.15 Interpretation and conclusions of economic evidence

3.15.1 Summary

In the base case cost-comparison analysis, treatment with donidalorsen in patients with HAE experiencing ≥ 2 attacks per month was associated with cost savings of £[REDACTED] against berotralstat, and a cost savings of £[REDACTED] against lanadelumab, and £[REDACTED] against C1-INH in the ≥ 8 attacks per month population.

[REDACTED]. Donidalorsen has demonstrated to be a well-tolerated, effective treatment with an option for a more convenient dosing regimen for patients [REDACTED]. With this positioning, the results from this appraisal show that donidalorsen demonstrates a cost-saving use of NHS resources, with an efficacy similar to that of, if not superior to, existing LTPs.

Uncertainty in the model results were explored through extensive deterministic sensitivity analysis, PSA and scenario analyses. The most influential parameters on results differed for each comparator and include the percentage of patients and the timepoint at which patients reduce to the donidalorsen Q2M or lanadelumab Q4W dosing regimen and age. The model was robust to parameter uncertainty, with the mean PSA results lying close to the deterministic results for the base case and for all scenarios considered.

3.15.2 Strengths and limitations

The main strengths of the analysis are:

- Efficacy data for donidalorsen is informed by data from OASIS-HAE, a robust phase III, multi-centre, double-blind, randomised, placebo-controlled study, for which the baseline characteristics were deemed representative of a typical UK HAE patient population by UK clinical experts in clinical validation meetings held in September 2025.¹⁹

- An NMA was performed to address the lack of head-to-head clinical trial data comparing donidalorsen, berotralstat, lanadelumab and C1-INH. The NMA followed a robust methodology (as described in Section 2.10.3) and the assumptions used in the economic analysis which were generated by the NMA results were validated by two clinical experts in clinical validation meetings held in September 2025.¹⁹
- The clinical outcomes predicted by the model and the assumptions underpinning it were ratified by UK clinical expert opinion at clinical validation meetings held in June and September 2025.¹⁹
- The two health-state cohort-level Markov model structure is a well-established model structure that aligns with previous NICE committee preferences in TA606 (lanadelumab) and TA738 (berotralstat) and accurately reflects the nature of HAE and the disease trajectory.^{9,18} The model inputs have been validated by UK clinical experts (in validation meetings held in September 2025) to ensure relevance to this appraisal as well as accurate representation of clinical practice.¹⁹
- The model includes cost categories appropriate for a UK NHS and PSS perspective, with costs and resource use inputs sourced from appropriate UK based sources and inflated to a 2024/25 cost year where necessary. Drug administration and resource use costs were obtained from NHS reference costs, while drug acquisition costs were taken from the BNF.^{114,118} The model has undergone rigorous and comprehensive internal and external quality checks and validation.
- The key sources of variable and parameter uncertainty in the cost-comparison have been tested through the deterministic OWSA, PSA and scenario analyses. The mean probabilistic results lie close to the deterministic results, demonstrating that the model is robust to parameter uncertainty.

While the analysis has many strengths, some limitations remain:

- The small population size in the pivotal trial for donidalorsen, OASIS-HAE, introduces uncertainty in the long-term extrapolations such as attack rate and treatment discontinuation.^{12,76} A small population size leading to uncertainty in

extrapolation of model inputs is a common limitation faced in rare diseases. However, the issues around the extrapolated long-term attack rate is mitigated by the use of a cost-comparison in the base case analysis which assumes the efficacy of all LTPs is equal to that of donidalorsen Q1M (see Section 3.7).

- The lack of any head-to-head trials comparing donidalorsen against the modelled comparators is a limitation. To overcome this, an NMA was conducted to estimate the clinical effectiveness of donidalorsen Q4W compared with donidalorsen Q8W, placebo and other LTPs for HAE. However, some uncertainty is introduced by default by using NMA results in the analysis, and a limitation of the analysis was the variation in how data on number of HAE attacks per month were presented between the relevant trials. Regression analysis was therefore required to derive the necessary inputs to facilitate comparison between trials (see Section 2.10.5). An NMA approach was accepted as part of the NICE evaluation of TA606 (lanadelumab) for the treatment of recurrent HAE attacks.¹⁸
- Given that in the base case cost-comparison analysis equal efficacy is assumed between donidalorsen Q1M and berotralstat, the berotralstat stopping rule is not incorporated into the model. However, the assumption that all patients treated with berotralstat robustly respond to treatment is favourable to berotralstat compared to donidalorsen, as berotralstat demonstrates a weaker efficacy profile than donidalorsen based upon clinical trial and real-world data.¹¹² Therefore, the company considers the exclusion of this stopping rule the most appropriate approach to mitigate these limitations.

3.15.3 Conclusion

This appraisal demonstrates the clinical and cost benefits of donidalorsen versus established clinical management in HAE patients experiencing ≥ 2 attacks per month (berotralstat) and patients experiencing ≥ 8 attack per month (lanadelumab, C1-INH) in the UK. The economic evaluation demonstrates that donidalorsen is cost-saving against all comparator LTPs in the base case analysis, with the inclusion of a simple PAS discount.

Given the significant burden of disease and limitations of current LTPs, there is a clear unmet need for a well-tolerated and convenient LTP option that can demonstrate efficacy in reducing patients' attack frequency, allowing patients to achieve control of the disease and to continue with normal daily living. Donidalorsen has been comprehensively demonstrated to be an effective LTP and offers an alternative therapy option that addresses the unmet need for patients who seek an efficacious, well-tolerated and less frequently administered LTP than those currently available in the treatment pathway. Donidalorsen provides a treatment alternative to berotralstat in patients experiencing ≥ 2 attacks per month, while providing a cost-saving of £[REDACTED] to the NHS. In patients experiencing ≥ 8 attacks per month, donidalorsen provides an effective treatment alternative to lanadelumab, with cost savings to the NHS of cost savings of £[REDACTED] against lanadelumab, and £[REDACTED] against C1-INH. In conclusion, donidalorsen provides patients with an efficacious, well-tolerated and convenient treatment option that is anticipated to be used in a wide population of patients who experience ≥ 2 attacks per month.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Donidalorsen for preventing hereditary angioedema attacks in people 12 years and over [ID6457]

Summary of Information for Patients (SIP)

October 2025

File name	Version	Contains confidential information	Date
ID6457_Donidalorsen in HAE – Summary of Information for Patients_v1.0 30Oct25	V1.0	No	30th October 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Donidalorsen (Dawnzera®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Donidalorsen is anticipated to be used for the routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The United Kingdom (UK) marketing authorisation for donidalorsen is being reviewed by the Medicines and Healthcare products Regulatory Agency (MRHA). The expected approval date is included in the company evidence submission, Section 1.2, Table 2.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

HAE UK (a UK registered patient organisation) have been invited to company meetings to share patient perspectives and challenges of living with HAE. The role of HAE UK is as a steering committee member, with remuneration for their time based on the company's standard operating procedure that defines fair market value (rate of pay); this is set at £70 per hour. The time commitment contracted is for 9.5 hours.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is hereditary angioedema?

HAE is a rare, chronic, genetic disorder which causes swelling attacks, that can occur in any part of the body; these are known as 'HAE attacks'.¹ Typically, areas affected include the hands, feet, face, stomach, genitals and throat. The frequency, duration, location and severity of HAE attacks differs widely between patients and across individual attack episodes. Although HAE attacks are generally unpredictable, approximately 50% of attacks have been found to be triggered by external factors, such as intense exercise, stress, injuries or other illness; however, the specific factors which determine HAE attack frequency, duration, location, and severity are not yet known.^{2,3} The severity of response to a particular trigger can be different for each person with HAE, and the same trigger may not always cause an attack.⁴ Even when patients are able to recognise potential triggers, HAE can still be unpredictable, as attacks can occur without a clear cause, and responses to known factors can vary.^{5,6}

People with HAE either do not have enough of a protein called 'C1 inhibitor' (C1-INH) or C1 inhibitor does not work properly.⁷ This leads to too much 'plasma kallikrein' in the body, which in turn produces higher levels of 'bradykinin' in their bloodstream.⁷ Too much bradykinin leads to symptoms of HAE such as swelling.⁷

There are three types of HAE, which are based on C1 inhibitor levels:

- **Type 1:** C1-INH is either not produced or produced in very low quantities (approximately 80-85% of cases)⁸
- **Type 2:** C1-INH does not function properly (approximately 15-20% of cases)⁸
- **Type 3:** C1-INH is produced at normal levels and it functions well, but other mutations in related genes cause swelling attacks.⁸⁻¹⁰

How many people are affected by hereditary angioedema?

HAE affects 1 in 59,000 people in the UK, although accurate recording is challenging, often due to misdiagnoses or missed symptoms stemming from a misunderstanding of the condition and a general lack of disease awareness.^{11,12}

How does hereditary angioedema affect the quality of life of patients, families and caregivers?

HAE significantly impacts patients' quality of life both during and in between attacks, impacting almost all aspects of daily living and resulting in lifelong consequences.¹³

The symptoms experienced by patients depend on the location of the attack. Stomach swelling attacks occur in 90% of patients and can cause pain, vomiting, diarrhoea and stomach cramping.⁴ Even more common are attacks on the hands and feet, which affect almost 100% of patients with HAE and cause discomfort.¹⁴ Throat swelling attacks occur in over half of patients with HAE at least once in their lifetime and can be life-threatening.^{1,4}

Many people with HAE report anxiety and depression due to the unpredictable nature and severity of attacks.¹⁵ A fear of future swelling episodes can impact patients' work, social life and family relationships. For example, people who experience many attacks every month may be too scared to commit to attending school or work due to the perceived shame or inconvenience of a potential attack, so they skip it. This can lead to lower work and school productivity.¹⁶ Families or carers of people with HAE are also affected with caregiving responsibilities leading to a decrease and work and/or leisure time.¹⁷

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Due to misdiagnoses, misunderstanding of symptoms and general lack of HAE awareness due to its rarity, patients typically experience symptoms for an average of 10 to 18 years before a diagnosis of HAE Type 1 and Type 2, respectively.¹⁸ These delays in diagnoses can cause patients to experience worsened symptoms, lower quality of life and increased risk of serious complication or even death.¹⁹ Timely diagnosis of HAE from the onset of symptoms is important for patients as it allows doctors to create a plan to prevent, manage and treat HAE attacks, leading to improved long-term control of their disease.

The diagnosis of HAE relies on the presentation of symptoms during an attack and clinician opinion, which should be validated through laboratory tests.²⁰ Recurrent skin swelling and gastrointestinal attacks are key symptoms, but HAE can also be linked to:^{21,22}

- A positive family history
- Onset of symptoms in childhood/adolescence
- Recurrent and painful abdominal symptoms
- Occurrence of upper airway oedema
- Failure to respond to standard anti-allergy treatments such as antihistamines, glucocorticoids, omalizumab, or epinephrine
- Presence of signs or symptoms before swelling
- Absence of wheals (raised, itchy bumps on the skin).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Currently there is no cure for HAE and treatment plans are aimed at managing the disease.²³ This includes:²²

- **On-demand treatment** to manage attacks as they happen to stop the progression of swelling and relieve symptoms.
- **Short-term prophylaxis (STP)** used as preventative treatment before planned events that may trigger an attack, such as surgical and dental procedures.
- **Long-term prophylaxis (LTP)** used regularly to proactively prevent HAE attacks and reduce burden of disease.

Achieving complete control of HAE and normalising a person's life can only be achieved by LTPs.²² Eligibility for specific LTPs is determined by patients' attack frequency. LTPs available to patients with HAE in the UK as established standard of care include:^{24–27}

- Berotralstat (Orladeyo[®]), for patients who experience two or more HAE attacks **per month**
- Lanadelumab (Takhzyro[®]), for patients who experience two or more HAE attacks **per week**
- IV C1-INHs, including Cinryze and Berinert (off label), for patients who experience two or more HAE attacks **per week**

These treatment options have different characteristics, including how the treatment is given, how often the treatment is given, and the side effects that patients may experience.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

As discussed in **Section 2a**, there is a substantial burden to both patients and caregivers or family members associated with HAE.

Impact of living with HAE on patient quality of life

HAE impacts almost all aspects of patients' lives, such as their physical and mental wellbeing, school or work life, and family life, and the consequences are lifelong.^{13,28} In a survey of 445 patients with HAE, almost half had some degree of anxiety and almost a quarter showed depressive symptoms.²⁸ These emotional challenges likely stem from the unpredictable nature, frequency, and severity of swelling episodes, which can have negative effects on an individual's work, social interactions, and family life.

In a patient survey conducted by the US Food and Drug Administration (FDA), one patient said *"During these attacks, I can't eat, I can't drink, you basically vomit every little bit that is in you"* when describing the symptoms associated with abdominal attacks.²⁹ Another patient described attacks of the extremities as *"...if the bottoms of your feet are swollen, you cannot walk anywhere. And if your hands swell up like a balloon... you cannot pick stuff up, you cannot pull up your pants... you cannot do anything, dress yourself, feed yourself... When both your hands and your feet are swollen, you cannot do anything except just sit there"*.²⁹

The unpredictability of HAE attacks and the impact of HAE on daily life leads people with HAE to experience fear, anxiety and depression between attacks, occurring not only due to the attacks themselves but also about reduced work/school productivity and limited career/educational achievement.^{15,30} A US patient survey found that approximately four out of 10 patients feel that HAE prevented them from going as far in school as they would have liked because they missed so much education.^{16,21} Almost seven out of 10 patients felt that they could not consider certain jobs because of HAE.^{16,21}

Impact on family and carer quality of life

Families and carers of patients with HAE are also impacted by the unpredictable nature, frequency, and severity of HAE attacks. They may face psychological problems, familial anxieties, worries about their loved one's wellbeing, and a reduced ability to maintain their daily activities. Results from the European HAE-BOIS study showed that almost six out of ten patients required carer help over the past 6 months, while just over half of patients required assistance from a carer during an attack.¹⁷ The need for support increases as attacks become more severe; carer support was required for almost seven out of ten patients with severe pain, over six out of ten patients with moderate pain and over a quarter of patients with no pain or mild pain.¹⁷ Caregiving responsibilities can lead to a decrease in work and/or leisure time for carers, with an average of 1.2 days of work/leisure missed for severe attacks, 1.2 days for moderate attacks and 1 day for mild attacks.¹⁷

Patient treatment preferences

Patient preference is a key factor when considering treatment options. One study found that patients had the strongest preference for a treatment that:³¹

- reduced attack frequency
- reduced risk of a gastrointestinal side effects
- oral tablet versus injections
- treatments taken once every eight weeks versus more frequently
- treatments with a lower risk of injection site reactions

Respondents placed the least importance on reducing the time for a treatment to reach maximum efficacy.³¹ Almost eight out of ten patients reported being willing to switch to a new prophylactic treatment, and those with poorly controlled HAE were more likely to consider switching treatment.³¹ As such, if a new treatment option was available that met patient preferences, it is likely patients would want to switch to the new treatment.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

The goal of treatment is to control disease through reducing the frequency of attacks, allowing patients to continue with their normal daily lives.³² Donidalorsen is a new LTP, with a different mechanism of action to current options, that offers long-term prevention of HAE attacks.³³

Donidalorsen is a type of medicine called an antisense oligonucleotide inhibitor.³³ It binds to ribonucleic acid (RNA) in the body's cells to reduce the production of prekallikrein.³³ This in turn blocks the activity of plasma kallikrein which helps to reduce the amount of bradykinin in a patient's bloodstream and prevents symptoms of HAE.³⁴

In targeting prekallikrein RNA, donidalorsen differs from current treatment options, such as berotralstat and lanadelumab, which work much later in the pathway.^{24,27,35} In doing so, donidalorsen offers improved control of HAE attacks by reducing how often patients experience attacks, potentially improving the quality of life for people with HAE.³³

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Donidalorsen is not intended to be used in combination with any other medicines. During an attack, patients are able to receive on-demand therapy as needed but this is not a combination therapy.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Donidalorsen is given as an injection under the skin (subcutaneous injection). Donidalorsen is provided in single-use, pre-filled auto-injector pens. Treatment will be started and managed under the supervision of a doctor experienced in the care of patients with HAE.³⁶

The anticipated recommended starting dose in adult and adolescent patients is 80 mg once a month, equivalent to one pre-filled pen once a month. An anticipated dosing interval of 80 mg once every 2 months may be considered if the patient is well controlled (e.g., attack free) for at least 3 months while receiving donidalorsen. This offers a reduced dosing schedule compared to the alternative LTPs of berotralstat, lanadelumab and C1-INHs, offering greater convenience for patients and less disruption to their daily lives.^{24-27,33}

Donidalorsen also gives patients the ability to take their medication at home, eliminating the need for hospital visits to receive their LTP and minimising the burden of treatment on their daily lives by only needed to take their LTP either once a month or once every two months.³⁶ The pre-filled

pen allows patients, or a caregiver, to easily give the injection at home, with no need to reconstitute (mix the medicine with a liquid) before it is given (unlike C1 inhibitors). Donidalorsen can be kept out of the fridge for six weeks, if stored below 30 degrees, which allows patients to be able to travel for work or social reasons for several weeks without needing to carry extensive medication supplies, providing patients with the option to travel with flexibility.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

OASIS-HAE

The safety and clinical efficacy of donidalorsen have been evaluated through the following studies:

- **OASIS-HAE (NCT05139810):**³³ a randomised, placebo-controlled study where neither the patients nor the researchers knew who was receiving treatment (double-blinded). The OASIS-HAE study included 21 sites in EU countries, 11 in North America, five in the Middle East and two in the UK. The study included patients aged 12 years or older with confirmed HAE type 1 or 2 who had at least two attacks in eight weeks preceding the study. This provides the main evidence for how effective donidalorsen is at preventing HAE attacks. A total of 90 patients were included and randomly assigned to donidalorsen 80 mg every four weeks (45 patients), donidalorsen 80 mg every eight weeks (23 patients) or a placebo (i.e. no treatment, 22 patients). Patients were treated for 24 weeks in the OASIS-HAE study.
- **OASISplus open-label extension (OLE) study:**^{37,38} 83 patients completed the OASIS-HAE trial and moved into the OASISplus study to investigate the long-term safety and efficacy of donidalorsen (the 'OLE cohort'); this study is ongoing. Patients received donidalorsen every four weeks (69 patients) or every eight weeks (14 patients). In addition, a further 64 patients were included in this study following previous treatment with a stable dose of lanadelumab (31 patients), berotralstat (11 patients), or C1-INH (22 patients) (the 'switch cohort'); these patients received donidalorsen 80mg every eight weeks.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The clinical efficacy of donidalorsen was evaluated through the 24-week OASIS-HAE study, with an ongoing long-term extension study (OASISplus) providing data for a 52-week treatment period, which could be extended up to 157 weeks.^{33,37,38}

OASIS-HAE

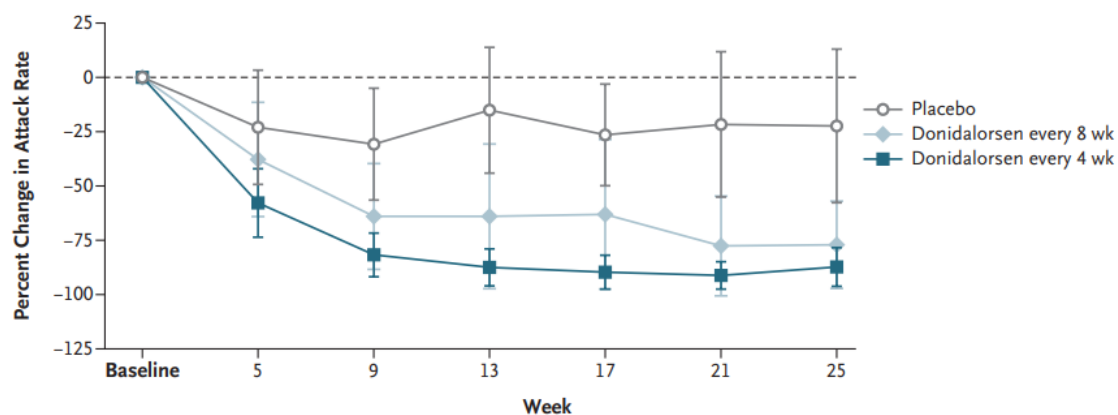
Primary endpoint – HAE attack rate (per four weeks), Week 1 to Week 25 of OASIS-HAE

Donidalorsen met its primary efficacy endpoint by demonstrating an 81% reduction in monthly attacks in patients treated with donidalorsen every four weeks compared to patients treated with placebo (**Figure 1**).³³ This shows that donidalorsen is an effective treatment option for people with

HAE, providing a significant reduction in attacks.³³ Fewer attacks means that people living with HAE can maintain their normal daily lives and have an improved quality of life, compared to those who have more frequent attacks.

Donidalorsen also resulted in a 55% reduction in monthly attacks in patients treated with donidalorsen every eight weeks compared to patients treated with placebo (**Figure 1**).³³ This shows that even with less frequent dosing, donidalorsen still reduces attacks for patients. This means patients have fewer reminders of their disease, as treatments are needed less frequently, and are also likely to have fewer side effects due to reduced treatment exposure.

Figure 1: Percent change in attack rates (per 4 weeks) for patients receiving donidalorsen every four weeks, donidalorsen every 8 weeks and receiving placebo in the OASIS-HAE study from Week 1 to Week 25



wk - week
Reidl et al. 2024³³

Secondary endpoint – HAE attack-free patients, Week 5 to Week 25 of OASIS-HAE

The attack-free status of patients was also substantially improved, with 53% of patients who took donidalorsen every four weeks attack-free, compared to 9% of patients who received placebo.³³ For patients who received donidalorsen every eight weeks, 35% were attack-free.³³ Having extended periods of attack freedom is crucial to alleviating the physical and mental burden which repeated attacks impose on patients, allowing patients to feel that they have achieved disease control and the burden of HAE on their daily life has been significantly reduced.

Secondary endpoint – Moderate or severe HAE attack rate (per four weeks), Week 5 to Week 25 of OASIS-HAE

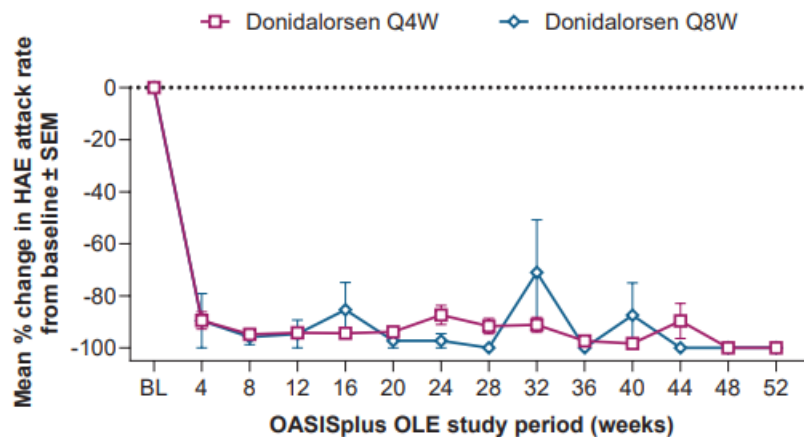
The number of moderate to severe attacks was also reduced by 89% for patients receiving donidalorsen every four weeks compared to patients who received placebo.³³ A reduction of 41% in the number of moderate or severe HAE attacks was also observed in patients who received donidalorsen every eight weeks compared to placebo.³³ Such reductions in the number of moderate or severe attacks are key to alleviating the significant physical burden which HAE patients suffer, making symptoms more manageable and minimising the impact potential attacks have on patient's ability to carry out their normal activities.

OASISplus study

OLE cohort – patients who completed the OASIS-HAE trial and continued to receive donidalorsen

In patients who had completed the OASIS-HAE trial and moved into the OASISplus study, donidalorsen resulted in a 92% reduction in monthly attacks compared to baseline in patients treated with donidalorsen when taken every four weeks and 93% reduction in monthly attacks in when taken every eight weeks (**Figure 2**).³⁸ These results show that the efficacy of donidalorsen does not deteriorate in long-term treatment (up to 157 weeks), for both once monthly and once every two months dosing regimens.

Figure 2: Percent change in HAE attack rate across the OASISplus study period compared to baseline



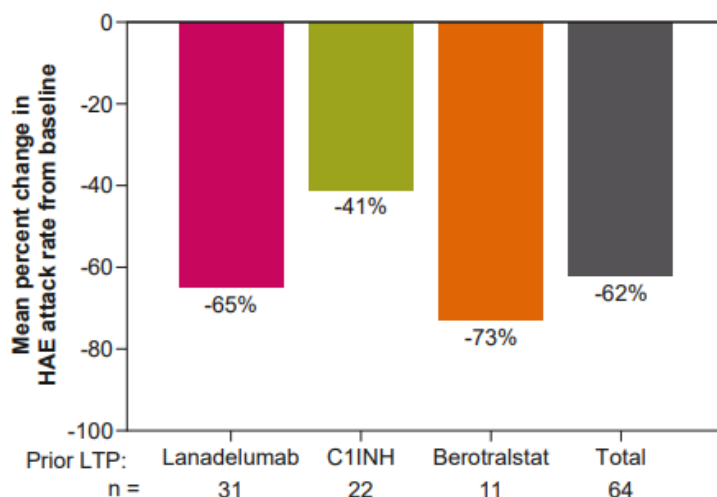
HAE – Hereditary angioedema; OLE – Open-label extension; Q4W - Once every four weeks; Q8W - Once every eight weeks; SEM - Standard error of the mean

Tachdjian et al. 2024³⁸

Switch cohort – patients who switched from treatment with other LTPs (berotralstat, lanadelumab or C1-INH) to donidalorsen

Patients with HAE who switched from other LTPs (berotralstat, lanadelumab or C1-INH) to donidalorsen every four weeks had a 62% reduction in monthly attacks; specifically, patients previously treated with berotralstat had a 73% reduction, those previously treated with lanadelumab had a 65% reduction and those previously treated with C1-INHs had a 41% reduction (**Figure 3**).³⁷ This demonstrates the patients can achieve a reduced attack rate when receiving donidalorsen after treatment with other LTPs.

Figure 3: Percent change in HAE attack rate in patients who switched from other LTPs (berotralstat, lanadelumab or C1-INH) to donidalorsen given once every 4 weeks in the OASISplus switch cohort



3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Treatment with donidalorsen significantly improved the quality of life of patients with HAE in the OASIS-HAE study compared to treatment with placebo. Two different assessments, specifically for patients with HAE, were used to measure patients' quality of life:

- Angioedema Quality of Life (AE-QoL) questionnaire: this contains 17 questions across four domains – functioning, fatigue/mood, fears/shame and food. Each question is scored as never = 0, rarely = 1, occasionally = 2, often = 3, very often = 4.
 - Treatment with donidalorsen every four weeks showed a clinically meaningful reduction of ≥ 6 points and improvement of 24.7 points in the mean AE-QoL total score, meaning patients' overall well-being, physical functioning and fears/shame around the disease were improved after receiving donidalorsen.^{33,39} For patients, this is a meaningful benefit, as it indicates that treatment does not diminish their quality of life, allowing them to manage their condition with minimal disruption to their everyday life.
- Angioedema control test (AECT): this measures HAE disease control through a questionnaire consisting of four questions based on attack frequency, quality of life, unpredictability, and control of HAE, with each question having five response choices - very often = 0, often = 1, sometimes = 2, seldom = 3, and not at all = 4. The total score is a sum of the four questions and a cutoff score of 10 was used to determine whether patients had poorly controlled disease (patients with scores less than 10 points have poorly controlled disease).
 - 91% of patients who received donidalorsen every four weeks and 74% of patients who received donidalorsen every eight weeks dosing had well-controlled disease compared to 41% of patients who received placebo.³³ This demonstrates that donidalorsen treatment can help patients achieve control of their disease, which is one of the key goals of HAE treatment.

Similar results were seen in the OASISplus study where patients who received donidalorsen either every four weeks or every eight weeks had improvement in their AE-QoL score, demonstrating an improved overall quality of life.³⁸ Over 90% of patients receiving donidalorsen reported well-controlled disease, based on AECT scores, meaning these patients had fewer attacks, improved quality of life and better overall control of their symptoms.³⁸

For patients who switched from another LTP, most patients also preferred treatment with donidalorsen due to better disease control, less time for administration, and less injection site pain or reactions.³⁷ These results show that patients can have sustained improvement of quality of life and disease control when receiving donidalorsen after treatment with other LTPs, and that treatment with donidalorsen is often preferable compared to other LTPs.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all medicines, donidalorsen can cause side effects, although not every patient will experience them. However, as shown in the OASIS-HAE study, donidalorsen has a favourable safety profile, and is well-tolerated in patients with HAE, meaning that most people who used it did not have serious side effects. In the OASIS-HAE study, more patients receiving placebo (i.e. no treatment) experienced side effects (82% of patients) than those receiving donidalorsen (73% of patients who received donidalorsen every four weeks, and 61% of patients who received it every eight weeks) further demonstrating the safety of donidalorsen.³³

The most common side effect reported in the OASIS-HAE study (affecting more than 1 in 10 people) was a reaction at the site where the injection is given, with symptoms such as change in skin colour, redness, pain and itching; all injection site reactions were mild in severity. Other side effects reported in patients treated with donidalorsen, affecting more than 1 in 10 people, were headache (13%) and nasopharyngitis (mild infection of the nose and throat that can produce symptoms such as a runny nose, sneezing, and coughing; 11% in the patient group treated with donidalorsen once every 4 weeks, and 18% in the patient group treated with donidalorsen once every 8 weeks). No major safety concerns were identified. No patients treated with donidalorsen in the OASIS-HAE trial experienced a severe side effect or stopped treatment due to donidalorsen.

During the OASISplus study, in the group of patients who switched to donidalorsen from another LTP, only one patient stopped receiving treatment due to side effects; the patient discontinued donidalorsen due to complications with ongoing congestive heart failure that were not considered related to the study.³⁷ In the OLE cohort of patients in the OASISplus study (patients who completed the OASIS-HAE trial and continued to receive donidalorsen), zero patients discontinued treatment with donidalorsen due to side effects.³⁸ The OASISplus study is ongoing and results presented are from a data cut off of February 2024. The results show that the safety profile of donidalorsen is sustained during long-term treatment.^{37,38}

Donidalorsen is associated with fewer side effects when compared to other LTPs. In the berotralstat study, 85% of patients receiving berotralstat experienced side effects.⁴⁰ In the lanadelumab study, 96% of patients receiving lanadelumab every two weeks and 90% of patients receiving lanadelumab every four weeks experienced side effects.⁴¹ This demonstrates donidalorsen is a well-tolerated treatment option for patients with HAE.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The development of LTPs has improved HAE management, however, there remains a significant unmet need for treatment options that can address key patient treatment priorities. Donidalorsen is a new treatment that works in a different way to currently available treatments to prevent recurrent HAE attacks.

Donidalorsen has been shown to be effective and well-tolerated through clinical trials

- The efficacy and safety of donidalorsen has been assessed across three trials over 10 years demonstrating the potential of donidalorsen to improve patients' lives.^{33,34,37,38}
- In an international, placebo-controlled, randomised trial, OASIS-HAE, donidalorsen reduced the number of attacks patients experience compared to placebo by 81% when used every four weeks, and by 55% when used every eight weeks.³³
- The results seen with donidalorsen were maintained in the OASISplus study, showing the long-term benefits of donidalorsen.³⁷
- Improvements in quality of life were seen after donidalorsen treatment, indicating that patients are able to preserve their well-being, emotional and physical functioning, as well as continuing normal daily activities.^{33,37}
- Donidalorsen demonstrated a favourable safety profile, with fewer side effects compared to current LTP options.
- Donidalorsen is as effective as current treatments in reducing attacks and allowing patients to continue their normal daily living.

Donidalorsen offers a reduced dosing regimen compared to currently available LTPs and a convenient method of administration

- It is anticipated that patients who are well-controlled (i.e. attack-free) for three months after taking donidalorsen once every month, are eligible to take donidalorsen once every two months. Due to the different mechanism of action of donidalorsen, it can be taken less frequently than alternative LTPs.^{24–27,36} This means patients are exposed to a smaller risk of side effects and reducing the burden of their disease in their daily lives.
- Donidalorsen is administered via an easy-to-use auto-injector pen, giving patients the ability to self-administer at home.³⁶ This increases the chances of people living with HAE staying on treatment and thus keeping their HAE under control.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The administration of donidalorsen via a subcutaneous injection (injection under the skin) may not be suitable for all patients. Some patients may be unable to self-administer donidalorsen subcutaneously and will therefore require injection support from a caregiver or nurse. This support will be required monthly, or once every two months in patients who are well controlled, which may create some disruption in patients' and carers' lives as they will be required to schedule an appointment to receive their injections. For patients who have a preference against receiving treatment via injections, donidalorsen may present itself as a less suitable LTP treatment option.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

For a treatment to be reimbursed by the National Health Service (NHS), the manufacturer must provide an economic model (also called a cost-effectiveness model) to demonstrate that the treatment will provide value for money and is therefore a good use of NHS resources. An overview of the economic model for donidalorsen versus the approved comparators, used as standard of care, considered in this appraisal (berotralstat, lanadelumab, and C1-INHs) in patients with HAE is provided below.

How the model reflects the condition

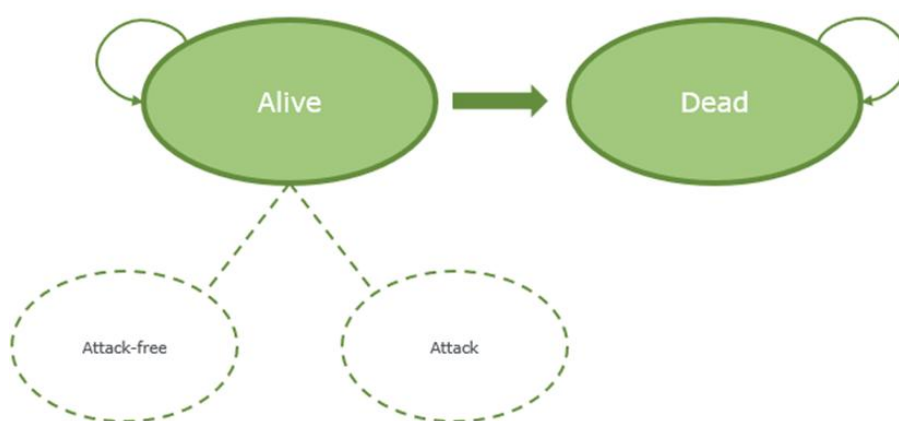
The economic model for this submission uses data from OASIS-HAE and published literature providing relevant HAE data to estimate the costs and benefits for patients with HAE receiving donidalorsen compared to berotralstat, lanadelumab, C1-INHs, over a lifetime period. The model captures the benefit of LTP therapy by demonstrating the reduction in number of HAE attacks associated with each treatment and the associated impact on costs and resource use to the NHS and the impact on patients' health.

HAE is a persistent condition characterised by acute attacks. The model consists of two health states to reflect the nature of HAE and course of the disease, defined as:

- Alive; comprised of patients who are:
 - Currently experiencing an HAE attack
 - Currently attack free
- Dead (natural mortality due to any cause)

All patients enter the model in the alive health state and receive treatment with either donidalorsen, berotralstat, lanadelumab, or C1-INH. Within the alive health state patients are either experiencing an HAE attack or are attack-free. If a patient dies, they are removed from the model and enter the 'death' health state, from which they cannot move back out of. Figure 4 presents a schematic of the model structure.

Figure 4: Cost-effectiveness model structure and patient flow



Modelling how much a treatment extends life

The life expectancy for patients with HAE is similar to that of the general population. In the model, we assume that this is the case. The survival rates (the percentage of people alive at a specific time after diagnosis) in the model are informed by the UK general population survival rates.⁴²

Modelling how much a treatment improves quality of life

Donidalorsen provides patients a well-tolerated and effective treatment option, while offering the opportunity to minimise the burden of treatment, and is therefore expected to improve patient's quality of life, as stated in **Section 3f**.

Patients are expected to experience an improved quality of life when they are attack-free. When an attack occurs, the patient's quality of life declines for the duration of the attack. The quality of life of 'attack' and 'attack-free' patients in the model were measured based on data from published studies.⁴³ The quality of life is also modelled for carers of patients with HAE. The quality of life of a carer declines when a patient experiences an attack based on data from published studies.⁴⁴

In the base case analysis, the effects of all treatments are assumed to be equal, and only the costs associated with treatments are measured. The quality of life benefits are assumed to be equal across all treatments.

Modelling how the costs of treatment differ with the new treatment

Costs included in the economic analysis are drug purchase costs, drug administration costs, and NHS resource use costs associated with HAE attacks. As described in **Section 2c** and **3c**, the profile of the comparators differs in terms of mode of administration, dosage requirements, and dosing frequency.

Uncertainty

Every effort has been made to reduce the impact of uncertainties in the economic model, including researching published data and discussion with HAE clinical experts. The uncertainty in assumptions and data sources used in the model have been explored through extensive analyses allowing the company to determine both best- and worst-care scenarios. HAE is a rare disease and there are limited data published regarding some costs, such as what healthcare support patients require when they experience an attack, therefore some uncertainties remain. In addition, as HAE attacks affect patients differently, and the types of attacks a patient experiences varies from one attack to another, there is variation in how each attack impacts patient's quality of life.

Cost effectiveness results

In the base-case analysis, donidalorsen is shown to be a cost-saving treatment option for patients with HAE to the NHS compared to other currently available LTPs (berotralstat, lanadelumab and C1-INH). This means donidalorsen is a less expensive treatment option to what is currently available to patients.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Donidalorsen is an innovative, first-in-class treatment that offers patients less frequent administration while still providing significant benefits

Due to the different mechanism of action of donidalorsen and how donidalorsen works, it provides an effective treatment option taken less frequently compared to current LTPs.⁴⁵

Donidalorsen can reduce the number of attacks a patient experiences, improving their disease control and ultimately improving quality of life.

Benefits not captured in the economic model that also need to be considered

None

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues [here](#)

Two currently available C1-INH treatments (Cinryze and Berinert) for patients with HAE are derived from human plasma, with which some religious groups may be unwilling to be treated with as blood-derived products. Accordingly, treatment options for individuals who decline human-derived products on the grounds of religious belief should be carefully considered to ensure that recommendations do not, directly or indirectly, result in discrimination on the basis of religion. Donidalorsen is not derived from human plasma.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open access materials or provide copies that patients can access.

HAE patient groups and charities:

- HAE UK: <https://www.haeuk.org/>
- HAE community: <https://www.discoverhae.com/hereditary-angioedema-community>

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Angioedema Control Test (AECT): The AECT is a patient-reported questionnaire that assess how well a person's recurring angioedema is controlled.

Angioedema Quality of Life Questionnaire (AE-QoL): The AE-QoL is a valuable tool to assess changes of QoL impairment in patients with recurrent angioedema.

Cost-effectiveness model (CEM): A CEM is an analytical framework that estimates the lifetime costs and health benefits of different interventions to help decision-makers determine which options provide the best value for money.

Data cut off: A specific date in a clinical trial after which any new data is excluded from a particular analysis. Only data collected up to this date is considered.

Efficacy: Efficacy is how well something works.

European HAE-BOIS: HAE-BOIS is a research study conducted in Denmark, Germany and Spain to understand the real-world experience of HAE.

Mechanism of action: The mechanism of action is the specific way a drug interacts with a biological system to produce its effects at the molecular or cellular level.

Open-label extension (OLE): An OLE is a phase of a trial where participants continue to receive a study drug for a longer period of time, and both the participants and the investigators know that the active treatment is being given.

Placebo-controlled: A placebo-controlled trial is a type of study where one group of participants receives the active treatment being tested and the other comparable group receives a placebo “dummy” treatment with no active ingredients.

Plasma kallikrein: A protein in your blood that helps your body respond to injury or infection.

Prekallikrein (PK): Prekallikrein is a protein involved in the coagulation pathway of blood clotting and inflammation.

Primary efficacy endpoint: A primary efficacy endpoint is the main outcome that a clinical trial uses to determine if a new treatment is effective.

Secondary efficacy endpoint: A secondary efficacy endpoint is an additional outcome measured in a clinical trial to provide supportive information to determine if a new treatment is effective.

Subcutaneous injection: A subcutaneous injection delivers medication into the fatty tissue just under the skin, allowing for a slower and more steady absorption compared to oral or intravenous methods.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Clarification questions

December 2025

File name	Version	Contains confidential information	Date
[ID6457] Donidalorsen Clarification Questions	Redacted	No	8 th December 2025

Notes for company

Highlighting in the template

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

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Decision problem (clinical effectiveness)

A1. [Priority question]: Garadacimab was excluded from the submission despite a recent NICE recommendation (October 2025). Please justify this exclusion and provide any available clinical, cost, and resource-use data to support future scenario analyses. Alternatively, please provide an assessment of the uncertainty the omission of garadacimab as a comparator introduces to the comparative clinical and cost effectiveness of donidalorsen.

Rationale for exclusion of garadacimab

Garadacimab was recommended by the National Institute for Health and Care Excellence (NICE) (NICE TA1101) on 8 October 2025, 22 days before the company evidence submission (CES) for donidalorsen in patients with hereditary angioedema (HAE) was provided. The phase III pivotal trial for garadacimab, VANGUARD, did not include any sites in the UK and implementation of TA1101 is still ongoing; there has been limited to no usage of garadacimab within the National Health Service (NHS) to the company's knowledge.^{1,2} The most recent NHS England high cost drugs commissioning list, updated 20th October 2025 (version 20.2), states that garadacimab is not yet routinely commissioned.³ Therefore, garadacimab is not considered established standard of care in clinical practice in England. The exclusion

of garadacimab as a comparator in the company's economic analysis is consistent with Section 2.2.12 of NICE manual, which specifies that comparators should reflect established clinical practice.⁴

Therefore, garadacimab is excluded from the company base-case analysis. However, clinical and economic data are provided below to support scenario analysis and assess the impact of this exclusion.

Clinical evidence

To assist the EAG, clinical data relating to garadacimab is included in this response. VANGUARD is a pivotal, Phase III, randomised-controlled trial (RCT) designed to evaluate the safety and efficacy of garadacimab versus placebo in patients with type I or type II hereditary angioedema (HAE).⁵ The clinical trial design, baseline attack rates and baseline characteristics are broadly similar between OASIS-HAE and VANGUARD; data are presented in the Appendix Question A1 to aid comparison between OASIS-HAE and VANGUARD.

The primary endpoint of the VANGUARD study was the investigator-assessed time-normalised number of HAE attacks (number of HAE attacks per month) during the 6-month treatment period (day 1 to day 182).⁵ During the 6-month treatment period, the mean number of investigator-confirmed HAE attacks per month was significantly lower in the garadacimab group (0.27, 95% CI: 0.05, 0.49) than in the placebo group (2.01, 95% CI: 1.44, 2.57; $p < 0.0001$), corresponding to an 87% reduction (95% CI: –96%, –58%; $p < 0.0001$). The results are very similar to those observed in the OASIS-HAE clinical trial; the time-normalised investigator-confirmed HAE attack rate was 0.44 (95% CI: 0.27, 0.73) for the donidalorsen once every four weeks (Q4W) group and 2.26 (95% CI: 1.66, 3.09) for the placebo group, representing an 81% reduction (95% CI: -89.3%, -64.9%; $p < 0.001$).⁶ The primary endpoint results from VANGUARD and OASIS-HAE are presented in Table 1 for naïve comparison.

The percentage reduction in the number of HAE attacks per month was similar for garadacimab and donidalorsen Q4W compared to placebo, 87% and 81%, respectively. While this is a naïve comparison, the VANGUARD and OASIS-HAE trials are broadly similar in their design, eligibility criteria and baseline attack rates indicating the results may be directly comparable. The broadly comparable primary

endpoint results in the placebo arm of the VANGUARD and OASIS-HAE trials indicates that the outcomes in the placebo arm are comparable between the studies. An important distinction between the VANGUARD and OASIS-HAE trials is that the VANGUARD trial does not include any patients from the UK whereas the OASIS-HAE trial included two sites in the UK.^{2,6} Therefore, data from the OASIS-HAE trial have direct evidence from the UK population which is relevant for this technology assessment, whereas the VANGUARD trial data does not. The similarity between garadacimab versus donidalorsen Q4W, when assessing the percentage difference compared to placebo (-87% and -81%, respectively), may indicate comparable outcomes between garadacimab and donidalorsen Q4W. As such, the exclusion of garadacimab from the company's base case economic analysis is not expected to increase uncertainty in the clinical efficacy of donidalorsen or the assumption of equal efficacy in the company's base case economic analysis.

Table 1: Primary endpoint results from VANGUARD and OASIS-HAE

	VANGUARD ⁵		OASIS-HAE ⁶	
	Garadacimab	Placebo	Donidalorsen Q4W	Placebo
Mean number of IC HAE attacks per month (95% CI)	0.27 (0.05, 0.49)	2.01 (1.44, 2.57)	0.44 (0.27, 0.73)	2.26 (1.66, 3.09)
Percentage difference compared to placebo (95% CI)	-87% (-96%, -58%)		-81% (-89.3%, -64.9%)	

Abbreviations: CI – Confidence interval; HAE – Hereditary angioedema; IC – Investigator-confirmed; Q4W- Once every four weeks

A study published by CSL Behring in November 2025 compared the clinical efficacy of garadacimab versus donidalorsen in patients with HAE via a matching-adjusted indirect comparison (MAIC).⁷ The objective of this study was to estimate the relative efficacy of garadacimab 200 mg Q1M compared to donidalorsen 80 mg Q4W and donidalorsen 80 mg Q8W.⁷ As part of the MAIC analysis, the individual patient data from the VANGUARD trial was reweighted to match the baseline characteristics reported in the OASIS-HAE trial.⁷ No statistically significant difference was observed between garadacimab and donidalorsen Q4W for time-normalised number of HAE attacks: the rate ratio was 0.61 (95% CI: 0.21, 1.75), the corresponding 95% confidence interval for the rate ratio included 1. The number of HAE attacks was the

primary outcome measure of both the VANGUARD and the OASIS-HAE trials and is the measure of clinical efficacy within the economic analysis of this appraisal.⁷ Based on the rate ratio for time-normalised number of HAE attacks reported in the MAIC, no statistically significant difference in efficacy between donidalorsen Q4W and garadacimab was observed.⁷

A naïve comparison of results from VANGUARD and OASIS-HAE for the mean number of attacks per month demonstrate the similarity of results between the intervention and control arms. The results from the MAIC presented by CSL Behring do not demonstrate a statistically significant difference in efficacy, as measured by the rate ratio for time-normalised number of HAE attacks, between garadacimab and donidalorsen Q4W. The company therefore consider it reasonable to also assume that the rate ratio of garadacimab versus placebo would be equivalent to the rate ratio applied for donidalorsen, berotralstat, lanadelumab and C1-INH in the economic model, consistent with the assumption of equal efficacy in the base-case.

Economic impact

In the company's base case cost-comparison analysis, only treatment acquisition, treatment administration and on-demand attack management drug costs are considered, as the clinical effectiveness is assumed to be equal amongst the LTPs. Health-care resource use (HCRU) and on-demand attack management for each comparator treatment is determined by the number of attacks experienced by patients; the number of HAE attacks is assumed to be the same for all treatments under the equal efficacy assumption. Therefore, the only costs that would differ between donidalorsen and garadacimab in a potential cost-comparison analysis are the treatment acquisition and administration costs. As demonstrated by the results presented in the donidalorsen CES, treatment acquisition costs are the main driver of the total costs for each treatment in the economic model. At a list price of £20,625.00 per pen for garadacimab and a PAS price of £[REDACTED] per pen for donidalorsen, donidalorsen is expected to deliver an annual cost saving of £[REDACTED] per patient compared with garadacimab. For a more detailed naïve cost comparison of donidalorsen versus garadacimab, please see the response to Question B8.

Garadacimab requires a loading dose of 400mg at treatment initiation and thereafter is administered Q1M at a dose of 200 mg. There is no dosing frequency reduction

available for patients on garadacimab. Additionally, the loading dose of 400 mg for garadacimab is administered as two SC injections of 200 mg each further increasing the administration burden on patients who receive garadacimab compared with patient who receive donidalorsen. Patients who receive donidalorsen initiate treatment at a dose of 80 mg Q1M and a dosing interval of [REDACTED]

[REDACTED].⁸ The option to reduce to a once every two months (Q2M) dosing regimen represents a less frequent and potentially more convenient dosing regimen compared with garadacimab reducing the administration burden on patients.

Assessment of uncertainty

The company maintains that garadacimab is not established standard of care in the NHS and is therefore excluded from the company's base case cost-comparison analysis for this appraisal. However, based on the available clinical evidence, such as indirect comparisons, including garadacimab into the economic analysis would not violate the equal efficacy assumption applied in the company base case cost-comparison analysis. As is demonstrated in the response to Question B8, a naïve cost comparison indicates that donidalorsen is expected to deliver annual cost savings of £[REDACTED] per patient compared with garadacimab. Overall, the exclusion of garadacimab introduces minimal uncertainty to the appraisal, and donidalorsen provides a comparable treatment alternative resulting in substantial cost savings for the NHS compared with garadacimab.

A2. Please justify exclusion of attack-free period and time to first attack

- Provide any available data on these endpoints from OASIS-HAE (even if exploratory) and explain whether their exclusion could underestimate donidalorsen's clinical benefit or affect comparability to prior NICE appraisals (e.g., TA606, TA738).

Attack-free period and time to first attack were not included as primary or secondary outcome measures in the pivotal phase III trial (OASIS-HAE) of donidalorsen, as discussed in the company's decision problem form and Table 1 of the CES.^{9,10} As a

result, these measures were not treated as principal outcomes for the economic analysis and did not inform the results.

In HAE trials that evaluate efficacy of an LTP, including C1-INH, lanadelumab, and berotralstat, it is standard to assess the number or rate of HAE attacks as the sole primary endpoint.^{11–13} Assessment of attack-free status varies across HAE LTPs. In the donidalorsen phase II, placebo-controlled ISIS 721744-CS2 attack-free status was assessed by the exploratory endpoint ‘Number of HAE attack-free patients by Week 17’. Subsequently, in the OASIS-HAE trial, attack-free status was assessed as ‘The percentage of Investigator-confirmed HAE attack-free patients from Week 5 to Week 25 compared to placebo’.^{6,10,14} This was considered a meaningful way to assess the proportion of patients who achieved complete prevention of attacks over the 24-week treatment period since the goal of LTPs is to reduce the burden of disease by preventing attacks.¹⁵ The primary and secondary endpoints included in OASIS-HAE comprehensively evaluate the clinical benefit of donidalorsen, in line with previously conducted trials assessing LTPs (see Section 2.3.1 of the CES for full details of trial endpoints); the company therefore does not consider the exclusion of ‘attack-free period’ and ‘time to first attack’ endpoints from OASIS-HAE to underestimate the clinical benefit of donidalorsen.

In addition, the attack-free period and time to first attack endpoints were not considered principal outcome measures in the economic analyses presented in the lanadelumab NICE appraisal (TA606) and berotralstat NICE appraisal (TA738). The exclusion of the attack-free period and time to first attack endpoints is also in line with the company’s response provided to the draft scope of this appraisal (ID6457).^{16,17}

In TA606, attack-free period data from HELP was presented but not used in the economic analysis.¹⁷ Time to first attack data from the HELP trial were used to estimate the proportion of patients who were attack-free on treatment with lanadelumab once every two weeks (Q2W) and eligible to transfer to lower frequency dosing of lanadelumab once every four weeks (Q4W).¹⁷ In comparison, the company estimated the switch from donidalorsen Q1M to donidalorsen Q2M using a post-hoc analysis. This analysis provided data of the proportion of patients who remained attack-free for [REDACTED] during OASIS-HAE (see

Section 3.5.1.3 for further details). This approach aligns with the anticipated marketing authorisation for donidalorsen and provides a suitable estimation of patients who would be eligible to transfer to less frequent dosing in clinical practice. The company therefore considers that excluding attack-free period and time to first attack from OASIS-HAE does not affect comparability to the lanadelumab NICE appraisal.

In TA738, both time to first attack and attack-free period were not measured or discussed in APeX-2.^{12,16} The company therefore considers that excluding these endpoints from OASIS-HAE does not affect comparability to the berotralstat NICE appraisal.

Overall, the primary and secondary endpoints assessed in OASIS-HAE sufficiently and comprehensively demonstrate the clinical benefit of donidalorsen. Furthermore, the limited use of attack-free period and time to first attack endpoints in prior NICE appraisals (lanadelumab in TA606 and berotralstat in TA738) means their exclusion has limited impact on the evaluation and comparability of this appraisal to the appraisals of comparator LTPs. The company therefore considers that excluding attack-free period and time to first attack from OASIS-HAE does not underestimate the clinical benefit of donidalorsen or affect comparability to prior NICE appraisals.

A3. Please elaborate on the company's reference to equality considerations regarding human plasma-derived products.

- Provide any evidence (market research, surveys, or registries) on the number of patients who may decline plasma-derived products for religious or ethical reasons.

The company's reference to equality considerations regarding human plasma-derived products is based on three key factors:

1. Religious and Ethical Concerns.

Certain religious groups may decline plasma-derived products, such as C1-INHs, based on their beliefs; religion is a protected characteristic under the Equality Act

2010.¹⁸ Donidalorsen would provide a treatment alternative to C1-INH which is not derived from human plasma.

2. Risk of Infection.

Plasma-derived therapies, such as C1-INHs, carry a theoretical risk of transmitting infections despite screening and viral inactivation processes. While manufacturing good practice reduces this risk, it may remain a consideration for some patients and clinicians.

Vaccination for hepatitis A and B should generally be considered for patients receiving regular or repeated administration of human plasma-derived products, including C1-INH.¹⁹

3. Risk of thromboembolic events.

Although rare, thromboembolic events have been reported in patients with underlying risk factors (e.g., implanted central venous catheters, oral contraceptive use), particularly with high doses and prolonged use of plasma-derived C1-INH.¹⁹

These considerations highlight the importance of non-plasma-derived alternatives, including donidalorsen, being available to ensure equality in access and patient choice.

Included studies (clinical effectiveness)

A4. [Priority Question]: Please provide a comprehensive list of all studies (including grey literature documents) excluded during the systematic literature review (SLR) process, including the reason for exclusion at both title/abstract and full-text screening stages.

A file containing a list of all excluded studies from the systematic literature review (SLR), at both title/abstract and full-text screening stages, is presented in the reference list of this document (Donidalorsen SLR full list of excluded studies, Otsuka, 2025).²⁰ A comprehensive list of all 6,455 identified studies (including grey literature) is provided in Sheet 1, studies excluded at title/abstract screening stage are listed in Sheet 2, and studies excluded at full-text screening stage are listed in Sheet 3.

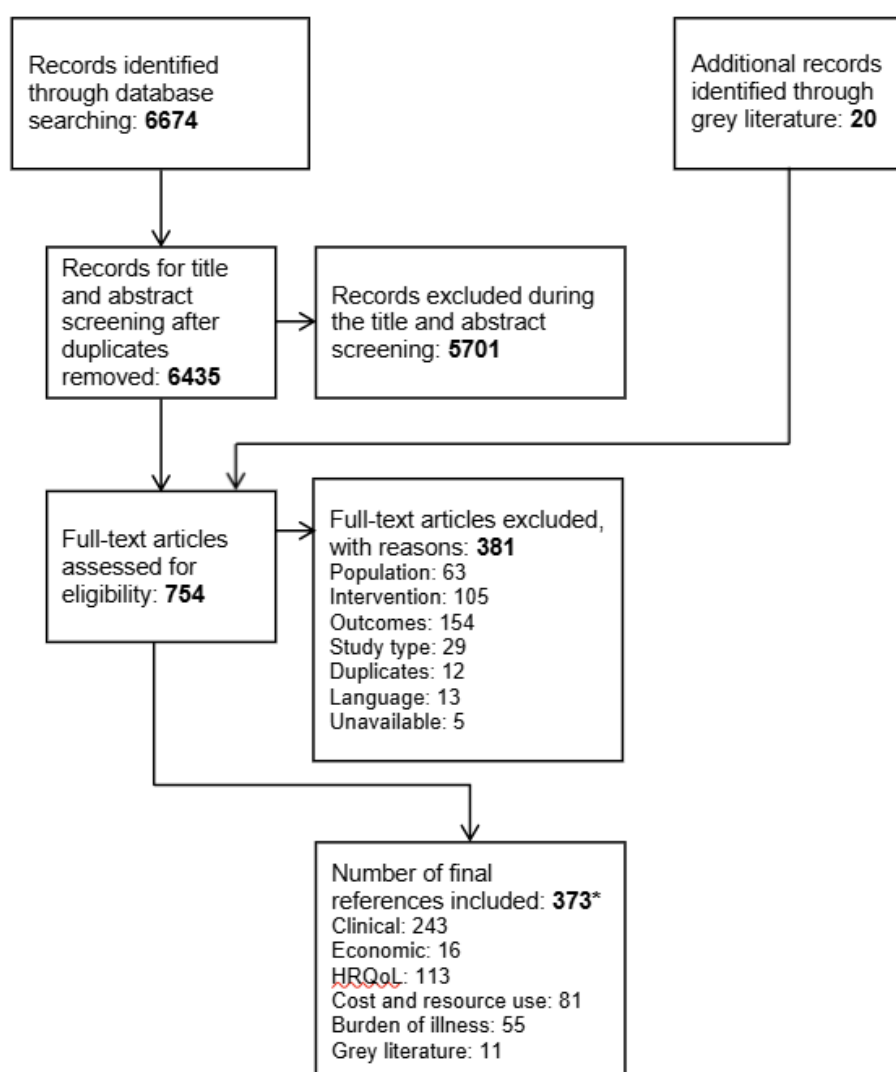
The company would like to highlight that the total number of studies excluded from the SLR, presented in the PRISMA diagram of the SLR report (1_CONFIDENTIAL_Otsuka_SLR_2025_doc.x), embedded in Appendix B, E, F and G of the CES and provided in the submission reference pack, does not align with the total number of excluded studies presented in the Excel file provided in response to this question and included in the reference pack of these clarification question responses.²⁰ This also explains the inconsistencies highlighted by the EAG in Question C3, which the company addresses further in the response to that question. The company would like to clarify that this misalignment in totals was a typographical error in the original PRISMA diagram of the number of excluded studies and does not impact the number of included studies in the SLR. We appreciate the EAG bringing this to the company's attention.

The original PRISMA diagram in the SLR report indicates that 734 studies were assessed at the full-text screening stage, and 361 of these were excluded; 63 did not meet the population criteria, 104 did not meet the intervention/comparator criteria, 141 did not meet the outcome criteria, 30 did not meet the study type criteria, 10 were duplicates, 11 were not in English, and two were unavailable. The updated PRISMA diagram (Figure 1) shows that 754 studies were assessed at the full-text screening stage; this now includes the 20 additional records identified through grey literature searches. At the full-text screening stage, 381 of the 754 studies were excluded; 63 still did not meet the population criteria, 105 did not meet the intervention/comparator criteria, 154 did not meet the outcome criteria, 29 did not meet the study type criteria, 12 were duplicates, 13 were not in English, and five were unavailable (not available online). Please see Figure 1 for the updated PRISMA diagram of evidence identified in the SLR, which aligns with both the Excel file referenced above, and the data extraction grid provided in response to Question C2.

In line with the updated PRISMA diagram presented in Figure 1, the database searches retrieved 6,674 references, of which 239 were duplicates, leaving 6,435 unique references for title/abstract screening. Of these, 5,701 references were excluded at the title/abstract screening stage. An additional 20 papers were found through grey literature searches, leaving 754 references (including the grey literature searches) to be assessed at the full-text screening stage. Of the 754 references

assessed, 381 were excluded at the full-text screening stage. Following the 381 exclusions at full-text screening stage, 373 references were included and considered for extraction. A total of 211 references were extracted as unique texts, while 162 were identified as linked publications to the 211 extracted texts, with no additional data to be extracted. As such, the 211 references are listed with a column titled 'Linked Publications' (column K), in which the remaining 162 references are stated, in the General Information sheet of the extraction grid provided in the reference list of this document.²¹

Figure 1: Updated SLR PRISMA diagram



*Of which n=120 were full texts and n=253 were abstracts. This is the total number of unique references, as some references are included in multiple research questions.

A5. Please provide the number and proportion of UK participants in OASIS-HAE, with baseline demographics, disease characteristics, and historical prophylaxis use.

There were [REDACTED] UK patients in the OASIS-HAE trial, with [REDACTED] patient in the placebo arm, [REDACTED] patient in the donidalorsen Q4W arm and [REDACTED] patients in the donidalorsen Q8W arm. UK patients make up a total of [REDACTED]% ([REDACTED]/90) of the patients included in the OASIS-HAE trial.

The baseline characteristics, disease characteristics and historical prophylaxis use for the UK participants in the OASIS-HAE trial are presented in Table 2, Table 3, and Table 4, respectively. Given the small sample size of UK patients in the OASIS-HAE

trial (1/90), it is not possible to provide a robust comparison to the OASIS-HAE intention-to-treat (ITT) population.

The baseline characteristics inputted into the economic model (mean age and proportion male) of the ITT population of the OASIS-HAE trial were presented to and validated by UK clinicals experts, who stated they were reflective of UK clinical practice.²²

Table 2: Baseline characteristics of the UK participants of the OASIS-HAE trial

Parameter	Placebo (N=1)	Donidalorsen 80 mg Q4W (N=1)	Donidalorsen 80 mg Q8W (N=3)
Age group (years), n (%)			
18 – 39			
40 – 64			
Sex, n (%)			
Male			
Female			
Race, n (%)			
Asian			
White			

Abbreviations: mg – milligram; N – number of patients in the analysis population; n – number of patients in the specific category; UK – United Kingdom

Source: Data on file. Post-hoc analysis of OASIS-HAE data²³

Table 3: Disease characteristics of the UK participants of the OASIS-HAE trial

Parameter	Placebo (N=1)	Donidalorsen 80 mg Q4W (N=1)	Donidalorsen 80 mg Q8W (N=3)
Type of HAE, n (%)			
Type I			
Type II			
Family history of HAE, n (%)			
Yes			
No			
Number of HAE attacks at Baseline, n (%)			
≥ 2 per 4-weeks			
≥ 8 per 4-weeks			
History of peripheral HAE attacks, n (%)			
Yes			
No			
History of abdominal HAE attacks, n (%)			
Yes			
No			
History of laryngeal HAE attacks, n (%)			
Yes			
No			

Abbreviations: HAE – Hereditary angioedema; mg – milligram; N – number of patients in the analysis population; n – number of patients in the specific category; UK – United Kingdom
Data on file. Post-hoc analysis of OASIS-HAE data²³

Table 4: Historical prophylaxis use of the UK participants of the OASIS-HAE trial

Parameter	Placebo (N=1)	Donidalorsen 80 mg Q4W (N=1)	Donidalorsen 80 mg Q8W (N=3)
Lanadelumab, n (%)			
Yes			
No			
Berotrastat, n (%)			
Yes			
No			
C1-INH, n (%)			
Yes			
No			

Abbreviations: C1-INH – C1-esterase inhibitor; mg – milligram; N – number of patients in the analysis population; n – number of patients in the specific category; UK – United Kingdom
Data on file. Post-hoc analysis of OASIS-HAE data²³

A6. [Priority Question]: Baseline prophylaxis use differed between arms (13% Once every four weeks (Q4W), 23% placebo). Please provide details on washout duration for patients previously treated with lanadelumab, berotrastat, or C1-INH; whether

attack frequency rebounded post-withdrawal; and whether prior long term prophylaxis (LTP) use was balanced and adjusted for in analyses?

In OASIS-HAE, the washout duration for patients previously treated with lanadelumab, berotralstat or C1-INH is defined in the exclusion criteria of the trial population.⁶ Patients were excluded from enrolling in the study if they had exposure to lanadelumab, berotralstat, or C1-INH (Cinryze/Berinert) within 10, 3, or 2 weeks prior to the beginning of the screening period (of up to 56 days), respectively.⁶ The washout duration for patients previously treated with LTPs was therefore 10 weeks for lanadelumab, 3 weeks for berotralstat, and 2 weeks for C1-INH, prior to screening.

Mean HAE attack rates were not measured post-withdrawal of previous prophylactics in patients who had been receiving other LTPs prior to the OASIS-HAE screening period. Consequently, these data cannot be used to determine whether attack frequency rebounded immediately after prior LTP withdrawal. However, subgroup data from OASIS-HAE, presented in Table 5, can be used to interpret the effect of prior LTP use on the mean HAE attack rates experienced by placebo- and donidalorsen-treated patients during the run-in period.⁶

As shown in Table 5, the distribution of patients who received prior prophylactic therapy before enrolment to OASIS-HAE was balanced across the trial treatment arms, with [REDACTED] patients in the pooled placebo group, [REDACTED] patients in the donidalorsen Q8W group and [REDACTED] patients in the donidalorsen Q4W arm.⁶ No formal statistical analysis was performed to determine the effect of prior LTP use on the outcomes of patients in the OASIS-HAE trial.

The mean HAE attack rates (per 4 weeks) during the run-in period were [REDACTED], [REDACTED], and [REDACTED] for the placebo, donidalorsen Q4W, and donidalorsen Q8W groups, respectively, with prior LTP use.⁶ In comparison, the mean HAE attack rates (per 4 weeks) during the run-in period were [REDACTED], [REDACTED], and [REDACTED] for the placebo, donidalorsen Q4W, and donidalorsen Q8W groups, respectively, without prior LTP use.⁶ There is no clear trend between the prior and no prior LTP exposure subgroups and no evidence of a consistently higher run-in attack rate for patients who received prior LTPs. Therefore, there is no evidence to support that prior LTP exposure resulted in a rebound of attack rates due to withdrawal of prior LTPs.

Furthermore, the data presented in Table 5 clearly demonstrate that the attack rate for patients receiving either donidalorsen Q4W or donidalorsen Q8W reduces substantially upon initiation of study drug compared to the run-in period, whereas the attack rate for the pooled placebo arm remains relatively high. The trend of HAE attacks for placebo, donidalorsen Q4W and donidalorsen Q8W are similar in both the prior and no prior LTP exposure subgroups. The consistency of results between patients with prior and no prior LTP exposure supports that the trial exclusion criteria for patients treated with prior LTPs were sufficient to ensure that prior LTP exposure did not impact the observed attack rates for patients in either subgroup, whether receiving placebo or donidalorsen.

Table 5: Summary of time-adjusted investigator-confirmed HAE attacks during screening and treatment period, depending on prior predefined prophylactic use

	Received any predefined prophylactic therapy, including lanadelumab, berotralstat or C1-INH					
	Yes			No		
Mean HAE attack rate (SD)	Pooled Placebo (■)	Donidalorse n Q4W (■)	Donidalorse n Q8W (■)	Pooled Placebo (■)	Donidalorse n Q4W (■)	Donidalorse n Q8W (■)
Run-in	■	■	■	■	■	■
Week 1-5	■	■	■	■	■	■
Week 1-25	■	■	■	■	■	■
Week 5-25	■	■	■	■	■	■

Abbreviations: C1-INH – C1-esterase inhibitor; SD – Standard deviation.

Source: OASIS-HAE CSR⁶

In addition, the results from the OASISplus switch cohort demonstrate that treatment with donidalorsen after withdrawal from prior LTPs leads to improved outcomes for patients, with further reductions in mean HAE attack rates for patients previously treated with lanadelumab, berotralstat and C1-INH.²⁴

As detailed in Section 2.6.3.2 of the CES, patients in the OASISplus switch cohort experienced a mean reduction in HAE attack rate from baseline of 62% after 16 weeks of treatment with donidalorsen Q4W after switching from a prior LTP.²⁵ Patients were enrolled into the OASISplus switch cohort following washout periods as per the open-label extension (OLE) trial protocol. The washout period for each prior LTP differs per treatment and is dependent on their respective half-lives. Given the relatively long half-life of lanadelumab, donidalorsen dosing was initiated at the end of lanadelumab dosing interval. Berotralstat and C1-esterase inhibitor were

administered concurrently with donidalorsen for 14 days given their short half-life to prevent any loss of efficacy.²⁴ Therefore, the switching protocol in the OASISplus switch cohort was as follows: the last dose of lanadelumab was administered 14 ± 3 days before the first dose of donidalorsen; patients continued taking berotralstat for 14 ± 3 days after the first dose of donidalorsen; patients continued taking C1-INHs for 14 ± 3 days after the first dose of donidalorsen.²⁴ The switch period for each LTP was designed based on the half-life of each drug (lanadelumab ~14 days, C1-INH and berotralstat ~3-4 days), with the goal of minimising HAE attacks while switching. In the OASISplus switch cohort, HAE attack rate decreased by 65%, 73%, and 41% for patients switching from lanadelumab, berotralstat, and C1-INH, respectively, after switching to donidalorsen.²⁵ These results demonstrate that patients can achieve and sustain reduced attack rates when switching from prior LTPs to donidalorsen, and demonstrate the potential for patients to have improved long-term outcomes when switching from prior LTPs to donidalorsen.

To conclude, the washout period for prior LTPs was defined by the exclusion criteria of OASIS-HAE; patients were excluded from enrolling in the study if they had exposure to lanadelumab, berotralstat, or C1-INH (Cinryze/Berinert) within 10, 3, or 2 weeks prior to the beginning of the screening period (of up to 56 days), respectively. While analyses were not adjusted for the use of prior LTPs, the distribution of patients who had received prior LTPs was balanced across the placebo, donidalorsen Q4W, and donidalorsen Q8W trial arms. There is no evidence to support that prior LTP exposure resulted in a rebound of attack rates due to withdrawal of prior LTPs. The attack rate data from OASIS-HAE demonstrates that irrespective of prior LTP exposure, donidalorsen substantially reduces attack rates relative to placebo. Additionally, data from the OASISplus switch cohort demonstrate that treatment with donidalorsen following withdrawal from prior LTPs leads to improved patient outcomes; patients can maintain reduced attack rates while switching from prior LTPs to donidalorsen.²⁵

A7. [Priority Question]: Please justify the adequacy of a 24-week duration for assessing long-term prophylactic efficacy and safety. Provide any available or

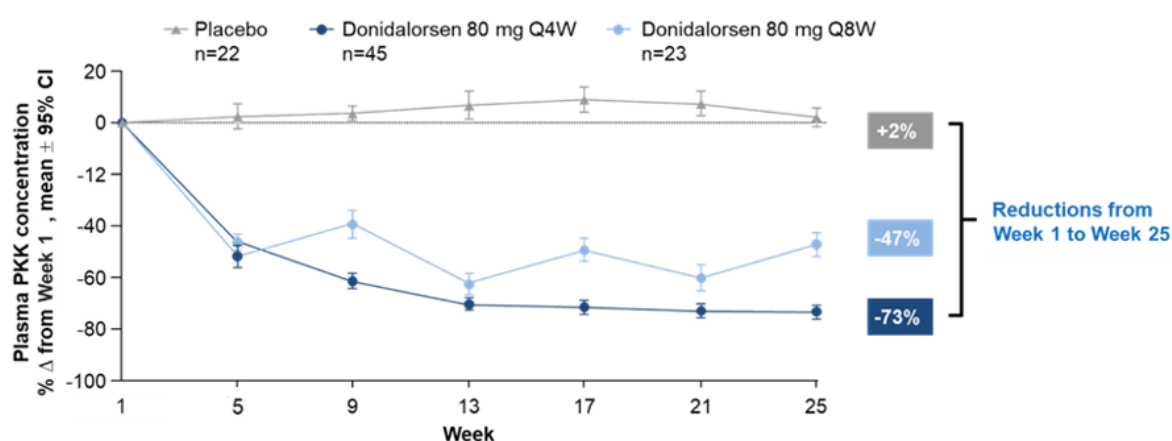
emerging data from OASISplus beyond Week 52 and discuss consistency with short-term results.

OASIS-HAE was conducted to evaluate the clinical safety and efficacy of donidalorsen in patients with HAE. The study consisted of a 24-week treatment period after which patients could complete an up to 13-week post-treatment period or could enrol in the OLE arm of the OASISplus study (OASISplus OLE cohort).⁹ The 24-week treatment period is consistent with other phase III randomised, controlled trials (RCTs) for LTPs, all of which evaluate the safety and efficacy of LTP over approximately six months (24 – 26 weeks): CHANGE (C1-INH) – 24 weeks; HELP (lanadelumab) – 26 weeks; APeX-2 (berotralstat) – 24 weeks; and VANGUARD (garadacimab) – 26 weeks.^{5,11–13} The six month treatment duration ensures patient adherence and trial feasibility, allows multiple dosing cycles for the Q4W and Q8W dosing regimens, and provides sufficient time to capture seasonal or stress-related triggers of HAE attacks.

Donidalorsen is a first-in-class, RNA-targeted plasma kallikrein (PKK) inhibitor.⁹ The clinical effect of donidalorsen is mediated through a reduction in plasma PKK concentrations, a key precursor in the kallikrein–kinin cascade.^{9,26} This prevents the production of bradykinin, a mediator that causes vasodilation and increases vascular permeability, leading to angioedema.²⁷ A stable reduction in PKK levels is a key marker of efficacy, demonstrating that the treatment has reached a steady state.^{9,28} Figure 2 presents the mean percentage change from Week 1 to Week 25 in PKK concentrations for placebo, donidalorsen 80 mg Q4W, and donidalorsen 80 mg Q8W in OASIS-HAE.⁹ By Week 5, donidalorsen decreased PKK concentrations from Week 1 by 46% in the Q4W dosing cohort and 52% in the Q8W dosing cohort, while an increase by 2% was observed in the placebo cohort.⁹ As shown in Figure 2, both donidalorsen Q4W and donidalorsen Q8W dosing regimens maintained the reduction in PKK concentrations observed from Week 1 to Week 5 through to Week 25, with reductions of 73% (95% CI: 68%, 78%) in donidalorsen Q4W and 47% (95% CI: 38%, 56%) in donidalorsen Q8W cohorts.⁹ An exposure-response analysis was conducted to further characterise the relationship between PKK concentrations and HAE attack rates following treatment with donidalorsen and to predict the efficacy of potential dosing regimens;²⁸ the average effective PKK concentrations leading to a 90% reduction in HAE attack rate was estimated to be 47.1 mg/L, corresponding to

an approximate 62% reduction in per 4-week average PKK concentrations from baseline.²⁹ The reduction in PKK concentration of 73% observed in the donidalorsen Q4W arm is above this 62% threshold, demonstrating that within the 24 week treatment period the PKK concentration reduced to a level that leads to 90% reduction from the maximum attack rate.^{9,29} As presented in Section 2.6 (Table 9 and Table 10) of the CES, donidalorsen demonstrated a significant reduction in HAE attack rates from Week 1 to Week 25 in patients treated with donidalorsen Q4W and Q8W compared with placebo, with reductions of 81% ($p<0.001$) and 55% ($p<0.004$), respectively.⁹ These results demonstrate that within the 24-week trial period, donidalorsen effectively reduced and stabilised plasma PKK levels, resulting in a significant reduction in HAE attacks compared to placebo. Therefore, the 24-week treatment period of OASIS-HAE was sufficient to demonstrate the clinical efficacy of donidalorsen as an LTP.

Figure 2: Mean ($\pm 95\%$ CI) percentage change from Week 1 in prekallikrein concentrations



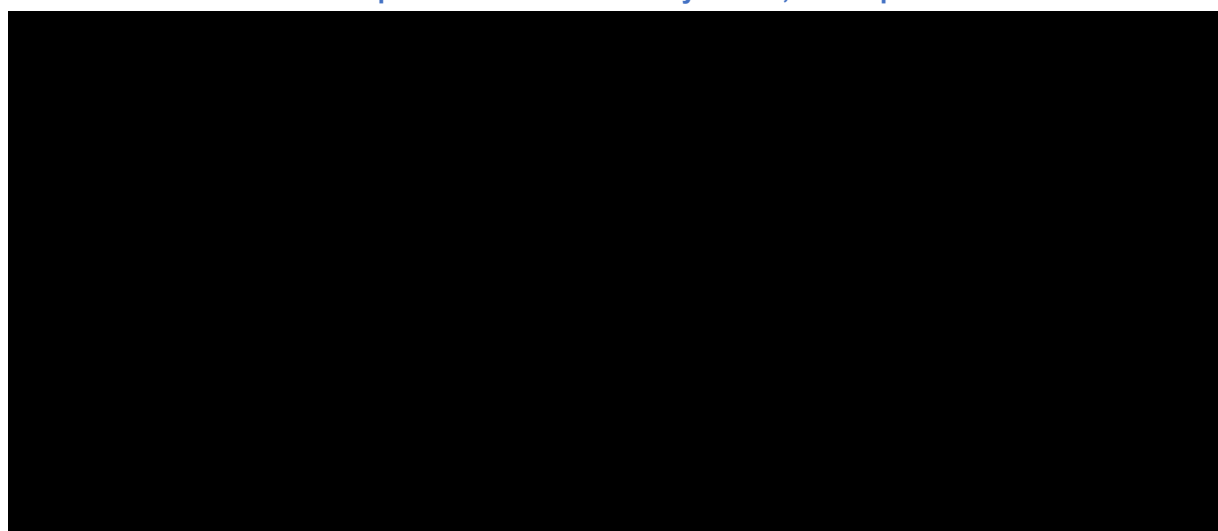
Abbreviations: CI – Confidence interval; PKK – Prekallikrein; Q4W – Once every four weeks; Q8W – Once every eight weeks

Source: Riedl et al. 2024⁹

To evaluate the long-term efficacy and safety of donidalorsen, 83 patients were enrolled into the OASISplus OLE cohort after completion of the OASIS-HAE trial at Week 25.³⁰ Data from OASISplus OLE cohort up to Week 53 are presented in Section 2.6.3.1 of the CES. Interim data up to Week 113, from the January 27, 2025 data cut-off, is available and presented below. The latest available data from the OASISplus OLE cohort show that a low attack rate was maintained throughout the study period up to Week 113 in both donidalorsen Q4W and donidalorsen Q8W groups.³¹ At Week 53 of OASISplus, a mean reduction in HAE attack rate from Week

1 of [REDACTED] for donidalorsen Q4W and [REDACTED] for donidalorsen Q8W was observed. As shown in Figure 3, patient numbers were below 10 in each arm of the OASISplus OLE cohort after Week 89; the small sample size beyond this timepoint results in 'spikes' in HAE attack rates and large error bars at Week 93 to Week 97 and Week 97 to Week 101 in the placebo and donidalorsen Q8W arm, respectively, when there were only 2 patients in each cohort at that time. Therefore, Week 89 was selected as the latest suitable timepoint to represent the reduction in HAE attacks observed in the study. At Week 89 of OASISplus, a mean reduction in HAE attack rate from Week 1 of [REDACTED] was observed for patients who had received donidalorsen Q4W and donidalorsen Q8W in OASIS-HAE.³¹ At Week 89 of OASISplus, a mean reduction in HAE attack rate from Week 1 of [REDACTED] was observed for patients who had received placebo in OASIS-HAE; these patients all switched from placebo in OASIS-HAE to receive donidalorsen Q4W upon enrolment into the OASISplus OLE cohort.³¹ Data from the OASISplus OLE cohort beyond Week 53 were consistent with the results from OASIS-HAE, demonstrating that donidalorsen further reduces HAE attack rates in long-term treatment and that the 24-week treatment period of OASIS-HAE was sufficient to evaluate and demonstrate the efficacy of donidalorsen.³¹

Figure 3: Percentage change from OASIS-HAE Baseline (+/-SEM) in the mean rate of Investigator-confirmed HAE Attacks by Every-4-Week (Integrated Treatment Period DY1*) from OASIS-HAE Week 1 to OASISplus Week 113 Full Analysis Set, OASISplus OLE cohort



Abbreviations: HAE – Hereditary angioedema; mg – Milligram; OLE – Open-label extension; Q4W – Once every four weeks; Q8W – Once every eight weeks; SEM – Standard error of the mean

*The Integrated Treatment Period DY1 is defined as from the first dose of donidalorsen administered in OASIS-HAE to 28 days after the last dose of donidalorsen in OASIS-HAE OLE for patients who are dosed every 4 weeks, or 56 days after the last dose of donidalorsen for patients who are dosed every 8 weeks, or last date of lost to follow-up, whichever happens first.

Source: Data on file. OASISplus One-Year Analysis³¹

As presented in Section 2.11, Table 25 of the CES, donidalorsen demonstrated a favourable safety profile in OASIS-HAE, with an absence of serious AEs and discontinuations related to the study drug over the course of the study.³² Interim safety data (data cut-off January 27, 2025) from the OASISplus OLE cohort were also consistent with OASIS-HAE, demonstrating donidalorsen is well-tolerated in long-term treatment.^{31,32} As shown in Table 6, there were [REDACTED] in the OASISplus OLE cohort who reported serious treatment-emergent adverse events (TEAEs) related to study drug up to the latest data cut-off.³¹ The consistency between the safety profiles for donidalorsen in OASIS-HAE and the OASISplus OLE cohort demonstrate that the 24-week treatment period duration in OASIS-HAE was sufficient to evaluate the safety of donidalorsen as an LTP.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]³³ [REDACTED]

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[REDACTED]

[REDACTED]

Table 6: Overview of adverse events, Safety set, OASISplus OLE cohort (data cut-off January 27, 2025)

Parameter	Donidalorsen 80 mg Q4W (N=69)	Donidalorsen 80 mg Q8W (N=14)
Patients with any TEAE n (%)	██████████	██████████
Patients with any TEAE by maximum severity		
Mild, n (%)	██████████	██████████
Moderate, n (%)	██████████	██████████
Severe, n (%)	██████████	██████████
Patients with any TEAE related to study drug n (%)	██████████	██████████
Patients with any TEAE related to study drug by maximum severity		
Mild, n (%)	██████████	██████████
Moderate, n (%)	██████████	█
Severe, n (%)	█	█
Patients with any serious TEAE, n (%)	██████████	█
Patients with any serious TEAE related to study drug, n (%)	█	█

Abbreviations: N – number of patients in the analysis population; n – number of patients in the specific category; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks; TEAE – Treatment-emergent adverse event.
Source: Data on file. OASISplus One-Year Analysis³¹

To conclude, the efficacy and safety outcomes of donidalorsen observed in the OASISplus OLE cohort are consistent with OASIS-HAE, demonstrating the long-term efficacy and tolerability of donidalorsen. These results demonstrate that the 24-week treatment period duration of OASIS-HAE was sufficient to evaluate the efficacy and safety of donidalorsen in an RCT.

A8. [Priority Question]: Please describe the operational definition and process for “investigator-confirmed” HAE attacks, including timing of confirmation (real-time vs retrospective), data source (patient diary, e-diary, telephone), and inter-rater reliability procedures.

During the OASIS-HAE study, the Investigator was required to confirm each attack reported by the patients.¹⁰ An Investigator-confirmed HAE attack was defined as an event with signs or symptoms consistent with an attack in at least one of the following locations: abdomen, periphery, or larynx. A discrete attack was counted if there was at least a 24-hour symptom-free period between attacks.

Patients were instructed to report details of any HAE attack using the Angioedema Activity Score (AAS) questionnaire on an ongoing basis and to contact the study site

within 72 hours of the onset of an attack.¹⁰ The AAS questionnaire was administered daily to the patient electronically using a YPrime handheld device.⁶

Throughout the screening, treatment, and post-treatment periods, contract research organisation site personnel contacted the patient approximately weekly to inquire about any attack that may have occurred.¹⁰ HAE attack details, including localisation, severity, and course were collected.¹⁰ The study site collected the attack details either in person (during a routine study visit) or on the phone, and the attacks were entered in the electronic data capture system (EDC) by the site personnel using source documentation. During study visits, site personnel inquired about any new HAE attack information that was not provided through patient contact with the site.¹⁰

The site personnel source-verified the details for all the attacks entered in the HAE attack case report form (CRF) within the EDC and ensured all collected attack information was entered into the EDC using the source documentation available at the site.¹⁰ The following data quality assurance measures were followed in the trial (as detailed in Section 9.6 of the OASIS-HAE protocol [included in the reference list of this document]):¹⁰

- Selection of qualified investigators and appropriate study centres
- Review of protocol procedures with study site personnel at individual site initiation visits
- Training of study staff on the EDC system and study requirements for data entry
- Internal data review procedures to ensure the accuracy, completeness, and verifiability of source data
- Routine monitoring of the study sites by the Sponsor or designee with 100% source data verification
- Study specific procedures manual and pharmacy manual provided to the study sites and reviewed with study personnel

- Direct entry of data into the clinical study database by the study staff via the EDC system and verification for accuracy by the Sponsor or designee
- Sponsor review of all completed CRFs for accuracy, completeness, and adherence to the protocol
- Resolution of any discrepancies in the data or questions regarding the data with the Investigator or designee and subsequent source verification
- Use of central laboratories in order to enhance data quality

A9. [Priority Question]: Please provide updated longer-term hepatic safety data from OASISplus, including incidence, severity, and resolution of ALT/AST abnormalities, through the latest data cut.

There has been no notable and clinically meaningful change in abnormal liver function TEAEs with a longer duration of exposure to donidalorsen.³³

[REDACTED]

[REDACTED]

[REDACTED]³² [REDACTED]

[REDACTED]

[REDACTED]^{32,37,38} [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]³³ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]³³

[REDACTED]

[REDACTED]

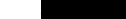
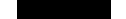
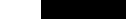
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Parameter	Donidalorsen 80 mg Q4W (N=69)	Donidalorsen 80 mg Q8W (N=14)
Alanine aminotransferase		
> 3 × ULN*, confirmed		
> 3 × ULN*, confirmed and total bilirubin > 1.5 × ULN		
> 5 × ULN, confirmed		
> 5 × ULN, confirmed and persistent for ≥ 2 weeks		
> 8 × ULN, confirmed		
Aspartate aminotransferase		

Parameter	Donidalorsen 80 mg Q4W (N=69)	Donidalorsen 80 mg Q8W (N=14)
> 3 × ULN, confirmed	■	■
> 3 × ULN, confirmed and total bilirubin > 1.5 × ULN	■	■
> 5 × ULN, confirmed	■	■
> 5 × ULN, confirmed and persistent for ≥ 2 weeks	■	■
> 8 × ULN, confirmed	■	■

*ALT or AST > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN).
Abbreviations: OLE – Open-label Extension, Q4W – every 4 weeks, Q8W – every 8 weeks; ULN – Upper limit of Normal.

Source: Data on file. OASISplus One-Year Analysis³¹

Table 8: Summary of patients with incidence of observed abnormality for liver function tests, OASISplus switch cohort, Safety Set (data cut-off January 27, 2025)

Parameter	Prior LTP		
	Lanadelumab (N=31)	Berotrastat (N=14)	C1-INH (N=22)
Alanine aminotransferase			
> 3 × ULN*, confirmed	■	■	■
> 3 × ULN*, confirmed and total bilirubin > 1.5 × ULN	■	■	■
> 5 × ULN, confirmed	■	■	■
> 5 × ULN, confirmed and persistent for ≥ 2 weeks	■	■	■
> 8 × ULN, confirmed	■	■	■
Aspartate aminotransferase			
> 3 × ULN*, confirmed	■	■	■
> 3 × ULN*, confirmed and total bilirubin > 1.5 × ULN	■	■	■
> 5 × ULN, confirmed	■	■	■
> 5 × ULN, confirmed and persistent for ≥ 2 weeks	■	■	■
> 8 × ULN, confirmed	■	■	■

*ALT or AST > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN).
Abbreviations: OLE – Open-label Extension; LTP – Long-term prophylaxis; Q4W – every 4 weeks, Q8W – every 8 weeks; ULN – Upper Limit of Normal.

Source: Data on file. OASISplus One-Year Analysis³¹

Table 9: Overview of hepatic safety adverse events, OASISplus OLE cohort, Safety Set (data cut-off January 27, 2025)

Parameter	Donidalorsen 80 mg Q4W (N=69)	Donidalorsen 80 mg Q8W (N=14)
Alanine aminotransferase increased		

Parameter	Donidalorsen 80 mg Q4W (N=69)	Donidalorsen 80 mg Q8W (N=14)
Patients with any TEAE n (%)		
Patients with any TEAE by maximum severity		
Mild, n (%)		
Moderate, n (%)		
Severe, n (%)		
Patients with any TEAE related to study drug n (%)		
Patients with any TEAE related to study drug by maximum severity		
Mild, n (%)		
Moderate, n (%)		
Severe, n (%)		
Patients with any serious TEAE, n (%)		
Patients with any serious TEAE related to study drug, n (%)		
Aspartate aminotransferase increased		
Patients with any TEAE n (%)		
Patients with any TEAE by maximum severity		
Mild, n (%)		
Moderate, n (%)		
Severe, n (%)		
Patients with any TEAE related to study drug n (%)		
Patients with any TEAE related to study drug by maximum severity		
Mild, n (%)		
Moderate, n (%)		
Severe, n (%)		
Patients with any serious TEAE, n (%)		
Patients with any serious TEAE related to study drug, n (%)		
Gamma-glutamyltransferase increased		
Patients with any TEAE n (%)		
Patients with any TEAE by maximum severity		
Mild, n (%)		
Moderate, n (%)		
Severe, n (%)		
Patients with any TEAE related to study drug n (%)		
Patients with any TEAE related to study drug by maximum severity		
Mild, n (%)		
Moderate, n (%)		
Severe, n (%)		
Patients with any serious		

Parameter	Donidalorsen 80 mg Q4W (N=69)	Donidalorsen 80 mg Q8W (N=14)
TEAE, n (%)		
Patients with any serious TEAE related to study drug, n (%)	■	■
Hepatic enzyme increased		
Patients with any TEAE n (%)	■	■
Patients with any TEAE by maximum severity		
Mild, n (%)	■	■
Moderate, n (%)	■	■
Severe, n (%)	■	■
Patients with any TEAE related to study drug n (%)	■	■
Patients with any TEAE related to study drug by maximum severity		
Mild, n (%)	■	■
Moderate, n (%)	■	■
Severe, n (%)	■	■
Patients with any serious TEAE, n (%)	■	■
Patients with any serious TEAE related to study drug, n (%)	■	■
Blood bilirubin decreased		
Patients with any TEAE n (%)	■	■
Patients with any TEAE by maximum severity		
Mild, n (%)	■	■
Moderate, n (%)	■	■
Severe, n (%)	■	■
Patients with any TEAE related to study drug n (%)	■	■
Patients with any TEAE related to study drug by maximum severity		
Mild, n (%)	■	■
Moderate, n (%)	■	■
Severe, n (%)	■	■
Patients with any serious TEAE, n (%)	■	■
Patients with any serious TEAE related to study drug, n (%)	■	■
Blood bilirubin increased		
Patients with any TEAE n (%)	■	■
Patients with any TEAE by maximum severity		
Mild, n (%)	■	■
Moderate, n (%)	■	■
Severe, n (%)	■	■
Patients with any TEAE related to study drug n (%)	■	■
Patients with any TEAE related to study drug by maximum severity		

Parameter	Donidalorsen 80 mg Q4W (N=69)	Donidalorsen 80 mg Q8W (N=14)
Mild, n (%)	■	■
Moderate, n (%)	■	■
Severe, n (%)	■	■
Patients with any serious TEAE, n (%)	■	■
Patients with any serious TEAE related to study drug, n (%)	■	■
Hepatic steatosis		
Patients with any TEAE n (%)	■	■
Patients with any TEAE by maximum severity		
Mild, n (%)	■	■
Moderate, n (%)	■	■
Severe, n (%)	■	■
Patients with any TEAE related to study drug n (%)	■	■
Patients with any serious TEAE, n (%)	■	■
Patients with any serious TEAE related to study drug, n (%)	■	■

Abbreviations: ALT – Alanine transaminase; AST – aspartate aminotransferase; N – number of patients in the analysis population; n – number of patients in the specific category; NR – Not reported; OLE – Open label extension; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks; TEAE – Treatment-emergent adverse event.

Source: Data on file. OASISplus One-Year Analysis³¹

Table 10: Overview of hepatic safety adverse events, OASISplus switch cohort, Safety Set, (data cut-off January 27, 2025)

	Prior LTP		
Parameter	Lanadelumab (N=31)	Berotrastat (N=11)	C1-INH (N=22)
Alanine aminotransferase increased			
Patients with any TEAE n (%)	■	■	■
Patients with any TEAE by maximum severity			
Mild, n (%)	■	■	■
Moderate, n (%)	■	■	■
Severe, n (%)	■	■	■
Patients with any TEAE related to study drug n (%)	■	■	■
Patients with any serious TEAE related to study drug, n (%)	■	■	■
Aspartate aminotransferase increased			
Patients with any TEAE n (%)	■	■	■

	Prior LTP		
Parameter	Lanadelumab (N=31)	Berotrastat (N=11)	C1-INH (N=22)
Patients with any TEAE by maximum severity			
Mild, n (%)			
Moderate, n (%)			
Severe, n (%)			
Patients with any TEAE related to study drug n (%)			
Patients with any serious TEAE, n (%)			
Patients with any serious TEAE related to study drug, n (%)			
Hepatic enzyme increased			
Patients with any TEAE n (%)			
Patients with any TEAE by maximum severity			
Mild, n (%)			
Moderate, n (%)			
Severe, n (%)			
Patients with any TEAE related to study drug n (%)			
Patients with any TEAE related to study drug by maximum severity			
Mild, n (%)			
Moderate, n (%)			
Severe, n (%)			
Patients with any serious TEAE, n (%)			
Patients with any serious TEAE related to study drug, n (%)			
Gamma-glutamyltransferase increased			
Patients with any TEAE n (%)			
Patients with any TEAE by maximum severity			
Mild, n (%)			
Moderate, n (%)			
Severe, n (%)			
Patients with any TEAE related to study drug n (%)			
Patients with any serious TEAE related to study drug, n (%)			
Steatohepatitis			
Patients with any TEAE n (%)			

A10. [Priority Question]: Please provide cumulative discontinuation data from OASISplus (to the latest data cut), specifying total discontinuations and reasons (AEs, lack of efficacy, withdrawal by patient, loss to follow-up).

Please find the requested, latest available discontinuation data from OASISplus (data cut-off 27 January 2025) presented in Table 11 (OASISplus OLE cohort) and Table 12 (OASISplus switch cohort) below.³¹

In the OASISplus OLE cohort, over █ of patients (█) treated with donidalorsen completed one year of treatment.³¹ Overall, █ patients (█%) discontinued the study early with the primary reason for discontinuation being patient withdrawal (█). A small number of patients discontinued due to AEs (█), and █ discontinued due to lack of efficacy.³¹

Similarly, in the OASISplus switch cohort, over █ of patients (█) treated with donidalorsen completed one year of treatment.³¹ Overall, █ patients discontinued (█%) with primary reasons for discontinuation rates being patient withdrawal (█) or lack of efficacy (█). Only █ discontinued due to AEs.³¹

Table 11: Patient disposition, OASISplus OLE cohort (data cut-off 27 January 2025)

	Donidalorsen 80 mg Q4W (N=69)	Donidalorsen 80 mg Q8W (N=14)	Total (N=83)
Patients who completed one-year study treatment, n (%)	█	█	█
Early termination, n (%)	█	█	█
Reason for early termination			
Withdrawal by subject	█	█	█
Adverse event	█	█	█
Pregnancy	█	█	█
Patients who completed the post-treatment follow-up	█	█	█
Patients who terminated the post-treatment follow-up early, n (%)	█	█	█
Reason for early termination from post-treatment follow up			
Withdrawal by subject	█	█	█
Adverse event	█	█	█

Abbreviations: N – number of patients in the analysis population; n – number of patients in the specific category; OLE – open label extension; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.
Source: Data on file. OASISplus One-Year Analysis³¹

Table 12: Patient disposition, OASISplus switch cohort (data cut-off 27 January 2025)

	Prior LTP			
	Lanadelumab (N=31)	Berotrastat (N=14)	C1-INH (N=22)	Total (N=65)
Patients who completed one-year study treatment, n (%)	██████	██████	██████	██████
Early termination, n (%)	██████	█	██████	██████
Reason for early termination				
Lack of efficacy	██████	█	██████	██████
Withdrawal by subject	██████	█	██████	██████
Adverse event	██████	█	█	██████
Lost to follow-up	██████	█	█	██████
Pregnancy	██████	█	█	██████
Other	██████	█	█	██████
Patients who completed the post-treatment follow-up	██████	█	██████	██████
Patients who terminated the post-treatment follow-up early, n (%)	██████	█	██████	██████
Reason for early termination from post-treatment follow up				
Withdrawal by subject	██████	█	██████	██████
Lost to follow-up	██████	█	█	██████
Other	██████	█	█	██████

Abbreviations: C1-INH – C1-esterase inhibitor; LTP – Long-term prophylaxis; N – number of patients in the analysis population; n – number of patients in the specific category.
Source: Data on file. OASISplus One-Year Analysis³¹

A11. [Priority Question]: Please provide full OASISplus data on the proportion of patients achieving and maintaining Q2M (Once every 2 months) dosing (≥ 6 , 12, 18, 24 months), relapse rates, and criteria for re-escalation.

In the ongoing OASISplus trial, patients are treated with donidalorsen 80 mg for an initial 52-week treatment period, with an extended treatment period up to 157 weeks

in total.⁴⁰ Patients in the OASISplus OLE cohort received either donidalorsen Q4W or donidalorsen Q8W, while all patients in the OASISplus switch cohort initiated treatment with donidalorsen Q4W (please see Section 2.3.2 of the CES for further details).^{30,41} As detailed in the response to Question C1, the company does not anticipate there to be a difference in efficacy outcomes for patients treated with donidalorsen Q1M compared to those treated with donidalorsen Q4W, and donidalorsen Q8W compared to donidalorsen Q2M.

In the OASISplus extended treatment period, patients continue to receive donidalorsen as per their prior dosing schedule (Q4W or Q8W) in the initial 52-week treatment period of OASISplus.⁴⁰ Patients who received donidalorsen Q8W may have their dosing frequency adjusted at any time to donidalorsen Q4W as determined by clinical symptoms (per Investigator).⁴⁰ Patients who received donidalorsen Q4W may have their dosing frequency adjusted at any time to donidalorsen Q8W.⁴⁰ There was no prespecified criteria for re-escalation of dosing in the trial. The trial dose adjustment criteria do not reflect the anticipated dosing transfer for patients in clinical practice. The anticipated market authorisation states that the “ [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]”.⁴²

The following clinical data for patients transferring from donidalorsen Q4W to Q8W support that efficacy is maintained following dose transfer; it is unlikely that patients on the Q2M dose in clinical practice will be required to revert dose. In the phase III OASISplus study, as of the cut-off date 27 January 2025, [REDACTED] patients transferred from donidalorsen Q4W to donidalorsen Q8W after Week 53.⁴³

- [REDACTED] OASISplus OLE cohort patients
 - [REDACTED] in the phase III RCT
 - [REDACTED] in the phase III RCT
- [REDACTED] OASISplus switch cohort patients

[REDACTED]

- [REDACTED]

The duration of time on donidalorsen Q8W ranged from [REDACTED]

[REDACTED]

[REDACTED] across the three OASISplus switch cohort patients.⁴³ Of the [REDACTED] patients who changed dosing regimen, [REDACTED] did not have an Investigator-confirmed HAE attack after changing to donidalorsen Q8W; the attack rates and time on treatment for each dose is presented for these [REDACTED] patients in Table 13.⁴³ This data demonstrates that patients are able to transfer from donidalorsen Q4W to donidalorsen Q8W and maintain treatment on the donidalorsen Q8W regimen with a sustained reduction in HAE attack rates.

To conclude, in the extended treatment period of OASISplus, patients may have their dosing frequency adjusted at any time from donidalorsen Q4W to donidalorsen Q8W, and vice versa.⁴⁰ There was no prespecified criteria for re-escalation of dosing in the trial. In clinical practice, patients may be considered to transfer from donidalorsen Q1M to donidalorsen Q2M

[REDACTED]

[REDACTED], per the anticipated market authorisation for donidalorsen.⁴² The long-term data from the phase III OASISplus studies demonstrate that patients are able to transfer from donidalorsen Q4W to Q8W dosing and experience equivalent efficacy on the less frequent dosing regimen, without the need to discontinue or revert to Q4W dosing.⁴³

Table 13: OASISplus calculated HAE attack rate – patients who changed from donidalorsen Q4W to donidalorsen Q8W (data cut-off 27 January 2025)

Patient	Treatment Group	HAE attacks per 28 days during on-treatment period when patient took donidalorsen Q4W (days on treatment)	HAE attacks per 28 days on-treatment period when patient took donidalorsen Q8W (days on treatment)
OLE cohort patients			
██████████	Donidalorsen Q4W – Index Study Donidalorsen Q4W	██████████	██████████
██████████		██████████	██████████
██████████		██████████	██████████
██████████		██████████	██████████
██████████		██████████	██████████
██████████		██████████	██████████
██████████		Donidalorsen Q4W – Index Study Placebo	██████████
██████████	██████████		██████████
██████████	██████████		██████████
Switch cohort patients			
██████████	Prior Berotralstat	██████████	██████████
██████████	Prior C1-esterase Inhibitor	██████████	██████████
██████████		██████████	██████████

Abbreviations: N/A – Not applicable; Q4W – Once every four weeks; Q8W – Once every eight weeks error of the mean

Source: Data on file. OASIS-HAE and OASISplus efficacy analyses⁴³

A12. Please provide a justification for the exclusion of Type III HAE patients from OASIS-HAE, including whether this limits generalisability to the broader HAE population.

HAE Type I and Type II are caused by an autosomal dominant mutation in the *SERPING1* gene, resulting in either decreased levels of C1-INH (Type I) or loss-of-function of this protein (Type 2).⁴⁴ The third form of HAE, Type III (also referred to as HAE-nC1INH), is associated with normal levels and function of C1-INH.⁴⁴ This form of HAE is not yet fully understood.⁴⁵ Therefore, it is unclear whether the mechanism of action for donidalorsen, which inhibits the production of prekallikrein in the C1-INH regulatory pathways, would be effective for these patients. For this reason, Type III patients were excluded from the OASIS-HAE study.^{9,46}

The exclusion of Type III patients from OASIS-HAE is consistent with other Phase III randomised, controlled trials (RCTs) for LTPs, all of which evaluate interventions targeting the C1-INH regulatory pathways relevant to Type I and Type II HAE: HELP

(lanadelumab); APeX-2 (berotralstat); and VANGUARD (garadacimab); and COMPACT (C1-INH) trials.^{5,11,12,47}

HAE Type III is extremely rare in the UK, with a minimum prevalence of 1 in 3,000,000, and is estimated to affect less than 2% of all HAE patients.⁴⁸ Given this low prevalence, the exclusion of Type III patients has minimal impact on the generalisability of OASIS-HAE to the broader HAE population.

A13. Please specify the minimal clinically important difference (MCID) used for AE-QoL and ACET scores, cite the supporting literature, and present observed mean changes relative to published thresholds.

The MCID for AE-QoL total score is defined as six points, based on a publication by Weller *et al.* (2016).⁴⁹ The mean change in AE-QoL from Week 1 to Week 25 of the OASIS-HAE trial for patients treated with donidalorsen Q4W and donidalorsen Q8W was [REDACTED] and [REDACTED], respectively (Table 14 in the CES), both substantially exceeding the MCID threshold of six points.³² This suggests a clinically meaningful improvement in AE-QoL for patients treated with donidalorsen Q4W and donidalorsen Q8W.⁴⁹

Furthermore, the incremental treatment difference in AE-QoL total score between placebo compared with donidalorsen Q4W and donidalorsen Q8W up to Week 25 is -18.56 and -13.65, respectively, also both substantially exceeding the MCID threshold of six points.³² This further indicates that donidalorsen Q4W and donidalorsen Q8W provide clinically meaningful improvement in AE-QoL for patients compared to placebo.^{49,50}

The MCID for AECT score is defined as three points, based on a study by Fijen *et al.* (2023).⁵⁰ The mean change from Week 1 to Week 25 of the OASIS-HAE trial for AECT score in the donidalorsen Q4W, donidalorsen Q8W and placebo arms were [REDACTED], [REDACTED] and [REDACTED], respectively.⁵¹ For donidalorsen Q4W and donidalorsen Q8W, these changes are substantially greater than the MCID threshold for AECT.⁵⁰ This indicates that donidalorsen Q4W and donidalorsen Q8W demonstrated a clinically meaningful change in AECT score compared to placebo.⁵⁰

A14. Please report the number and percentage of participants continuing androgens or tranexamic acid during treatment, and indicate whether sensitivity analyses excluding these patients were performed.

The number and percentage of patients continuing androgens or tranexamic acid during treatment in the OASIS-HAE trial are presented in Table 14 and can be found in Table 14.1.3.2 of the OASIS-HAE Clinical Study Report (CSR).⁵¹ As per the pre-defined subgroup analyses of OASIS-HAE (as described in Section 11.4.2.8 of the CSR), sensitivity analyses have not been performed excluding these patients. Only [REDACTED] continued receiving androgens during treatment (placebo: [REDACTED], donidalorsen Q4W: [REDACTED], donidalorsen Q8W: [REDACTED]) and only [REDACTED] received tranexamic acid.

Table 14: Number and percentage of patients receiving ongoing androgen and tranexamic acid treatment in OASIS-HAE

Concomitant medication	Placebo (N=22) n (%)	Donidalorsen Q4W (N=45) n (%)	Donidalorsen Q8W (N=23) n (%)	All patients (N=90) n (%)
Tranexamic acid	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Danazol	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

N = number of patients in the analysis population; n = number of patients in the specific category.
Source: OASIS-HAE CSR³²

A15. Please provide the clinical and statistical rationale for the ≥ 5 attacks/month threshold defining “lack of efficacy.” Was this criterion predefined in the protocol or determined post hoc?

In OASIS-HAE, patients were randomised to donidalorsen Q4W, donidalorsen Q8W, or placebo for the duration of the trial.¹⁰ Patients who experienced at least five attacks per month for two consecutive months after Week 5 could terminate from the treatment period and either continue in the post-treatment period or enter into the OLE (OASISplus OLE cohort).¹⁰ This criterion was predefined in Section 6.1.2 of the OASIS-HAE trial protocol (included in the reference list of this document).¹⁰

The criterion was included solely as a safety measure for all patients, both those receiving placebo and those receiving donidalorsen, and not as an absolute measure to determine lack of efficacy in patients receiving donidalorsen. This measure ensured patients experiencing frequent attacks who were receiving placebo could

immediately receive treatment with an active drug by entering the OLE study to receive donidalorsen.

In OASIS-HAE, only two patients treated with donidalorsen (one [1/45, 2.2%] in the donidalorsen Q4W group and one [1/23, 4.3%] in the donidalorsen Q8W group) and three patients treated with placebo (3/22, 13.6%) discontinued treatment due to lack of efficacy.⁹ These five patients were subsequently enrolled in the OASISplus OLE cohort.^{6,9} To the company's current understanding, no formal definition of lack of efficacy exists for prophylactic HAE treatments; decisions regarding treatment discontinuation are made by the treating physician based on their clinical judgement, in conjunction with patients.

In summary, the prespecified ≥ 5 attacks/month threshold, applied in OASIS-HAE as criterion for the termination of the treatment period for patients, was not intended as a criterion to determine lack of efficacy, but rather as a safety criterion to ensure patients experiencing frequent attacks could discontinue treatment or, for those receiving placebo, receive donidalorsen in the OLE study. In practice, no formal definition of lack of efficacy exists for prophylactic HAE treatments, and decisions regarding treatment discontinuation are made by the treating physician based on clinical judgement, in discussion with patients.⁴³

A16. Please specify how "attack-free status" was defined (e.g., continuous absence of attacks from Week 5–25, or any single 4-week attack-free interval). Confirm whether this definition aligns with previous HAE trial conventions.

In OASIS-HAE, attack-free status was assessed by the secondary endpoint 'Percentage of Investigator-Confirmed HAE Attack-Free Patients from Week 5 to Week 25'. A patient was considered an attack-free clinical responder if they achieved a 100% reduction in HAE attacks from Week 5 to Week 25 compared to baseline, i.e. no attacks from Week 5 to Week 25.^{9,51} As discussed further in the response to Question A27, analyses of certain clinical endpoints in OASIS-HAE from Week 5 were conducted to align with the steady state period (consistent therapeutic effect) of donidalorsen.⁶

Across clinical trials evaluating LTPs in HAE (HELP and APeX-2), attack-free status was consistently defined based on the continuous absence of HAE attacks (i.e. a

100% reduction in HAE attack rate).^{11,12} The timepoints for assessing attack-free status vary between trials because each treatment reaches a steady state at different times, and each trial uses the specific steady state period for the relevant treatment.

In the pivotal trial for lanadelumab (HELP), attack-free status was assessed by the prespecified exploratory endpoint 'percentage of patients who were attack-free' over the 26-week treatment period.¹¹ This endpoint was derived based on the length of time during which patients experienced attack-free days.^{11,17} An attack-free day was defined as a calendar day with no investigator-confirmed HAE attack.^{11,17} Attack-free status was assessed at one month, three months, until the Day 182 visit during the treatment period (Day 0 to Day 182), and during the steady state treatment period (Day 70 to Day 182).^{11,17} The time to reach the steady state period is approximately 10 weeks for lanadelumab; therefore, the assessment of attack-free status from Day 70 in the HELP trial aligns with the assessment of the attack-free status from the steady state period in OASIS-HAE.^{6,52}

In the pivotal trial for berotralstat (APeX-2), attack-free status was assessed by the exploratory endpoint 'proportion of patients with no attacks over 24 weeks'.¹² The trial publication and the berotralstat NICE appraisal (TA738) did not define this endpoint.^{11,16}

Endpoints assessing attack-free status were not reported in the CHANGE trial, which evaluated C1-INH as an LTP.¹³

To conclude, attack-free status in OASIS-HAE was defined as patients who achieved a 100% reduction in HAE attacks from baseline from Week 5 to Week 25, i.e. no HAE attacks from Week 5 to Week 25.^{9,51} This is consistent with HELP and APeX-2 trials, where attack-free status was defined based on the continuous absence of HAE attacks.^{11,12} The timepoints for assessing attack-free status differ between trials to align with when the treatment reaches the steady state.

A17. Please confirm whether any unblinding occurred before OASISplus enrolment, and whether post-hoc analyses were conducted to assess potential bias in patient-reported outcomes following crossover.

The OASISplus trial is an open-label study, meaning that this study is unblinded for the Sponsor, Investigator, Study Centre Personnel and patients involved in OASISplus.⁴⁰ In order to ensure maintenance of the study blind in OASIS-HAE, plasma PKK, plasma pharmacokinetics and anti-drug antibody (immunogenicity) in OASISplus trial were not available to the Sponsor, Investigators, Study Centre Personnel, or the patients until the OASIS-HAE study was unblinded.⁴⁰ Unblinding did not occur before OASISplus enrolment; the interim analysis of OASISplus did not reveal the treatment group (of the OASIS-HAE trial) for OLE patients until the database of the OASIS-HAE trial was final, locked, and unblinded.²⁴

No post-hoc analyses were conducted to assess potential bias in patient-reported outcomes following crossover.

Responder analyses of AE-QoL questionnaire scores conducted in OASIS-HAE and OASISplus OLE cohort are presented in Table 15 and Table 16. These data report the number of patients with at least a 6-point improvement (reduction) in the AE-QoL total score, compared to the OASIS-HAE run-in baseline. (i.e. responders) at Week 25 of OASIS-HAE and Week 53 of OASISplus.^{6,31} For patients who received donidalorsen Q4W in OASIS-HAE (index donidalorsen Q4W), the proportion of patients considered responders was ■■■ and ■■■ in OASIS-HAE and OASISplus, respectively.^{6,31} For patients who received donidalorsen Q8W in OASIS-HAE (index donidalorsen Q8W), the proportion of patients considered responders was ■■■ and ■■■ in OASIS-HAE and OASISplus, respectively.^{6,31} The proportion of patients considered responders from the index donidalorsen Q8W group was ■■■ and ■■■ for those receiving donidalorsen Q4W and donidalorsen Q8W in the OASISplus OLE cohort, respectively.³¹ For patients who received placebo in OASIS-HAE (index placebo), the proportion of patients considered responders was ■■■ and ■■■ in OASIS-HAE and OASISplus, respectively.^{6,31} The analyses show that the proportion of patients from the index donidalorsen Q4W and Q8W groups who were considered responders remained consistent between the blinded OASIS-HAE and unblinded OASISplus studies. This indicates that the unblinding between OASIS-HAE and

OASISplus did not have a notable impact on AE-QoL scores in OASISplus. The observed difference in the proportion of patients considered responders in the index placebo group between OASIS-HAE and OASISplus can be attributed to the crossover from placebo to treatment with donidalorsen Q4W, rather than the unblinding of the studies.

Response analyses of Angioedema Control Test (AECT) scores from OASIS-HAE and OASISplus OLE cohort are presented in Table 17 and Table 18. These data report the number of patients with a score greater than 9 points (10 to 16) in the AECT (i.e. well-controlled) at Week 25 of OASIS-HAE and Week 53 of OASISplus.^{6,31} For the index donidalorsen Q4W group, the proportion of well-controlled patients was ■■■ and ■■■ in OASIS-HAE and OASISplus, respectively.^{6,31} For the index donidalorsen Q8W group, the proportion of well-controlled patients was ■■■ and ■■■ in OASIS-HAE and OASISplus, respectively.^{6,31} For the index placebo group, the proportion of well-controlled patients was ■■■ and ■■■ in OASIS-HAE and OASISplus, respectively.^{6,31} As was observed for AE-QoL scores, the analyses show that the proportion of patients from the index donidalorsen Q4W and Q8W groups who were considered well-controlled in the AECT remained consistent between the blinded OASIS-HAE and unblinded OASISplus studies. This indicates that the unblinding between OASIS-HAE and OASISplus did not have a notable impact on AECT scores in OASISplus. The observed difference in the proportion of well-controlled patients in the index placebo group between OASIS-HAE and OASISplus can be attributed to the crossover from placebo to treatment with donidalorsen rather than the unblinding of the studies.

Overall, the consistency in AE-QoL and AECT patient scores observed between OASIS-HAE (blinded) and OASISplus (unblinded) suggests that unblinding of the studies did not have a notable impact or introduce bias in patient-reported outcomes following patient crossover.

Table 15: Responder analysis of AE-QoL questionnaire total score at Week 25, OASIS-HAE, Full Analysis Set

	Pooled placebo (N=22)	Donidalorsen 80 mg Q4W (N=45)	Donidalorsen 80 mg Q8W (N=23)
Patients who are considered as either responders or non-responders (denominator) at Week 25, n	■	■	■
Patients who are considered as responders at Week 25*, n (%)	■■■■■	■■■■■	■■■■■
Patients who are considered as non-responders at Week 25*, n (%)	■■■■■	■■■■■	■■■■■
Odds ratio (95% CI)**	■	■■■■■ ■■■■■	■■■■■ ■■■■■
P-value	■	■■■■■	■■■■■

*Patients with at least 6-point improvement (reduction) from baseline in the AE-QoL total score (i.e. post-baseline – baseline ≤ -6) at Week 25 are considered as responders. Patients who early discontinued treatment period due to reasons of adverse events or lack of efficacy are considered as non-responders; due to other reasons, patients are considered as missing.

**The odds ratio, its 95% confidence interval and p-value are calculated based on a logistic regression with the baseline and the treatment-by-baseline interaction as a covariate.

Abbreviations: CI – Confidence interval; N – number of patients in the analysis population; n – number of patients in the specific category; Q4W – every 4 weeks; Q8W – every 8 weeks.

Source: OASIS-HAE CSR⁶

Table 16: Responder analysis of AE-QoL questionnaire total score at OASISplus Week 53 compared to OASIS-HAE run-in baseline, OASISplus OLE cohort, Full Analysis Set

OASISplus OLE cohort treatment arm	OLE donidalorsen Q4W			OLE donidalorsen Q8W
Index (OASIS-HAE) treatment arm	Donidalorsen 80 mg Q4W (N=44)	Donidalorsen 80 mg Q8W (N=6)	Pooled placebo (N=19)	Donidalorsen 80 mg Q8W (N=14)
Patients who are considered as either responders or non-responders (denominator) at Week 25*, n	■	■	■	■
Patients who are considered as responders at Week 53*, n (%)	■	■	■	■
Patients who are considered as non-responders at Week 53, n (%)	■	■	■	■

*Clinical response is defined as at least 6-point improvement from baseline in AE-QoL total score, i.e. post-baseline – baseline $\leq$ -6.

Abbreviations: OLE – Open-label Extension; N – number of patients in the analysis population; n – number of patients in the specific category; Q4W – every 4 weeks; Q8W – every 8 weeks.

Source: Data on file. OASISplus One-Year Analysis³¹

Table 17: Responder analysis of the percentage of well-controlled patients on the AECT at Week 25, OASIS-HAE, Full Analysis Set

	Pooled placebo (N=22)	Donidalorsen 80 mg Q4W (N=45)	Donidalorsen 80 mg Q8W (N=23)
Patients who have AECT measurement at Week 25 (denominator), n	■	■	■
Patients who are well-controlled on the AECT at Week 25*, n (%)	■	■	■
Patients who are not well-controlled at Week 25*, n (%)	■	■	■

*Patients with the score greater than 9 points (10 to 16) in the AECT are considered to be well-controlled.

Abbreviations: AECT – Angioedema Control Test; N – number of patients in the analysis population; n – number of patients in the specific category; Q4W – every 4 weeks; Q8W – every 8 weeks.

Source: OASIS-HAE CSR⁶

Table 18: Responder analysis of the percentage of well-controlled patients on the AECT at OASISplus Week 53 compared to OASIS-HAE run-in baseline, OASISplus OLE cohort, Full Analysis Set

OASISplus OLE cohort treatment arm	OLE donidalorsen Q4W			OLE donidalorsen Q8W
Index (OASIS-HAE) treatment arm	Donidalorsen 80 mg Q4W (N=44)	Donidalorsen 80 mg Q8W (N=6)	Pooled placebo (N=19)	Donidalorsen 80 mg Q4W (N=14)
Patients who have AECT measurement at Week 53 (denominator), n	■	■	■	■
Patients who are well-controlled on the AECT at Week 53*, n (%)	■■■■■■■■■■	■■■■■■■■■■	■■■■■■■■■■	■■■■■■■■■■
Patients who are not well-controlled at Week 53*, n (%)	■■■■■■■■■■	■	■■■■■■■■■■	■

*Patients with the score greater than 9 points (10 to 16) in the AECT are considered to be well-controlled. Abbreviations: AECT – Angioedema Control Test; N – number of patients in the analysis population; n – number of patients in the specific category; Q4W – every 4 weeks; Q8W – every 8 weeks. Source: Data on file. OASISplus One-Year Analysis³¹

A18. Where there observed differences in baseline characteristics and outcomes between the two placebo groups (those randomised to placebo Q4W versus placebo Q8W) within OASIS-HAE? If this was not analysed, please provide this information.

The company have conducted additional analyses to present the baseline characteristics and outcomes between the two placebo groups within OASIS-HAE. Patients were randomised 2:1 to receive either 4-week dosing interval or 8-week dosing interval of over a 24-week treatment period.⁹ Within each dosing cohort, patients were then randomised 3:1 to receive 80 mg donidalorsen or a matching volume of placebo.⁹ Therefore, there are approximately twice as many patients in the placebo Q4W cohort compared to the placebo Q8W cohort. The baseline characteristics, presented in Table 19, are broadly well matched between the two patient cohorts; however, given the relatively small sample size in each cohort (placebo Q4W n=15, placebo Q8W n=7), some variation is expected.²³

The efficacy data presented in Table 20 and Table 21 demonstrate that outcomes were balanced across the two placebo groups, with comparable least squares mean attack rates observed for the primary efficacy endpoint and the rates of moderate or

severe attacks, both showing substantial overlap in confidence intervals between the groups.²³

The safety outcomes for the two placebo groups are presented in Table 22. The incidence of adverse events were also broadly comparable between the placebo groups.²³ There were only [REDACTED] TEAEs related to trial regimen in the pooled placebo group, [REDACTED]

[REDACTED]⁶ Due to the low incidence of adverse events and small sample size of the placebo cohorts, the company does not consider there to be sufficient data to inform a meaningful cohort placebo analysis.

Table 19: Summary of patient demographics and baseline characteristics, placebo Q4W and placebo Q8W groups (full analysis set), OASIS-HAE

Demographics/ baseline characteristics	Placebo Q4W (N=15)	Placebo Q8W (N=7)
Age (years)		
Mean (SD)	[REDACTED]	[REDACTED]
Age Group (years), n (%)		
18 to 39	[REDACTED]	[REDACTED]
40 to 64	[REDACTED]	[REDACTED]
Sex, n (%)		
Male	[REDACTED]	[REDACTED]
Female	[REDACTED]	[REDACTED]
Ethnicity n (%)		
Hispanic or Latino	[REDACTED]	[REDACTED]
Not Hispanic or Latino	[REDACTED]	[REDACTED]
Race n (%)		
American Indian or Alaskan Native	[REDACTED]	[REDACTED]
Black or African American	[REDACTED]	[REDACTED]
White	[REDACTED]	[REDACTED]
Multiple	[REDACTED]	[REDACTED]
BMI (kg/m²)		
Mean, (SD) ^a	[REDACTED]	[REDACTED]
Family History of HAE, n (%)		

Demographics/ baseline characteristics	Placebo Q4W (N=15)	Placebo Q8W (N=7)
Yes		
No		
Type of HAE, n (%)		
HAE-1		
HAE-2		
Any Predefined Prophylactic Therapy Use, n (%)^b		
Yes		
No		
Run-in period attack rate per 4 weeks		
Mean, (SD) ^c		
Run-in period HAE Attack Rate, n (%)		
≥ 2 attacks/4-weeks		
> 8 attacks/4-weeks		

Abbreviations: BMI – Body mass index; C1-INH – C1-inhibitor; CI – Confidence interval; HAE – Hereditary angioedema; kg – kilogram; m – metre; mg – milligrams; Q4W – once every 4 weeks; Q8W – once every 8 weeks; SD – Standard deviation

Notes: ^a Total number of patients analysed for BMI in placebo group n = 21.

^bFirst-line prophylactic agents and excluded attenuated androgens and tranexamic acid.

^cThe run-in period (Screening) HAE attack rate for each patient was calculated as the number of investigator-confirmed HAE attacks occurring during the run-in period divided by the number of days the patient contributed to the run-in period and then multiplied by 28.

Data on file. Post-hoc analysis of OASIS-HAE data²³

Table 20: Investigator-confirmed HAE attack rate (per 4 weeks) from Week 1 to Week 25 for the placebo Q4W and placebo Q8W groups (FAS)

Time-normalised HAE attacks	Placebo Q4W (N=15)	Placebo Q8W (N=7)
Time-normalised HAE attack rate from Week 1 to Week 25^a		
Least square mean rate (95% CI) ^b		

Abbreviations: CI – confidence interval; FAS – Full analysis set; HAE – Hereditary angioedema; Q4W – once every 4 weeks; Q8W – once every 8 weeks

^aThe time-normalised HAE attack rate (per 4 weeks) was calculated as number of Investigator-confirmed HAE attacks that occurred from Week 5 to Week 25, divided by the number of days the patient contributed to that period, and then multiplied by 28.

^bThe Poisson regression model included treatment groups, Baseline (the run-in period HAE attack rate), the Treatment-by-Baseline interaction as a covariate, and the logarithm of time per 4 weeks that each patient was observed from Week 1 to Week 25 used as an offset variable (e.g., log (6) if the patient stayed in the study for 24 weeks). Pearson chi-square scaling of standard errors was used to account for potential overdispersion.

Data on file. Post-hoc analysis of OASIS-HAE data²³

Table 21: Investigator-confirmed moderate or severe HAE attack rate (per 4 weeks) from Week 5 to Week 25 for the placebo Q4W and placebo Q8W groups (FAS)

Time-normalised HAE attacks	Placebo Q4W (N=15)	Placebo Q8W (N=7)
Time-normalised HAE attack rate from Week 5 to Week 25^a		
Least square mean rate (95% CI) ^b		

Abbreviations: CI – confidence interval; FAS – Full analysis set; HAE – Hereditary angioedema; Q4W – once every 4 weeks; Q8W – once every 8 weeks

^aThe time-normalised HAE attack rate (per 4 weeks) was calculated as number of Investigator-confirmed HAE attacks that occurred from Week 5 to Week 25, divided by the number of days the patient contributed to that period, and then multiplied by 28.

^bThe Poisson regression model included treatment groups, Baseline (the run-in period HAE attack rate), the Treatment-by-Baseline interaction as a covariate, and the logarithm of time per 4 weeks that each patient was observed from Week 1 to Week 25 used as an offset variable (e.g., log (6) if the patient stayed in the study for 24 weeks). Pearson chi-square scaling of standard errors was used to account for potential overdispersion. Data on file. Post-hoc analysis of OASIS-HAE data²³

Table 22: Overview of adverse events, Safety set, OASIS-HAE, placebo Q4W and placebo Q8W groups

Parameter	Placebo Q4W (N=15)	Placebo Q8W (N=7)
Patients with any adverse event, n (%)	██████	██████
Patients with any adverse event related to trial regimen), n (%)	██████	██████
Any adverse event leading to discontinuation of trial regimen, n (%)	█	█
Any severe adverse event, n (%)	██████	██████
Any severe adverse event related to trial regimen, n (%)	█	█
Any serious adverse event, n (%)	██████	█
Any serious adverse event related to trial regimen, n (%)	█	█

Abbreviations: Q4W – once every 4 weeks; Q8W – once every 8 weeks

Source: Data on file. Post-hoc analysis of OASIS-HAE data²³

Network Meta analyses (clinical effectiveness)

A19. Please provide the statistical analysis plan/protocol for the network meta-analysis.

The statistical analysis plan, conducted as part of the UK NMA, is presented in the reference list of this document (Donidalorsen UK NMA Statistical Analysis Plan, Otsuka, 2025).⁵³

A20. [Priority Question] Please provide the full feasibility assessment/report for the network meta-analysis (NMA) (if this has been included (in full) in the submission, please provide the location). This includes, but is not limited to:

- A comparison of the baseline characteristics between the included studies tables (including demographic and disease-related variables such as age, sex, HAE type, baseline attack frequency, prior LTP use, and concomitant

treatments) and all efficacy outcome data for each comparator study included in the NMA.

- A comparison of key treatment effect modifiers (TEMs)/prognostic factors between the included studies, with justification why these factors were identified as TEMs (clinical opinion/literature/etc).
- For the two points above:
 - Identify the sources and data cuts used for each trial.
 - Indicate which trials were connected in the NMA evidence network and which were used only in sensitivity analyses.
 - Confirm whether any adjustments for baseline imbalance were made (e.g., attack frequency or prior treatment).
- A comparison of placebo response between studies for each outcome.
- A discussion of the potential impact of between-study differences on the validity of the NMA.
- A comparison of how attack severity was measured between studies.

The feasibility assessment (FA), conducted as part of the UK NMA, is presented in the reference list of this document (Donidalorsen UK NMA Feasibility Assessment, Otsuka, 2025).⁵⁴

The FA contains the following information and data, as requested by the EAG above:

- Comparison of baseline characteristics between the included studies (Section 3.2.2).
- Efficacy outcomes for each comparator study (Section 3.4.1).
- Comparison of key treatment effect modifiers/prognostic factors (Section 3.2.2).

- Explanation on why the treatment effect modifiers and prognostic factors and were identified (Section 4).
- Discussion of the potential impact of between study differences on the validity of the NMA (Section 3).
- Comparison of measurement of attack severity between studies (Section 3.4.1.2).

The company did not additionally compare placebo responses during the FA because feasibility largely focuses on evaluating study design, population comparability, endpoint alignment, and network connectivity, rather than assessing absolute placebo risk. As outlined in NICE DSU TSD 4, variation in baseline risk does not determine whether an NMA is feasible, instead, it contributes to between-study heterogeneity, which is addressed at the modelling stage, by fitting a random-effects NMA model.⁵⁵ In the company's evidence base, placebo acted as a consistent and clearly defined anchor across all trials, ensuring structural transitivity.

Although placebo outcomes can differ across studies, these differences typically arise from underlying design factors such as baseline disease severity captured by baseline attack rate in the RCT analysis, eligibility criteria, background therapy, and rescue-medication rules. The company assessed these factors directly as part of the feasibility checks. Since these design features and baseline characteristics were sufficiently aligned across the evidence base, and all studies reported compatible relative treatment effects for the endpoints of interest, an additional comparison of placebo response levels would not have altered the feasibility judgement nor the structure of the network. For these reasons, a placebo-response comparison was not included in the FA.

A21. Please provide diagnostics for the NMA, such as goodness-of-fit, tau, I-squared, treatment rank, among others.

To aid interpretation of the NMAs conducted for the appraisal of donidalorsen in HAE, the company have assessed goodness-of-fit statistics, between-study heterogeneity (tau), surface under the cumulative ranking (SUCRA) values, posterior treatment ranks, and R-hat values for each outcome of company's NMA;

performance metrics for the mean number of HAE attacks are presented below, and the metrics for all remaining endpoints are presented in Appendix Question A21.

Residual deviance, effective number of parameters (pD) and the number of data points together demonstrate goodness-of-fit by showing how well the model fits the data and whether there is an appropriate balance between model fit and complexity. Values of the Deviance Information Criterion (DIC) are not included as the DIC is designed to compare if the fit of two or more different models fit to the same data. Since only random effects models are presented, the stand-alone DIC values would not offer meaningful insight because only one model has been considered appropriate to use. Please refer to Section 3.3.1.2 in the donidalorsen CES for further justification of the selection of the RE model.

Tau quantifies the between-study heterogeneity, that is, how much the true treatment effects vary across studies beyond what would be expected from within-study sampling error, and therefore provides statistical justification for using a random-effects model rather than a fixed-effects model.⁵⁶

SUCRA values summarise the entire ranking distribution for each treatment on a 0-1 scale, with higher values indicating a higher probability of being amongst the most effective options.⁵⁷

R-hat, the Gelman-Rubin convergence diagnostic, assesses whether the Markov Chain Monte Carlo (MCMC) chains have converged to a stable posterior distribution, with values close to 1, but below 1.1, indicating good convergence and supporting the robustness of NMA conclusions.⁵⁸

I-squared, quantifies heterogeneity only when multiple studies contribute to the same direct comparison.⁵⁹ In the NMAs conducted by the company for this appraisal (Section 10.3.4 in the CES), each comparison is informed by a single study, and so I-squared is not a relevant metric and is not reported.

Together these metrics address the key dimensions of model performance for an NMA, they provide a comprehensive and methodologically appropriate assessment of model validity. These metrics demonstrate that the company's NMAs are robust, showing adequate model fit, appropriately handling between-study heterogeneity,

producing stable and interpretable treatment rankings, and sufficient MCMC convergence. Therefore, these metrics provide assurance that the comparative effectiveness estimates are robust and suitable for decision-making.

Mean number of HAE attacks per month:

Goodness-of-fit statistics

Table 23 shows that the residual deviance () for the NMA conducted for the mean number of HAE attacks per month is very close to the total number of data points (). This indicates that the model fits the observed data well, as a residual deviance approximately equal to the number of data points suggests the model explains the data accurately with little evidence for misfit to the data in the network.⁵⁶ The effective number of parameters, pD, () is also very close to the total number of data points, indicating the model fits suitably well.

Table 23: Goodness-of-fit statistics – mean number of HAE attacks per month

Parameter	Value
Residual deviance	
pD	
Number of data points	

Abbreviations: HAE – Hereditary angioedema; pD – effective number of parameters.

Tau

In Table 24, the median value of tau () suggests there is moderate heterogeneity in treatment effects across studies. The wide 95% credible interval (CrI) () reflects the uncertainty in this estimate, likely due to limited data to estimate this parameter across the network.

The estimated tau strongly supports the use of the company’s base-case random effects (RE) model. The presence of between-study heterogeneity means that assuming a single common treatment effect, as required under a fixed effects (FE) model, would be inappropriate. In contrast, the RE model correctly accommodates this heterogeneity, providing a statistically defensible basis for inference.

Table 24: Between-study heterogeneity – mean number of HAE attacks per month

Parameter	Value
Median value for tau	██████
(95% CrI)	██████████

Abbreviations: CrI – Credible interval, HAE – Hereditary angioedema.

SUCRA and rank probabilities

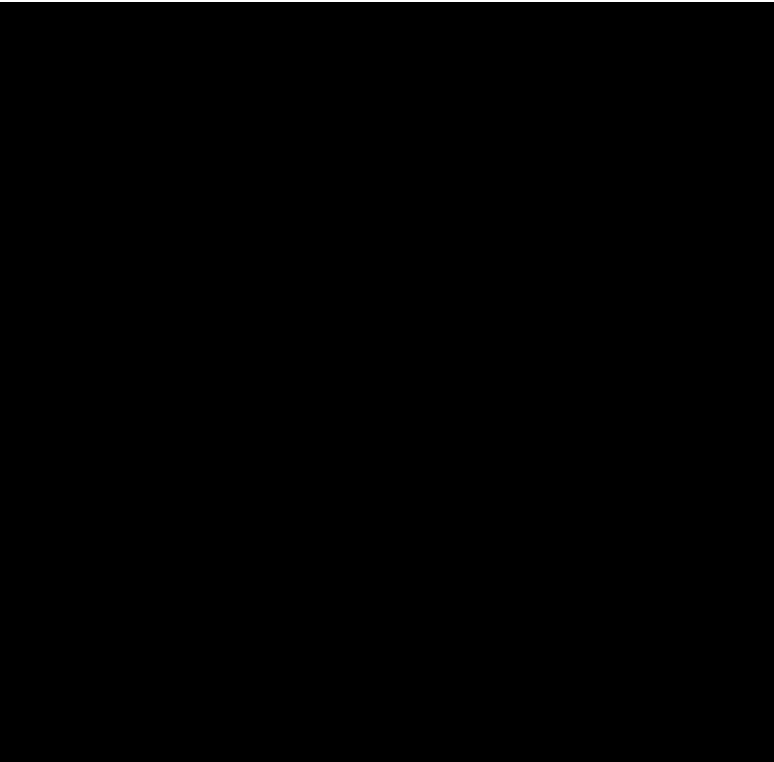
As presented in Table 25, donidalorsen Q4W and donidalorsen Q8W have the ██████ and ██████ highest SUCRA values, respectively. Figure 4 presents the posterior rank plot, where the bold bars represent the 66% credible interval and the thin bars represent the 95% CrI. Therefore, while donidalorsen Q4W and donidalorsen Q8W achieved numerically higher rankings than berotralstat and C1 INH-nf, credible intervals overlap between treatments, indicating comparable efficacy across active treatments. Moreover, while lanadelumab Q2W and lanadelumab Q4W achieved numerically higher rankings than donidalorsen Q4W and donidalorsen Q8W, respectively, credible intervals overlap between treatments, indicating comparable efficacy across active treatments.

Table 25: SUCRA – mean number of HAE attacks per month

Treatment	SUCRA
Donidalorsen Q4W	██████
Berotralstat	██████
C1 INH-nf	██████
Donidalorsen Q8W	██████
Lanadelumab Q2W	██████
Lanadelumab Q4W	██████
Placebo	██████

Abbreviations: C1 INH-nf – Nano filtered C1 esterase inhibitor; HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks; SUCRA – Surface under the cumulative ranking curve.

Figure 4: Posterior rank plot – mean number of HAE attacks per month



Abbreviations: C1 INH-nf – Nano filtered C1 esterase inhibitor; HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

R-hat values

The R-hat values presented in Table 26 are all [REDACTED] to two decimal places, indicating that the MCMC chains in the NMA have converged successfully and the resulting treatment effect estimates are robust.

Table 26: Treatment effect R-hat value per treatment versus donidalorsen Q4W – mean number of HAE attacks per month

Treatment	R-hat
Berotralstat	[REDACTED]
C1 INH-nf	[REDACTED]
Donidalorsen Q8W	[REDACTED]
Lanadelumab Q2W	[REDACTED]
Lanadelumab Q4W	[REDACTED]
Placebo	[REDACTED]

Abbreviations: C1 INH-nf – Nano filtered C1 esterase inhibitor; HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

Overall, the performance metrics indicate that the NMA model fits the observed data for the outcome of mean number of HAE attacks per month suitably well and provides robust estimates. The residual deviance and effective number of

parameters closely match the number of data points, demonstrating strong model fit. The median tau value of 0.351 confirms moderate between-study heterogeneity, supporting the choice of a RE model. The posterior rank plot with overlapping credible intervals demonstrates comparable efficacy among active treatments. Finally, R-hat values near 1.00 confirm that the MCMC chains converged successfully, ensuring the stability and reliability of the treatment effect estimates.

A22. [Priority Question]: Please provide a sample of the R code and data used to run the NMA. The code/data used for the primary outcome will be sufficient.

Please find the sample of the R code used to run the company's NMA presented in Table 17 of the CES, in Appendix Question A22. The data used to run the NMA are provided as an Excel file in the reference list of this document (Analysis_data LSM.xlsx).

A23. Were sensitivity analyses conducted for the NMA? If so, please present these results. If not, please explain why.

Sensitivity analyses

The company have conducted sensitivity analyses on the base-case NMA presented in Section 2.10 of the CES. As discussed in Section 2.10.1 of the CES, the only plasma-derived IV C1-INH with RCT data available was Cinryze (CHANGE), which is also used as a proxy for IV Berinert in the economic analysis. CHANGE was not captured in the SLR as it includes patients aged six years and over, beyond the standard 12 years and over inclusion criteria of the SLR.⁶⁰ CHANGE was still included in the FA of the NMA to ensure the relevant comparators for donidalorsen were assessed. The inclusion of CHANGE in the NMA was validated by clinical experts.

Therefore, a sensitivity analysis with the exclusion of CHANGE from the NMA network was conducted to test the robustness of the base-case NMA results.

For the purpose of this sensitivity analysis, only the outcome of mean number of HAE attacks per month was run as this aligns with the primary outcomes of the clinical trials and the primary measure of efficacy in the economic analysis.

Exclusion of CHANGE from the NMA network

The sensitivity analysis excluding CHANGE from the NMA network follows the same NMA methodology as the company's base-case NMA outlined in Section 2.10 of the CES.

Median rate ratios for the mean number of HAE attacks per month and 95% CrIs from the NMA excluding CHANGE are shown in Table 27 and Figure 5. No statistically significant differences were observed for the mean number of attacks per month, as informed by the mean rate ratios, in treatment with donidalorsen Q4W, and donidalorsen Q8W, lanadelumab Q2W, lanadelumab Q4W or berotralstat.

Treatment with donidalorsen Q4W was associated with [REDACTED]. [REDACTED]. The results for donidalorsen Q4W showed a [REDACTED], however, as stated above, this difference was not statistically significant.

The wide and overlapping CrIs observed in the forest plot, presented in Figure 5, demonstrate that there is no statistically significant difference between the median rate ratios of donidalorsen Q4W and LTP comparators.

A [REDACTED].

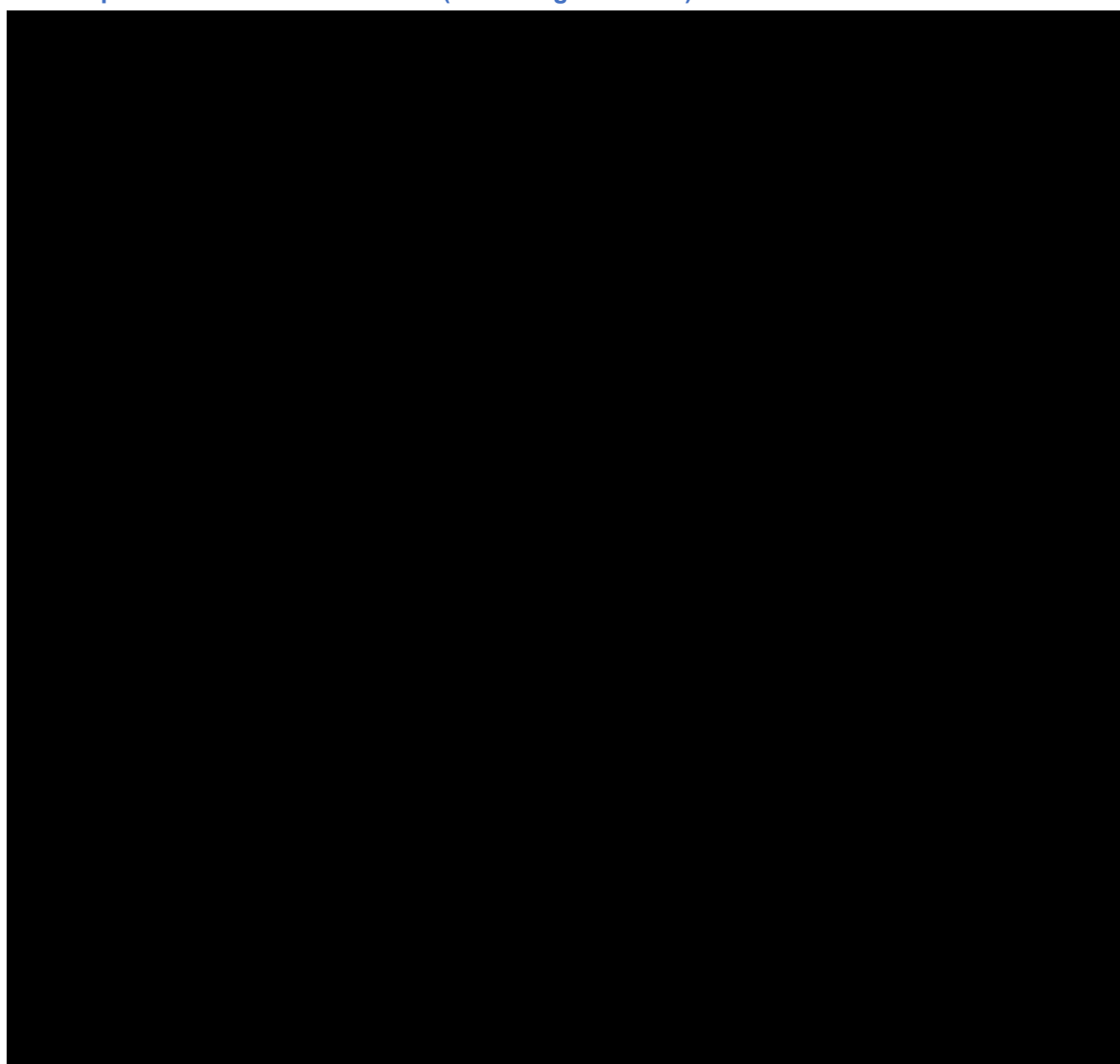
Table 27: Median rate ratios and 95% CrIs for mean number of HAE attacks per month excluding CHANGE

Treatment	Median rate ratio (95% CrI)
Berotralstat	[REDACTED]
Donidalorsen_Q8W	[REDACTED]
Lanadelumab_Q2W	[REDACTED]
Lanadelumab_Q4W	[REDACTED]
Placebo	[REDACTED]

*95% CrI does not include 1 and is therefore considered statistically significant

Abbreviations: CrI – Credible interval; HAE – Hereditary angioedema; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks.

Figure 5: Forest plot of median rate ratios and 95% CrIs – endpoint: mean number of HAE attacks per month treatment effects (excluding CHANGE)



Abbreviations: CrIs – credible intervals; HAE – Hereditary angioedema; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks.

The results of the sensitivity analysis (excluding CHANGE from the NMA network) are consistent with the results presented in the company's base-case NMA (Section 2.10 of the CES). For the comparison of donidalorsen Q4W with donidalorsen Q8W, lanadelumab Q2W, donidalorsen Q4W and berotralstat, no statistically significant differences were observed, mirroring the NMA from the base-case analysis and demonstrating the robustness of the original NMA approach. This provides further evidence to demonstrate equal efficacy is reasonable for the company's base case economic analysis.

Additional NMAs – steady state analysis

Additional NMAs were conducted to determine the comparative efficacy of donidalorsen, lanadelumab and berotralstat during each trial's respective steady state period as sensitivity analyses. The steady state period is when the treatment is assumed to have reached maximum effectiveness, characterised by a consistent therapeutic effect. Table 28 summarises the steady state periods and outcomes available for each LTP trial.

Table 28 – Steady state analysis periods and outcome availability

Clinical trial(s)	OASIS-HAE ⁹	HELP ^{61,62}	APeX-2 ⁶³
Steady state period	Weeks 5-25	Days 70-182	Days 8-168
Feasible outcomes	• Mean number of attacks • Moderate or severe attacks • Attacks requiring on demand medication	• Mean number of attacks • Moderate or severe attacks • Attacks requiring on demand medication	• Mean number of attacks

Abbreviations: HAE – Hereditary angioedema

Source: Riedl et al. (2024)⁹, Banerji et al. (2018)¹⁷, Riedl et al. (2020)¹⁸, Zuraw et al. (2021)⁶³

The steady state NMA follows the same methodology of the existing NMA presented in Section 2.10 of the CES. Data to inform the mean number of attacks for patients on lanadelumab were sourced from Banerji 2018 (HELP), however this publication did not report the number of moderate or severe attacks and attacks requiring on-demand medication during the steady state period; instead Riedl 2020 (HELP) reported outcomes during two distinct periods: days 0-69 of treatment, as well as the mean differences between outcomes during days 70-182 (the steady state period) and days 0-69.^{52,61} It was therefore assumed that outcomes in the steady state period are the differences between the two periods reported in Riedl 2020 (HELP) as described below:

Outcomes in steady state period

= (Mean differences in outcomes between steady state period and treatment initiation period)
– (Outcomes in treatment initiation period)

Across all outcomes, the steady state NMA results were highly consistent with the base-case NMA analyses presented in the CES. For most comparisons in the steady state NMA, no statistically significant differences were identified between

donidalorsen Q4W and lanadelumab or berotralstat, reinforcing the robustness of the base-case findings. The steady state analysis therefore supports the conclusion that treatment effect comparisons remain stable even when restricted to steady-state periods.

Mean number of HAE attacks per month

Median rate ratios for the mean number of HAE attacks per month and 95% CrIs from the steady state NMA are shown in Table 29 and Figure 6. No statistically significant differences were observed for the mean number of attacks per month, as informed by the mean rate ratios, in treatment with donidalorsen Q4W, and donidalorsen Q8W, lanadelumab Q2W, lanadelumab Q4W or berotralstat. Treatment with donidalorsen Q4W was associated with

[REDACTED]
[REDACTED]. The results for donidalorsen Q4W showed a

[REDACTED]
[REDACTED], however, as stated above, this difference was not statistically significant.

The wide and overlapping CrIs observed in the forest plot, presented in Figure 6, demonstrate that there is no statistically significant difference between the median rate ratios of donidalorsen Q4W and LTP comparators.

A [REDACTED]
[REDACTED].

Table 29: Median rate ratios and 95% CrIs for SS mean number of HAE attacks per month

Treatment	Median rate ratio (95% CrI)
Berotrastat	██████████
Donidalorsen_Q8W	██████████
Lanadelumab_Q2W	██████████
Lanadelumab_Q4W	██████████
Placebo	██████████

*95% CrI does not include 1 and is therefore considered statistically significant

Abbreviations: CrI – Credible interval; HAE – Hereditary angioedema; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks; SS – Steady state.

Figure 6: Forest plot of median rate ratios and 95% CrIs – endpoint: SS mean number of HAE attacks per month treatment effects



Abbreviations: CrIs – credible intervals; HAE – Hereditary angioedema; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks; RE – Random effects; SS – Steady state.

Results for the steady state NMA for the mean number of moderate or severe HAE attacks and mean number of HAE attacks requiring on demand medication are presented in Appendix Question A23.

The results of the steady state NMA presented above, as well as for the results presented for additional outcomes in Appendix Question A23, are consistent with the results presented in the company's base-case NMA (Section 2.10 of the CES). For the comparison of donidalorsen Q4W with donidalorsen Q8W, lanadelumab Q2W,

donidalorsen Q4W and berotralstat, no statistically significant differences were observed, mirroring the NMA from the base-case analysis. This provides further evidence to demonstrate equal efficacy is reasonable for the company's base case economic analysis.

A24. Reference 87 (in the main submission) for the CHANGE study is the Zuraw et al. 2010 publication in the reference pack which contains results for the Acute-Attack Treatment Trial and the Prophylaxis Trial. Please confirm whether these trials together form the CHANGE trial referenced in section 2.10 of the CS or if results of only one of these trials were used in the NMA and confirm which of these two studies were used in the NMA for C1INH-nf.

The Zuraw *et al.* (2010) publication, referred to as the CHANGE trial in the CES, consisted of two double-blind placebo-controlled studies: the first study evaluated C1-INH and placebo for acute attack treatment, and the second study evaluated C1-INH and placebo for prophylaxis treatment during a 24-week crossover period (two 12-week treatment periods). Subjects who had been randomly assigned to a study drug in the acute attack treatment study, and who also had a history of at least two attacks per month, were eligible to participate in the prophylaxis study

Only data from the prophylaxis study in the CHANGE trial were used in the NMA. The results labelled as "C1-INH (Cinryze)" in Table 17 of the CES are from the prophylaxis study in the CHANGE trial.¹³ The trial design and duration of the CHANGE study presented in Table 16 of the CES (summary of the studies included in the NMA feasibility assessment) are also from the prophylaxis study.

A25. It appears that the berotralstat 110 mg arm was not included in the NMA despite being included in Table 16 of the CS. Please confirm that results of the berotralstat 150 mg arm from APeX-2 was included and that the 110 mg group was excluded.

Table 16 of the CES provides an overview of the studies included in the NMA. The APeX-2 trial included treatment with berotralstat 150 mg, berotralstat 110 mg and placebo, and all three arms are presented in Table 16 of the CES.¹² The licensed dose in the berotralstat SmPC, and the dose reflected in the NICE recommendation for berotralstat, is 150 mg; therefore, the NMA only includes data from the berotralstat 150 mg arm of the APeX-2 trial and excludes data from the berotralstat

110mg arm.^{16,64} Only the berotralstat 150 mg arm is included in the network diagrams presented in Appendix J (Figure 1 – Figure 7) of the CES.

A26. Did the company consider the multi-level network meta-regression model due to the availability of individualised patient data from OASIS-HAE, assuming a difference in distribution of effect modifiers across studies (the data of which were not supplied to the EAG)?

In the CES, the efficacy of donidalorsen and relevant comparators is informed by outputs from an NMA performed by the company. Details on the NMA can be found in Section 2.10 and Appendix J of the CES. The NMA was conducted in a robust manner, ensuring that both the data and outcomes used were appropriate for making valid comparisons between all treatments. The analysis was undertaken in line with best practice for conducting and reporting NMA, aligned with NICE reference case methods.⁴ A comprehensive SLR was conducted to identify all relevant evidence, and each included study underwent rigorous risk-of-bias assessment to ensure that only data of sufficient quality informed the analysis. Potential sources of heterogeneity were evaluated through a feasibility assessment to highlight sources of across-study heterogeneity, and sensitivity and face-validity checks were performed on the results. The company therefore posits that, despite the acknowledged limitations of certain datasets, this NMA is the most robust analysis possible for the comparative efficacy and effect on quality of life of donidalorsen and its comparator LTPs, based on the data available.

As part of the feasibility assessment to determine the methodology appropriate for an indirect treatment comparison (ITC) to be implemented as part of this CES, a multi-level network meta-regression (ML-NMR) was considered but was deemed inappropriate for the purpose of this analysis. This is because an ML-NMR would not resolve any uncertainty introduced by using an NMA and instead would introduce additional uncertainty. Therefore, the company considers the NMA to be the most robust approach to inform the efficacy of donidalorsen and relevant comparators in the economic analysis. The results of the NMA were validated by UK clinical experts in September 2025, in validation meetings conducted by the company.²²

The company consider that an ML-NMR is inappropriate due to several key methodological constraints.

With respect to the primary endpoint of interest (mean number of HAE attacks per month):

1. Baseline attack rate as an effect modifier.

Baseline attack rate is an important effect-modifying variable and has been included as an adjustment factor in the patient-level analyses of mean number of attacks within all comparator trials. Only VANGUARD and HELP reported *unadjusted* mean attack rates. Conducting an ML-NMR across all comparator trials would therefore lead to double-adjustment, as least-squares means (LSMs) already incorporate this baseline adjustment through model-based estimation.

2. Restrictive model structure and sparse network.

Given the sparse treatment network and the issue outlined in point 1, only a fixed-effects ML-NMR would be technically feasible. This would imply that all studies estimate a single true treatment effect, which is clinically implausible. A random-effects specification would be more appropriate; however, with such a small network, convergence issues were expected due to the computational demands of the model.

3. Outcome distributional issues.

Examination of the patient-level data from OASIS-HAE showed clear overdispersion for this and all count outcomes, indicating that a Poisson model would not provide an adequate fit at individual-patient level. A negative binomial distribution would typically be more suitable, but this option is not currently available in the *multinma* R package used to implement ML-NMR.⁶⁵

For these reasons, the company concluded that an ML-NMR analysis was deemed inappropriate for this analysis. Therefore, the company considers the NMA conducted to be the most appropriate source to inform the efficacy of donidalorsen and relevant comparators in the economic model.

Excluded patient relevant outcomes

A27. The company explicitly excluded outcomes like 'time to first attack' from the economic decision problem, as they were not primary or secondary outcomes in the OASIS-HAE trial.

- Given that 'time to first attack' is highly patient-relevant and informs patient peace of mind and long-term risk, please provide an exploratory analysis showing the estimated median time to first attack for donidalorsen Q4W/Q8W versus placebo, and justify the rationale for omitting them from the model when assessing comparative clinical benefit.

As discussed in the response to Question A2, attack-free period and time to first attack were not included as primary or secondary outcome measures in the pivotal phase III trial of donidalorsen, OASIS-HAE.^{9,10} The company considers that the endpoints assessed in OASIS-HAE (detailed in Section 2.6.3 of the CES) comprehensively evaluate and demonstrate the clinical benefit of donidalorsen.

Specifically, regarding the exclusion of time to first attack from OASIS-HAE, the company does not consider analysis of this endpoint to be appropriate for evaluating the efficacy of donidalorsen, given the time taken for patients to reach the steady state period after initiating treatment. Donidalorsen interacts directly with prekallikrein (PKK) messenger RNA (mRNA) in hepatocytes, as discussed in the response to Question A7.²⁶ Existing plasma PKK has an estimated half-life of approximately five days and must degrade before the onset of clinical effect.^{26,66,67} The reduction in plasma PKK levels is, therefore, not expected to be immediate. The steady state period, characterised by a consistent therapeutic effect, is assessed by the stable reduction of plasma PKK levels; donidalorsen is expected to reach the steady state period at approximately 25 to 30 days (i.e. after the first four-week dosing period).^{6,9} Accordingly, analyses of certain clinical endpoints in OASIS-HAE from Week 5 were conducted.⁶

As time to first attack was not included as an endpoint in OASIS-HAE, this outcome was not assessed in the company's NMA. This outcome was therefore also not used in the company's economic analysis to assess the comparative clinical benefit of LTPs, which is in line with the economic analyses from prior NICE appraisals

(lanadelumab, TA606; berotralstat, TA738).^{16,17} Furthermore, as these data were not collected in OASIS-HAE and APeX-2, clinical assumptions would have to be made to incorporate such data into the economic model (e.g. estimation of mean time to first attack based on clinical validation or assumed equivalence to comparators), which would increase the uncertainty of the economic analysis.^{9,12} The company considers the use of the attack rate data from the primary endpoints across the comparator trials a more suitable representation of HAE attack incidence during the first 24 weeks of the model. This approach is preferred compared to the estimation of a specific timepoint, only after which patients begin to experience attacks in each treatment arm (in line with the measured trial attack rates). Trial HAE attack rate data inherently captures the time to first attack; to also apply a fixed timepoint where patients are assumed to experience no attacks until that point limits the economic analysis. This limitation is due to the costs and outcomes associated with attacks some patients would experience not being captured, as the time to first attack timepoint would be derived from an average within the respective trial cohorts. This means, in practice, attacks that some patients would still experience before reaching this point are not captured in the analysis. The company therefore considers excluding time to first attack from the economic model to be justified and does not view this as a limitation in assessing the comparative efficacy of LTPs.

The company considers the assessment of attack-free status in OASIS-HAE, defined as 'The percentage of Investigator-confirmed HAE attack-free patients from Week 5 to Week 25 compared to placebo', a meaningful way to assess the proportion of patients who achieved complete prevention of attacks over the 24-week treatment period, once a consistent therapeutic effect has been reached.^{6,9} This endpoint informs patients of their long-term risk of experiencing an attack and their ability to remain attack-free for substantial periods while treated with donidalorsen. Furthermore, the company conducted a post-hoc analysis of the proportion of patients who remained attack-free for [REDACTED] during OASIS-HAE (see Section 3.5.1.3 for further details), demonstrating that [REDACTED]% of patients remained attack-free for [REDACTED] during the 24-week treatment period.⁶⁸ The company consider these analyses to present highly patient-relevant outcomes which inform patient peace of mind and long-term risk.

Overall, the clinical endpoints assessed in OASIS-HAE comprehensively evaluate the efficacy of donidalorsen as an LTP.^{6,9} The company does not consider the analysis of time to first attack to be appropriate for evaluating the efficacy of donidalorsen, given the time taken for patients to reach the steady state period after initiating treatment. The endpoints assessed in OASIS-HAE provide patient-relevant evidence of the clinical benefit of donidalorsen, which inform patient peace of mind and long-term risk. Furthermore, excluding time to first attack from the economic model aligns with the economic analyses of prior NICE appraisals for LTPs.^{16,17} Therefore, the company considers excluding this endpoint from the economic analysis to be justified and appropriate for the clinical and economic evaluation of donidalorsen as an LTP.

Time to treatment discontinuation

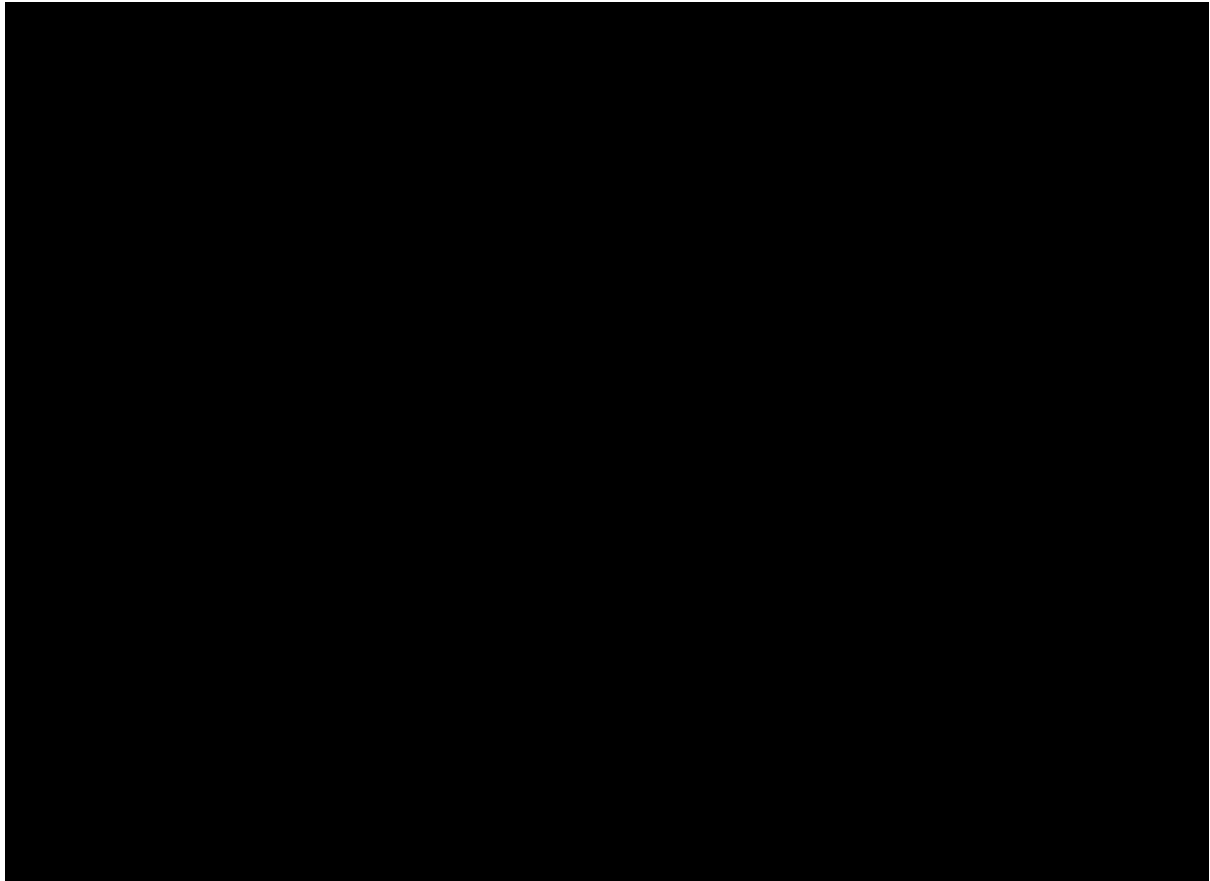
A28. Please provide the Kaplan-Meier (KM) survival curves (with numbers at risk) from the OASIS-HAE and OASISplus studies for Time to Treatment Discontinuation (TTD) for both the Q1M and Q2M groups

The KM survival curves for TTD, including number at risk, from OASIS-HAE and OASISplus OLE cohort are presented in Figure 7 and Figure 8, respectively. While no KM data are available for the OASISplus switch cohort, Table 12 in response to Question A10 presents the discontinuation data available from the 27 January 2025 data cut-off for the OASISplus switch cohort.

Overall, treatment discontinuation was low in the OASIS-HAE trial, as demonstrated by the KM data in Figure 7. As discussed in Section 2.3.1.1 of the CES, a higher proportion of patients in the donidalorsen Q4W group (44 [95.7%]) and the donidalorsen Q8W group (21 [91.3%]) completed treatment compared with the placebo group (18 [81.8%]).⁶

The long-term data from OASISplus (data cut-off January 27, 2025) demonstrated that the majority of patients remain on treatment long term, as demonstrated by the KM data presented in Figure 8. As discussed in the response to Question A10, in the OASISplus OLE cohort discontinuation rates were low and no patients discontinued to the lack of efficacy.³¹

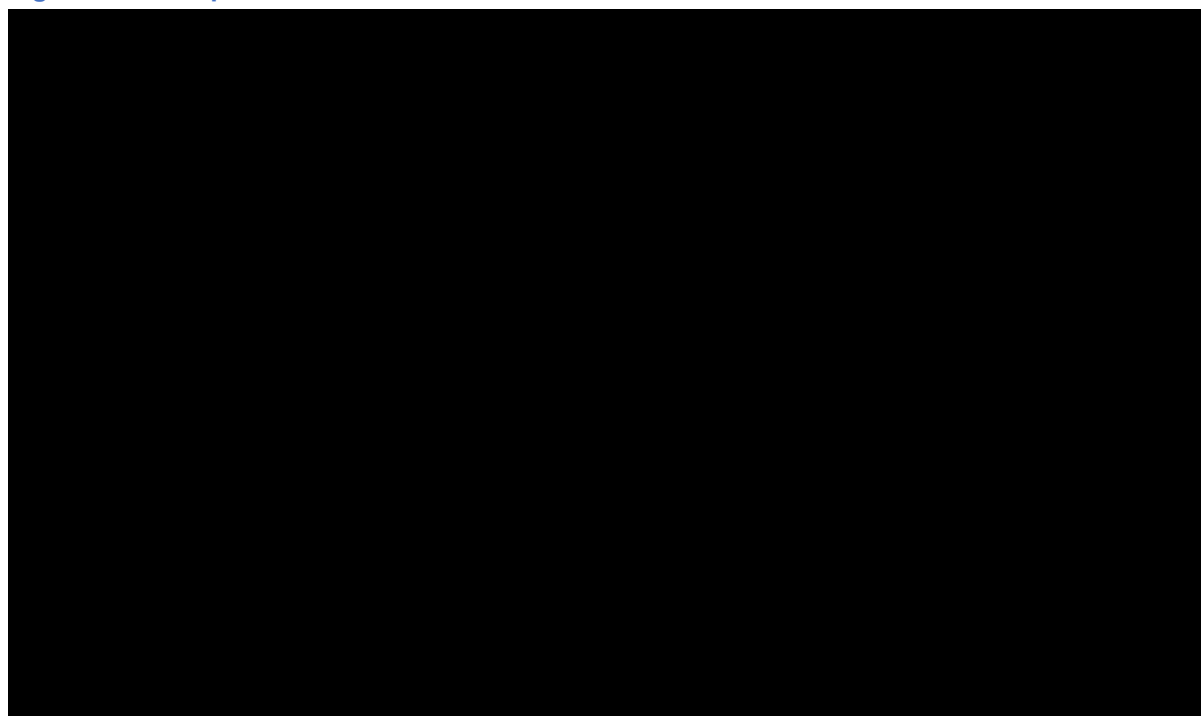
Figure 7: OASIS-HAE trial TTD KM curves



Abbreviations: DQ4W – Donidalorsen once every 4 weeks; DQ8W – Donidalorsen once every 8 weeks; KM – Kaplan-Meier; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks; TTD – Time to Treatment Discontinuation.

Data on file. Post-hoc analysis of OASIS-HAE data²³

Figure 8: OASISplus OLE cohort TTD KM curves



Abbreviations: DQ4W – Donidalorsen once every 4 weeks; DQ8W – Donidalorsen once every 8 weeks; KM – Kaplan-Meier; OLE – Open-label extension; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks; TTD – Time to Treatment Discontinuation.

Data on file. Post-hoc analysis of OASISplus data²³

Section B: Clarification on cost-effectiveness data

B1. [Priority Question]: Please run scenario analyses incorporating an efficacy-based stopping rule for berotralstat for both the cost-comparison and cost-utility analyses (presented in Appendix K). Please clearly document how the stopping rule is operationalised in the model.

Treatment with berotralstat for patients in England and Wales is subject to an efficacy-based stopping rule; patients must discontinue treatment if they do not achieve at least a 50% reduction in the monthly attack rate from baseline after three months of treatment.¹⁶ In the APeX-2 trial, 42% of patients receiving berotralstat failed to achieve at least a 50% reduction in monthly attacks from baseline, highlighting that a large proportion of patients do not respond sufficiently to berotralstat.¹²

Based on the clinical evidence and the results of the NMA, both explained in Section 2 of the CES, the assumption of equal efficacy across LTPs is applied in the company's base case cost-comparison. The clinical plausibility of the equal efficacy

assumption and interpretation of NMA results was validated by UK clinical experts in September 2025 (see Section 3.3.1.3 for further detail).²²

The company considers it unreasonable and implausible to apply an efficacy-based stopping rule for berotralstat while also assuming equal efficacy across LTPs, including berotralstat. Including the stopping rule would remove treatment costs for patients who do not respond to berotralstat but would not recognise the poorer health outcomes (increased number of attacks) experienced by patients who receive no LTP. Assuming that patients discontinue berotralstat for efficacy-based reasons also contradicts with the equal efficacy assumption of the company's base case analysis. Therefore, including the berotralstat stopping rule would give an inaccurate representation of both cost and treatment outcomes with berotralstat.

Therefore, for the company's economic analysis, the berotralstat stopping rule was excluded, in line with the base case assumption of equal efficacy across all LTPs in the base case. In the company's base case cost-comparison analysis, it is assumed that all patients treated with berotralstat respond well to treatment and do not need to discontinue for reasons of lack of efficacy. As such, patients receiving berotralstat discontinue treatment at the same rate as those receiving donidalorsen and other LTPs. This assumption is likely favourable to berotralstat, as it implies a better clinical profile for berotralstat than is typically observed in clinical practice and was observed in the APeX-2 trial, where a large proportion of patients (42%) did not respond sufficiently to berotralstat.^{12,22} While the company acknowledge that excluding the efficacy-based stopping rule for berotralstat is a limitation, the company maintains that using the same assumption of equal efficacy and discontinuation across all LTPs is the most appropriate approach. Therefore, the company have not included the berotralstat stopping rule in the base case cost-comparison analysis and does not consider it suitable to present as a scenario. For further details regarding the specific considerations for berotralstat in the economic analysis, refer to Section 3.3.1.3 of the CES.

In the cost-utility analysis presented in Appendix K of the CES, the company also excluded the berotralstat stopping rule to align with the approach of the base-case analysis. However, to assist the EAG in their analyses, the company have presented a scenario of the cost-utility analysis with the berotralstat stopping rule applied.

Data from the pivotal trial for berotralstat, APeX-2, were used to determine how many patients do not achieve at least a 50% reduction in HAE attack rate versus baseline; these patients are assumed to discontinue treatment with berotralstat after three months in the cost-utility analysis.¹² The APeX-2 trial shows that 58% of patients receiving 150 mg dose of berotralstat achieved at least a 50% reduction in HAE attacks (i.e. responders).¹² Based on these data, 42% of patients (100%-58%) did not achieve a 50% reduction in HAE attacks (i.e. non-responders). Therefore, in the economic model, 42% of patients are assumed to discontinue berotralstat from three months in the cost-utility analysis. Patients who discontinue LTPs then receive 'no LTP'. This means that 42% of patients receiving berotralstat move to receive 'no LTP' from three months for the remainder of the model time horizon.

As detailed in Section 1.2 of Appendix K, HAE attack rates for donidalorsen and comparator LTPs in the company's cost-utility scenario analysis are derived from the NMA median rate ratio point estimates of the mean number of HAE attacks per month relative to placebo (Table 5 of Appendix K of the CES). For patients receiving berotralstat, the point estimates from the company's NMA are applied irrespective of their responder status. The weekly attack rates from Week 1 to Week 25, from the placebo arm in the OASIS-HAE trial, are used to inform the attack rate for 'no LTP' for the first 24 weeks in the model (for details on the extrapolation of attack rates from week 25 in the economic model, please see Section 1.2.4 of Appendix K).

The results for the cost-utility analysis when incorporating an efficacy-based stopping rule are presented in Table 30. These results use the list price of berotralstat and a PAS discount of [REDACTED] % with a net price of [REDACTED] per 80 mg pre-filled pen for donidalorsen. Over a lifetime time horizon, treatment with donidalorsen in patients with HAE experiencing ≥ 2 attacks per month resulted in an ICER of [REDACTED] versus berotralstat. As shown in Table 31, which compares the disaggregated cost results of the cost-utility analysis with and without the berotralstat stopping rule, LTP acquisition costs for berotralstat decrease from [REDACTED] to [REDACTED], resulting in a large impact on the ICER.

In this cost-utility analysis, despite the superior incremental QALYs ([REDACTED]) for donidalorsen versus berotralstat, the results are predominantly driven by treatment acquisition costs. When applying the berotralstat stopping rule, the incremental 'LTP

acquisition' cost between donidalorsen and berotralstat is [REDACTED], making LTP acquisition costs the [REDACTED] of incremental costs and [REDACTED] the total net incremental costs ([REDACTED]). This shows that treatment acquisition costs are the predominant driver of the total incremental costs and, therefore, a key driver of the ICER.

Furthermore, when applying the berotralstat stopping rule, 42% of patients no longer incur berotralstat treatment costs after three months in the model. The analysis assumes that these berotralstat non-responders then receive 'no LTP', instead of an alternative LTP, therefore not incurring any further LTP acquisition costs. The company believe this assumption substantially underestimates the treatment costs associated with berotralstat non-responder cohort for the majority of the time horizon in the economic model.

As shown in Table 31, the main cost driver for berotralstat when the stopping rule is applied is costs of treatment of acute HAE attacks, increasing the HAE attack pharmacological and HCRU costs post-discontinuation from [REDACTED] to [REDACTED] for berotralstat. This is driven by the higher HAE attack rate associated with 'no LTP' versus berotralstat in those patients that do not respond to treatment and discontinue. When the berotralstat stopping rule is applied, a significant proportion of patients in the berotralstat treatment arm receive 'no LTP' and incur higher acute attack management costs. This, combined with substantially lower LTP acquisition costs, generates [REDACTED] incremental costs that result in a [REDACTED] ICER for donidalorsen versus berotralstat. In comparison, when the efficacy-based stopping rule is not applied, [REDACTED] incremental costs are generated ([REDACTED]) that result in a [REDACTED] ICER for donidalorsen versus berotralstat. When the efficacy-based stopping rule is applied, there is a substantial reduction in total costs for berotralstat compared to when the stopping rule is excluded. However, there is considerable uncertainty in the total costs for the berotralstat cohort when the stopping rule is applied, due to the uncertainty of the costs associated with treating acute HAE attacks in the economic model. Due to limited literature on HCRU associated with HAE attacks, these costs are estimated based on HCRU inputs sought from clinical experts.²² Consequently, the costs incurred by the berotralstat

non-responder population may be underestimated, and therefore the total costs for the berotralstat cohort are anticipated to be underestimated.

Overall, there is significant uncertainty in this scenario due to two key factors: the uncertainty in costs associated with HAE attacks, and the lack of LTP acquisition and administration costs after three months for 42% of patients in the berotralstat cohort post-discontinuation. It is important that the final interpretation of donidalorsen's cost-effectiveness versus berotralstat takes this into account. For these reasons, the company maintain that the base case cost-comparison analysis and the cost-utility scenario, which exclude the berotralstat efficacy-based stopping rule (presented in the CES and Appendix K, respectively), represent the most appropriate analyses to evaluate the cost-savings and cost-effectiveness of donidalorsen.

Table 30: Cost-utility scenario including the berotralstat efficacy based stopping rule

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
2+ attacks per month population								
Donidalorsen	██████	22.515	██████	██████	-	██████	-	-
Berotralstat	██████	22.515	██████	██████	0.000	██████	██████	██████

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years.

Table 31: Comparison of cost-utility analysis disaggregated cost results with and without berotralstat stopping rule

Costs	Stopping rule excluded		Stopping rule included	
	Donidalorsen	Berotralstat	Donidalorsen	Berotralstat
LTP acquisition cost (£)	██████	██████	██████	██████
LTP administration cost (£)	██████	██████	██████	██████
HAE attack pharmacological costs (£) - initial treatment	██████	██████	██████	██████
HAE attack HCRU costs (£) - initial treatment	██████	██████	██████	██████
Total pharmacological and HCRU costs (£) – initial treatment	██████	██████	██████	██████

Costs	Stopping rule excluded		Stopping rule included	
	Donidalorsen	Berotrastat	Donidalorsen	Berotrastat
HAE attack pharmacological costs (£) - post discontinuation treatment	██████	██████	██████	██████
HAE attack HCRU costs (£) - post discontinuation treatment	██████	██████	██████	██████
Total pharmacological and HCRU costs – post discontinuation	██████	██████	██████	██████
Post discontinuation treatment costs (£)	█	█	█	█
Total cost (£)	██████	██████	██████	██████

Abbreviations: HCRU – Healthcare resource use.

B2. [Priority Question]: Please provide adverse event tables for each comparator as reported in the relevant Technology Appraisals. These should match the AE sources cited in the submission.

- For each comparator: (a) AE incidence (n, %), (b) AE severity (grades or seriousness where available), (c) AE definitions and MedDRA preferred terms used, (d) source references (TA ID / appendix / page). If multiple TAs are relevant, please provide a crosswalk table linking each AE table to its TA source.

The company have collated information from the relevant company submission documents from NICE TAs for each comparator: NICE TA738 for berotrastat and NICE TA606 for lanadelumab.^{16,69} As C1-INH was not appraised by NICE, there is no NICE TA for available; as such, the AE rates are sourced from the COMPACT trial, presented in a paper by Longhurst *et al.* (2017).⁴⁷ An overview of the AE data per comparator are presented below. The AE data reported in NICE TA738, NICE TA606 and Longhurst *et al.* (2017) are aligned with the data used in the donidalorsen CES.^{16,47,69}

Berotrastat:

On page 88 of the berotrastat company submission (NICE TA738), it is stated that “no SAEs or drug-related grade 3 or 4 TEAE were observed in patients with

berotralstat 150mg during the APeX-2 study”. Therefore, the economic model in TA738 did not include the impact of adverse events. An overview of the TEAEs, based on Table 17 (page 66) of TA738 using the APeX-2 CSR data, is presented in Table 32.¹⁶

Table 32: Berotralstat AE data from NICE TA738

TEAE Summary	Berotralstat 150 mg (N=40)	Placebo (N=39)
Any TEAE, n (%)	34 (85.0%)	30 (76.9%)
Any drug-related TEAE ^a , n (%)	15 (37.5%)	13 (33.3%)
Any SAE, n (%)	0	3 (7.7%)
Any drug-related SAE, n (%)	0	0
Any Grade 3 or 4 TEAE, n (%)	Redacted	Redacted
Any drug-related Grade 3 or 4 TEAE, n (%)	0	0
Any TEAE leading to interruption of study drug ^b , n (%)	Redacted	Redacted
Any TEAE leading to discontinuation of study drug, n (%)	1 (2.5%)	1 (2.6%)
Any investigator-identified rash ^c , n (%)	1 (2.5%)	0
Any GI abdominal TEAE ^d , n (%)	20 (50%)	14 (35/9%)
Any GI abdominal TEAE leading to discontinuation of study drug, n (%)	0	0

Abbreviations: AE – Adverse event; eCRF – electronic case report form; GI – gastrointestinal; MedDRA – Medical Dictionary for Regulatory Activities; N – number of patients; n – number of patients who experienced the event; PT – preferred term; SAE – serious adverse event; TEAE – treatment-emergent adverse event

^a A drug-related TEAE was defined as any AE where the investigator defines the relationship to blinded study drug as Possibly Related, Probably Related, or Definitely Related.

^b An AE leading to interruption of study drug was any AE where the Action Taken on the AE eCRF was marked as 'Drug Interrupted'.

^c An investigator identified rash was any AE that the investigator noted as an AE of special interest on the AE eCRF.

^d GI abdominal AE was any AE with a PT within the MedDRA 19.1 hierarchy under the High-level Group Terms of 1) GI signs and symptoms or 2) GI motility and defaecation conditions.

Source: NICE TA738¹⁶ (APeX-2 CSR)

C1-INH:

No TA is available for C1-INH, instead data from the COMPACT trial, a Phase III trial which evaluated the efficacy and safety of C1-INH, is presented in Table 33.⁴⁷ This data has been taken from the pivotal trial publication by Longhurst *et al.* (2017),

which presented the AEs reported during the COMPACT trial in Table 3 (page 1138) of the publication.⁴⁷

Table 33: Adverse events reported during the COMPACT trial^a

Event	C1-INH Dose Groups		Total C1-INH (N=86)	Placebo (N=86)
	40 IU (N=43)	60 IU (N=43)		
Any adverse event, n (%)	29 (67)	30 (70)	59 (69)	57 (66)
Any related adverse event ^b , n (%)	14 (33)	15 (35)	29 (34)	22 (26)
Any serious adverse event, n (%)	1 (2)	0	1 (1)	2 (2)
Any related serious adverse event ^b , n (%)	0	0	0	1 (1)
Adverse event leading to trial discontinuation, n (%)	0	2 (5)	2 (2)	1 (1)
Nonserious adverse event in ≥5% of patients, n (%)				
Injection-site reaction ^c , n (%)	12 (28)	15 (35)	27 (31)	21 (24)
Nasopharyngitis, n (%)	1 (2)	8 (19)	9 (11)	6 (7)
Upper-respiratory-tract infection, n (%)	3 (7)	3 (7)	6 (7)	6 (7)
Hypersensitivity ^d , n (%)	2 (5)	3 (7)	5 (6)	1 (1)
Dizziness, n (%)	4 (9)	0	4 (5)	1 (1)
Fatigue, n (%)	1 (2)	1 (2)	2 (2)	6 (7)
Back pain, n (%)	1 (2)	1 (2)	2 (2)	5 (6)

Abbreviations: C1-INH – C1-esterase inhibitor; IU – international unit.

^a The safety analysis included all the patients in the intention-to-treat population who had received at least one dose of a study drug. Included are adverse events that had an onset within 24 hours after administration, which were followed until they resolved.

^b Related adverse events were adverse events that were classified by the investigator as being related to CSL830.

^c Injection-site reactions included bruising, erythema, pain, swelling, edema, hemorrhage, and induration.

^d Hypersensitivity included pruritus, rash, and urticaria.

Source: Longhurst et al. (2017)⁴⁷

Lanadelumab:

As reported on page 163 and in Table 52 (page 164) of the lanadelumab company submission (NICE TA606), the costs of only two AEs were included in the economic model. The impact of AEs on HRQoL, in line with the TA738 for berotralstat and the

donidalorsen CES, was not included in the economic model. An overview of TEAE during the treatment period presented in Table 24 (page 107-108) of the lanadelumab submission (TA606), based on data from the HELP-03 CSR, are presented in Table 34.⁶⁹

Table 34: Lanadelumab AE data from NICE TA606

Event, N (%) m	Placebo (n=41)	Lanadelumab	
		300 mg Q2W (n=27)	300 mg Q4W (n=29)
Any TEAE	31 (75.6) 231	26 (96.3) 235	25 (86.2) 182
Any treatment-related TEAE	14 (34.1) 85	19 (70.4) 131	14 (48.3) 121
Any serious TEAE	0 (0.0) 0	1 (3.7) 1	3 (10.3) 3
Risk difference (95% CI)		3.70 (-20.34, 27.39)	10.34 (-13.36, 33.42)
Any related serious TEAE	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Any severe TEAE	4 (9.8) 7	2 (7.4) 2	4 (13.8) 6
Any related severe TEAE	1 (2.4) 4	0 (0.0) 0	1 (3.4) 2
Any investigator-reported AESI	0 (0.0) 0	3 (11.1) 4	1 (3.4) 2
Deaths due to TEAE	0 (0.0) -	0 (0.0) -	0 (0.0) -
Hospitalisation due to TEAE	0 (0.0) 0	1 (3.7) 1	3 (10.3) 3
Discontinuation due to TEAE	1 (2.4) -	0 (0.0) 0	1 (3.4) -

Abbreviations: AE – Adverse event; AESI – adverse event of special interest; EDC – electronic data capture; HAE – hereditary angioedema; n – number of patients experiencing the event; NE – non-estimated; m – number of events; q2w – every 2 weeks; q4w – every 4 weeks; TEAE – treatment-emergent adverse event.

Source: TA606⁶⁹ (HELP-03 CSR)

Overall, the CES for NICE TA606 (lanadelumab) only includes the costs associated with two AEs and NICE TA738 (berotralstat) does not include any impact of AEs on costs or HRQoL, the latter is in line with the CES for donidalorsen.^{16,69} The data in the tables above are in line with the sources referenced in the CES for donidalorsen, as highlighted in Section 3.4.1 on page 155 of the CES.

B3. [Priority Question]: Please incorporate full healthcare resource use (HCRU) into the cost-comparison analysis so total costs per treatment arm are captured even if resource use costs are similar across comparators

In the company's base case cost-comparison analysis, efficacy of all LTPs is assumed to be equal, based on the results of the company's NMA (Section 3.3.1.3 of the CES). No HCRU data are included in the company base case cost-comparison analysis. The efficacy of all treatments is assumed to be equal and therefore HCRU is the same across all LTPs (Section 3.5.2 of the CES).

In the economic model, HCRU per HAE attack depends on attack severity, and the proportion of attacks in each category of severity (mild, moderate/severe or laryngeal) is equal for all patients treated with each LTP. Therefore, the weighted HCRU associated with each attack is assumed to be the same for each LTP and the HCRU costs are weighted to reflect the proportion and costs of attacks in each severity category. The company's base case cost-comparison assumes equal efficacy for all LTPs, so the number of HAE attacks, and the distribution of attacks by severity category, is the same across all LTPs. Therefore, HCRU does not impact incremental costs.

To support the EAG to assess the impact of including HCRU, the company have explored a scenario which includes HCRU in the cost-comparison analysis. Version 2.0 of the economic model includes a switch in the Settings sheet that allows the user to include HCRU in the cost-comparison analysis.

HCRU inputs included in the cost-comparison analysis are the same as HCRU inputs in the cost-utility analysis, as presented in Table 12 of Appendix K. These inputs were derived from data collected by Mendivil *et al.* (2023) for moderate/severe attacks, supplemented by additional input and validation from clinical experts.^{22,70} The resource use estimates per HAE attack sourced from Mendivil *et al.* (2023) were presented to UK clinical experts in validation meetings held in September 2025, alongside the estimated resource use for mild and laryngeal attacks; the resource use estimates were updated according to expert opinion using an average of the clinical experts' responses.²² As such, the resource use estimates implemented in the economic model utilise data from both Mendivil *et al.* (2023) and UK clinical expert opinion (obtained in clinical validation meetings held in June and September

of 2025).^{22,70} An overview of the HCRU, as presented in Table 12 in Appendix K, as well as the associated costs can be found below in Table 35 and Table 36, respectively.

Table 35: HCRU per attack

Resource	Proportion of patients requiring resource use per attack (%)		
	Mild attack	Moderate/severe attack	Laryngeal attack
A&E visit	■	■	■
One day inpatient stay	■	■	■
Intubation	■	■	■
Radiography	■	■	■
Ambulance transport	■	■	■
Blood tests	■	■	■
Outpatient appointment - consultant led	■	■	■
Outpatient appointment – non-consultant led	■	■	■

Abbreviations: A&E – Accident and emergency; HCRU – Healthcare resource utilisation

Source: Moderate/ severe attack resource use informed by Mendivil et al. (2023).⁷⁰ Mild and laryngeal HCRU proportions calculate relative to the moderate/ severe HCRU. Validated by UK clinicians.²²

Table 36: Cost per HCRU

Resource	Unit cost (£)	Source
A&E visit	188.63	Code 180 - Emergency Medicine Service. Weighted average across consultant led and non-consultant led; National Cost Collection from the NHS 2023/24 ⁷¹
One day inpatient stay	618.04	WJ11Z - Other Disorders of Immunity – Admitted Patient Care – Regular Day or Night Admissions; National Cost Collection from the NHS 2023/24 ⁷¹
Intubation	282.40	RN18A - Lung Ventilation or Perfusion Scan, 19 years and over - Directly Accessed Diagnostic Services; National Cost Collection from the NHS 2023/24 ⁷¹
Radiography	1014.20	RD40Z - Ultrasound Scan with duration of less than 20 minutes, without Contrast. Directly Accessed Diagnostic Services – Ear Nose and Throat Service; National Cost Collection from the NHS 2023/24 ⁷¹
Ambulance transport	458.73	Table 6.1.1 Unit costs for hospital services – Ambulance: See and convey; Unit Costs of Health and Social Care 2024 ⁷²
Blood tests	9.20	PATH08 Phlebotomy. Directly Accessed Pathology Services 303. Clinical Haematology Service; National Cost Collection from the NHS 2023/24 ⁷¹

Resource	Unit cost (£)	Source
Outpatient appointment - consultant led	617.70	WF01A Clinical Immunology Service (Consultant led). Non-Admitted Face-to-Face Attendance, First; National Cost Collection from the NHS 2023/24 ⁷¹
Outpatient appointment – non-consultant led	135.05	WF01B Ear Nose and Throat Service (Non-consultant led). Non-Admitted Face-to-Face Attendance, First; National Cost Collection from the NHS 2023/24 ⁷¹

Abbreviations: A&E – Accident and emergency; HAE – Hereditary angioedema; HCRU – Healthcare resource utilisation; NHS – National Health Service

To incorporate the HCRU into the cost-comparison analysis, the same approach is used as in the cost-utility analysis. Every HAE attack experienced by a patient is categorised by attack severity; the distribution of attacks categorised by severity is based on data from the OASIS-HAE trial; a weighted cost per HAE attack, reflecting the distribution of severity, is detailed in Table 37. This weighted HCRU cost per attack is applied for each attack experienced by a patient.

Table 37: Proportion of attacks and HCRU by severity

Attack classification	Proportion of all attacks	Source	Weighted HCRU per attack
All	-	OASIS-HAE, donidalorsen Q4W all attacks Weeks 1-25 LSM ⁶	
Laryngeal	■	OASIS-HAE, donidalorsen Q4W laryngeal attacks Weeks 1-25 LSM ⁶	■
Moderate/severe (excluding laryngeal attacks)	■	OASIS-HAE, donidalorsen Q4W moderate/severe Weeks 1-25 LSM ⁶	■
Mild	■	Assumed to be 1 minus moderate/severe proportion	■
Total HCRU cost per attack			■

Abbreviations: HAE – Hereditary angioedema; Q4W – Once every four weeks

The results when incorporating the above HCRU into the company's base case cost-comparison analysis are presented in Table 38 and Table 39 for the ≥ 2 attacks and ≥ 8 attacks groups, respectively. Including HCRU increases the total costs for each treatment in the model, but the incremental costs stay the same. This is demonstrated by the incremental costs presented in Table 38 and Table 39 matching those presented in the CES in Table 40 and Table 41, respectively. Donidalorsen remains cost-saving against all comparator LTPs when including HCRU into the cost-comparison analysis. Over a lifetime time horizon, treatment with donidalorsen in patients with HAE experiencing ≥ 2 attacks per month was associated with cost savings of £■ per patient versus berotralstat. In patients with HAE experiencing

≥8 attacks per month, treatment with donidalorsen was associated with cost savings over a lifetime time horizon of £ [REDACTED] per patient versus lanadelumab and cost savings of [REDACTED] per patient versus C1-INH, resulting in donidalorsen providing cost-savings to the NHS versus all comparators.

Table 38: Cost-comparison deterministic results including HCRU costs (≥2 attacks per month)

Intervention/comparator	Total costs per patient (£)	Incremental costs versus donidalorsen (£)
Donidalorsen	[REDACTED]	[REDACTED]
Berotrastat	[REDACTED]	[REDACTED]

Abbreviations: HCRU – Health-care resource use.

Table 39: Cost-comparison deterministic results including HCRU costs (≥8 attacks per month)

Intervention/comparator	Total costs per patient (£)	Incremental costs versus donidalorsen (£)
Donidalorsen	[REDACTED]	[REDACTED]
Lanadelumab	[REDACTED]	[REDACTED]
C1-INH	[REDACTED]	[REDACTED]

Abbreviations: C1-INH – C1 Inhibitor; HCRU – Health-care resource use.

B4. For completeness, please provide the EQ-5D-5L utility values collected in the OASIS-HAE trial. The CSR cites “Table 14.2.1.1-1 EuroQoL-5-Dimensions Quality of Life Questionnaire (EQ-5D-5L) by Visit – Full Analysis Set” but the table is not included. Please supply the missing table and, if possible, the underpinning dataset variables or summary statistics.

Table 14.2.11.1 “Summary of EuroQoL-5-Dimensions Quality of Life Questionnaire (EQ-5D-5L) by Visit Full Analysis Set” from the OASIS-HAE CSR is presented in Table 40 below.³²

Table 40: Summary of EuroQoL-5-Dimensions Quality of Life Questionnaire (EQ-5D-5L) by Visit Full Analysis Set

	Pooled Placebo (N=22)	Donidalorsen Q4W (N=45)	Donidalorsen Q8W (N=23)
Health index score			
Baseline [1]			
n	[REDACTED]	[REDACTED]	[REDACTED]
Mean (SD, SEM)	[REDACTED]	[REDACTED]	[REDACTED]
Median (P25, P75)	[REDACTED]	[REDACTED]	[REDACTED]
Min, Max	[REDACTED]	[REDACTED]	[REDACTED]
Mean 95% CI	[REDACTED]	[REDACTED]	[REDACTED]

	Pooled Placebo (N=22)	Donidalorsen Q4W (N=45)	Donidalorsen Q8W (N=23)
Week 13 Day 85			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Change from Baseline to Week 13 Day 85			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Percent Change from Baseline to Week 13 Day 85			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Week 25 Day 169			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Change from Baseline to Week 25 Day 169			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Percent Change from Baseline to Week 25 Day 169			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Post-Treatment Week 13 Day 91			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			

	Pooled Placebo (N=22)	Donidalorsen Q4W (N=45)	Donidalorsen Q8W (N=23)
Change from Baseline to Post-Treatment Week 13 Day 91			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Percent Change from Baseline to Post-Treatment Week 13 Day 91			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
EQ VAS Score			
Baseline [1]			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Week 13 Day 85			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Change from Baseline to Week 13 day 85			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Percent Change from Baseline to Week 13 Day 85			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Week 25 Day 169			
n			
Mean (SD, SEM)			

	Pooled Placebo (N=22)	Donidalorsen Q4W (N=45)	Donidalorsen Q8W (N=23)
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Change from Baseline to Week 25 Day 169			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Percent Change from Baseline to Week 25 Day 169			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Post-Treatment Week 13 Day 91			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Change from Baseline to Post-Treatment Week 13 Day 91			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			
Percent Change from Baseline to Post-Treatment Week 13 Day 91			
n			
Mean (SD, SEM)			
Median (P25, P75)			
Min, Max			
Mean 95% CI			

Abbreviations: CI – Confidence Interval; EQ VAS – EuroQol Visual Analogue Scale; Max – maximum; Min – minimum; N – number of patients in the analysis set; n – number of patients in the specific category; NC – not calculated; Q4W – Once every 4 weeks; Q8W – once every 8 weeks; SD – Standard deviation; SEM – Standard Error of the Mean; P25 – 25th percentile; P75 – 75th percentile;

The EQ-5D health index score is derived as 1 - sum of weights from responses of 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), where the weight is based on the value sets issued by EuroQoL group.

The EQ VAS records a self-rating of health status on a vertical VAS anchored at 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom.

[1] Baseline is defined as the score on Study Day 1.

Source: OASIS-HAE CSR (Table 14.2.11.1)³²

B5. Please present the on-demand treatments received by participants during the OASIS-HAE trial, and the doses administered, separately for the donidalorsen and placebo groups. This should include rescue/on-demand medication types, dose, frequency, and timing relative to attacks (if available).

Data categories used to collect data from the OASIS-HAE trial did not include a rescue medication type, hence, only data for on-demand treatment is presented in this response.

The on-demand treatments received by participants during the OASIS-trial were complement C1-INH, conestat alfa, icatibant, icatibant acetate, and tranexamic acid.²³

An overview of the on-demand treatments used in the OASIS-HAE trial is presented in Table 41. In the placebo arm, the on-demand treatment with the highest reported use is complement C1-INH, whereas the highest reported on-demand treatment is icatibant acetate for the patients in the donidalorsen Q4W and donidalorsen Q8W arms.²³ While data for use of on-demand treatments relative to the timing of HAE attack are not available, the total frequency of on-demand treatment usage reported in the OASIS-HAE trial is reported in Table 42. Overall, patients in the placebo arm of the OASIS-HAE trial reported the highest average frequency of on-demand treatment usage, followed by donidalorsen Q8W and donidalorsen Q4W respectively. Data on the total dose of on-demand therapy received by patients are split into two data category types, mg and IU, in line with the dosing options. This data can be found in Table 43.

Table 41: On-demand treatments in the OASIS-HAE trial

Parameter	Placebo (N=22)	Donidalorsen 80 mg Q4W (N=45)	Donidalorsen 80 mg Q8W (N=23)
Complement C1-INH	■	■	■
Conestat alfa	■	■	■
Icatibant	■	■	■
Icatibant acetate	■	■	■
Tranexamic acid	■	■	■

Abbreviations: C1-INH - c1 esterase inhibitor; N – number of patients in the analysis population; n – number of patients in the specific category; Q4Q – Once every 4 weeks; Q8W – Once every 8 weeks.
Data on file. Post-hoc analysis of OASIS-HAE data²³

Table 42: Frequency of on-demand treatment use in the OASIS-HAE trial

Parameter	Placebo (N=22)	Donidalorsen 80 mg Q4W (N=45)	Donidalorsen 80 mg Q8W (N=23)
Total number of reported uses of on-demand therapy	■	■	■
Frequency of on-demand therapy use per patient*	■	■	■

*Calculated as a simple arithmetic mean by dividing the number of reported uses of on-demand therapy in the treatment arm by the number of patients in the treatment arm.

Abbreviations: N – number of patients in the analysis population; n – number of patients in the specific category; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

Data on file. Post-hoc analysis of OASIS-HAE data²³

Table 43: Number of events and required dosage for on-demand treatments used in the OASIS-HAE trial

Parameter	Placebo (N=22)	Donidalorsen 80 mg Q4W (N=45)	Donidalorsen 80 mg Q8W (N=23)
On-demand treatment dose received (IU)			
Mean (SD)	■	■	■
On-demand treatment dose received (mg)			
Mean (SD)	■	■	■

Abbreviations: mg – milligram; N – number of patients in the analysis population; n – number of patients in the specific category; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks; SD – Standard deviation; IU – International unit.

Data on file. Post-hoc analysis of OASIS-HAE data²³

B6. In the CS Pg 161, it was stated on demand medications C1-INH (Berinert, Cinryze), icatibant (Firazyr, and Ruconest injections are administered at home and therefore no administration costs are applied. Please explain why administration costs are applied to LTPs including C1-INH that are administered at home and not applied to on-demand medications administered at home.

In the company's base case cost-comparison analysis, documented in the CES, it is assumed that all on-demand treatments are administered at home. The assumption that there are no administration costs associated with on-demand treatments is in line with the assumption accepted as part of the berotralstat NICE TA738.¹⁶

However, for the LTPs it is assumed that ■% and ■% of patients of patients require administration support for SC and IV treatments, respectively. The percentage of

patients who require administration support for treatment with LTPs is based on insights from clinicians (June 2025).²²

In the company's base case cost-comparison analysis, all comparators in the model are assumed to have equal efficacy, supported by the results of the company's NMA (Section 3.3.1.3 in the CES). On-demand attack management for each comparator treatment is determined by the number of attacks experienced by patients. With the equal efficacy assumption, patients treated with each LTP are assumed to have the same number of HAE attacks. Therefore, the on-demand attack management costs, including administration costs, are assumed to be equal between donidalorsen and comparator LTPs in the company's base case cost-comparison analysis.

To support the EAG to assess the overall costs associated with HAE attacks, the company have explored a scenario which assumes that there are no administration costs of administration of LTPs in line with the assumption for on-demand treatment administration. However, the company continue to consider it is appropriate to include administration costs associated with administration of LTPs, as presented in the base case cost-comparison.

The results of this scenario cost-comparison analysis when assuming no administration costs for LTPs are presented in Table 44 and Table 45 for the ≥ 2 attacks and ≥ 8 attacks groups, respectively. Over a lifetime time horizon, treatment with donidalorsen in patients with HAE experiencing ≥ 2 attacks per month was associated with cost savings of £ [REDACTED] per patient versus berotralstat. In patients with HAE experiencing ≥ 8 attacks per month, treatment with donidalorsen was associated with cost savings over a lifetime time horizon of £ [REDACTED] per patient versus lanadelumab and cost savings of [REDACTED] per patient versus C1-INH, resulting in donidalorsen providing cost-savings to the NHS versus all comparators. Excluding administration costs associated with LTPs in the cost-comparison analysis demonstrates that donidalorsen remains cost-saving against all comparator LTPs, with the inclusion of a simple PAS discount.

Table 44: Cost-comparison deterministic results excluding on-demand treatment administration costs (≥ 2 attacks per month)

Intervention/comparator	Total costs (£)	Incremental costs versus donidalorsen (£)
Donidalorsen		
Berotrastat		

Table 45: Cost-comparison deterministic results excluding on-demand treatment administration costs (≥ 8 attacks per month)

Intervention/comparator	Total costs (£)	Incremental costs versus donidalorsen (£)
Donidalorsen		
Lanadelumab		
C1-INH		

Abbreviations: C1-INH – C1 Inhibitor

B7. The baseline attack rate of the mean run-in period HAE attack rate in the placebo arm of the OASIS-HAE trial was used in the model for all LTPs (pg 144 CS, section 3.3.1). Please provide a sensitivity analysis using pooled baseline attack rate for all LTPs compared.

In the company's base case cost-comparison analysis, the baseline HAE attack rate is defined by the run-in period HAE attack rate in the placebo arm of the OASIS-HAE trial: the baseline attack rate for the ≥ 2 attacks per month population in the model is 0.725 attacks per week, which is equivalent to the mean run-in period HAE attack rate in the placebo arm of the OASIS-HAE of 2.90 per 4-weeks.^{6,73} For the population of patients experiencing ≥ 8 attacks per month, the baseline attack rate is 2 attacks per week, equivalent to 8 attacks per 4 weeks in line with the lanadelumab reimbursement criteria and C1-INH commissioning policy.^{17,74} The baseline attack rates for both populations were validated by clinical experts in meetings held in September 2025.²²

The company have explored a scenario in the company's base case cost-comparison analysis which uses a pooled baseline attack rate for all LTPs where a baseline attack rate is available (berotrastat and lanadelumab) for the ≥ 2 attack per month population. The baseline attack rate for the ≥ 8 attack per month population is 8 attacks per month; this is in line with the minimum number of attacks patients must experience to be eligible for treatment, as per the reimbursement criteria for lanadelumab and the commissioning policy for C1-INH; no scenario is explored for

this population.^{9,69,74} Using a pooled baseline attack rate from clinical trial data would result in a baseline attack rate below the reimbursement and commissioning criteria for lanadelumab and C1-INH. Therefore, this scenario only explores a pooled baseline attack rate for the ≥ 2 attack per month population.

In line with the efficacy sources used in the NMA (Section 2.10 of the CES), the pooled baseline attack rates for berotralstat and lanadelumab have been sourced from the primary publication for APeX-2 and HELP trials, respectively.^{11,12} In the NMA, the efficacy for C1-INH is based on data from the CHANGE trial, presented in the publication by Zuraw *et al.* (2010).¹³ However, the publication by Zuraw *et al.* (2010) does not report the baseline attack rates (although only patients who had a history of at least two attacks per month were eligible to enter the prophylaxis study) and therefore, the pooled baseline attack rate is based on the placebo baseline attack rates from the OASIS-HAE (donidalorsen), APeX-2 (berotralstat) and HELP (lanadelumab) trials only.^{9,11,12} The placebo arm from the OASIS-HAE trial is used as the reference treatment in the NMA, therefore the placebo arm baseline attack rates from the APeX-2 and HELP trial have been used in this scenario.

The placebo baseline attack rates reported in the OASIS-HAE, APeX-2 and HELP primary publications, which have been used in this exploratory analysis, are presented in Table 46.^{9,11,12} The resulting pooled baseline attack rate is 0.818 per week.

Table 46: Placebo baseline attack rates as sourced from each LTP trial

Intervention/comparator	Clinical trial; publication used	Baseline attack rate reported in the publication (table in publication)	Baseline attack rate per week
Placebo	OASIS-HAE; Riedl <i>et al.</i> (2024) ⁹	2.9 per 4 weeks (Table 1)	0.725 (2.9/4)
Placebo	APeX-2; Zuraw <i>et al.</i> (2021) ¹²	2.91 per month* (Table 1)	0.728 (2.91/4)
Placebo	HELP; Banerji <i>et al.</i> (2018) ¹¹	4 per month* (Table 1)	1.000 (4/4)
Pooled baseline attack rate			0.818

*In the APeX-2 and HELP-3 studies, one month was defined as 28-days.

Results from using the pooled baseline attack rate in the company's base case cost-comparison analysis for the ≥ 2 attacks population are presented in Table 47. For the ≥ 2 attacks per month group, this exploratory analysis increases the baseline attack rate from 0.725 to 0.818. The increase in baseline attack rate increases the overall costs associated with HAE attacks, as patients now experience a higher number of HAE attacks. However, as it is assumed that the number of HAE attacks is the same for each LTP in the cost-comparison analysis via the equal efficacy assumption, the incremental cost savings difference between the donidalorsen and berotralstat remains the same as presented in the CES. This is demonstrated by the incremental costs presented in Table 47 being the same as those presented in the CES in Table 40 (page 170). Exploring the use of a pooled baseline attack rate in the cost-comparison analysis demonstrates that donidalorsen remains cost-saving against berotralstat with an annual cost saving of £[REDACTED] per patient, with the inclusion of a simple PAS discount.

Table 47: Cost-comparison results when using a pooled baseline attack rate of 0.818 (≥ 2 attacks per month)

Intervention/comparator	Total costs (£)	Incremental costs versus donidalorsen (£)
Donidalorsen	[REDACTED]	-
Berotralstat	[REDACTED]	[REDACTED]

B8. Related to question A1 - Please run scenario analyses with garadacimab included as comparator.

As stated in the response to Question A1, the company do not consider garadacimab to be established standard of care for treating patients with HAE in the NHS in England and have therefore not included it as a comparator in the base-case economic analysis. However, to support the EAG in their assessment of the evidence, the company have conducted a naïve cost-comparison analysis to garadacimab using the anticipated clinical efficacy and treatment acquisition costs.

The MAIC conducted by CSL Behring, as presented in the response to Question A1, indicates no statistically significant difference between garadacimab Q1M compared with donidalorsen Q4W, in terms of time-normalised number of HAE attacks, with the rate ratio 95% confidence intervals overlapping with 1.⁷ The number of HAE attacks

was the primary endpoint of both the VANGUARD and the OASIS-HAE trials and is also the measure of clinical efficacy within the economic analysis of this appraisal.⁷

Therefore, the assumption of equal efficacy in the company's base case cost-comparison analysis is expected to hold; for the analysis presented in this response, it is assumed that there is equal efficacy between donidalorsen and garadacimab. As a result, the number of HAE attacks, and consequently the HCRU and on-demand attack management, are considered to be equal. Therefore, the only relevant costs to incorporate into this analysis are treatment acquisition costs.

An overview of the predicted annual cost savings associated with donidalorsen compared to garadacimab are presented in Table 48. Both garadacimab and donidalorsen are administered subcutaneously. In line with the company's base-case analysis, and based on clinical validation meetings with UK clinical experts held in June 2025, it is assumed that █% of patients who take a subcutaneous medication require injection support.²² The cost per administration associated with subcutaneous administration costs is £█. Given that only █% of patients require administration support with subcutaneous injections, a negligible weighted administration cost of £█ (46.50×0.05) is incurred per patient treated, and so administration costs have been excluded from this analysis.

Assuming a █%/█% split of Q1M/Q2M for donidalorsen treatment, in line with the base-case economic analysis after month six (please refer to Section 2.6.4 of the CES for further details), it is estimated that donidalorsen (at donidalorsen PAS price) would bring an annual treatment acquisition cost saving compared to garadacimab of £█ per patient (£247,500.00 - £█).

Table 48: Overview of donidalorsen and garadacimab acquisition costs

	Donidalorsen	Garadacimab
Dosing schedule	Patients initiate treatment on is [REDACTED] [REDACTED] [REDACTED] [REDACTED]	Patients start treatment with an initial loading dose of 400 mg followed by a monthly dose of 200 mg
Price per pen	List price: £ [REDACTED] PAS price: £ [REDACTED]	£20,625
Annual acquisition cost per patient	Assuming a [REDACTED]%/ [REDACTED]% split of Q1M/Q2M (in line with the base-case economic analysis after month six): £ [REDACTED] (with PAS discount)	£247,500
Incremental cost versus donidalorsen per patient	-	£ [REDACTED]

Abbreviations: PAS – Patient Access Scheme; Q1M – Once every month; Q2M – Once every 2 months.

In addition to delivering annual cost savings to the NHS, donidalorsen addresses the unmet need for an alternative treatment option for patients experiencing ≥ 2 attacks per month. For patients receiving donidalorsen who are [REDACTED], the option to reduce to a once-every-two-month (Q2M) dosing regimen provides a less frequent and potentially more convenient dosing regimen compared with existing LTPs (berotralstat, lanadelumab and C1-INHs), as well as garadacimab.^{8,9,64,75–78}

Overall, although garadacimab has not been included as a comparator in the economic analysis because it is not established standard of care, donidalorsen is expected to provide a substantially cost-saving alternative treatment option for patients with HAE compared to garadacimab.

Section C: Textual clarification and additional points

Clinical efficacy and dosing assumptions

C1. The model uses data from the Q4W and Q8W regimens of the OASIS-HAE trial but uses the terminology Q1M and Q2M, assuming that "No differences in outcomes are expected" between Q4W and Q1M dosing, or between Q8W and Q2M dosing.

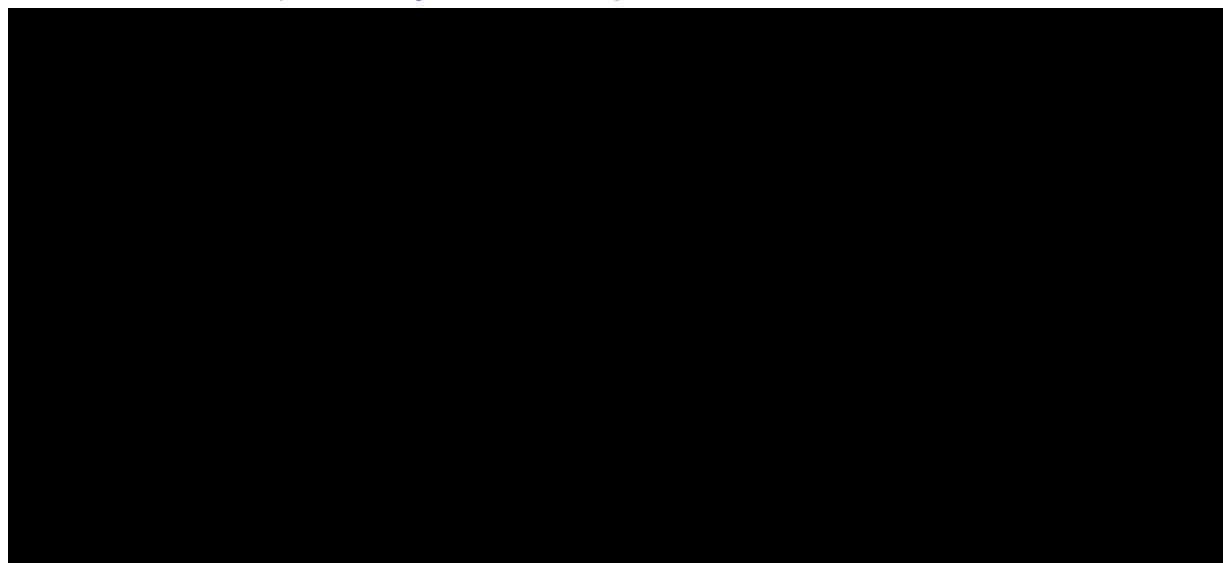
- Please confirm whether these intervals are identical in practice (28 days vs calendar month)
- Please provide the specific clinical and pharmacokinetic (PK/PD) data that definitively demonstrates the assumed equivalence in efficacy, safety, and long-term pharmacological response (e.g., prekallikrein reduction) between the Q4W and Q1M dosing schedules, and between the Q8W and Q2M dosing schedules.

The anticipated market authorisation for donidalorsen states that the “

”.⁸ In OASIS-HAE, patients were randomised to donidalorsen dosing regimens of either 80 mg Q4W or 80 mg Q8W.^{9,32} The Q4W/Q8W and Q1M/Q2M dosing intervals are not identical in clinical practice, however, no meaningful difference in outcome is expected between the dosing regimens. The visit windows for study drug administration during the treatment period were defined at 28-day intervals, with an allowed range of ± 3 days around each scheduled timepoint.³² The efficacy of donidalorsen Q4W reported in OASIS-HAE, therefore, can reflect dosing intervals of up to 31 days, effectively aligning the Q4W regimen with Q1M dosing.³² Furthermore, based on the clinical evidence for donidalorsen detailed below, the company does not anticipate there to be a difference in efficacy outcomes for donidalorsen Q1M compared to donidalorsen Q4W, and donidalorsen Q8W compared to donidalorsen Q2M.

Pharmacodynamics were assessed in OASIS-HAE by comparing the change from Week 1 in the measured PKK levels at each visit during the treatment period between donidalorsen and placebo.⁷³ The pharmacodynamic data demonstrates the stability in PKK levels between the donidalorsen Q4W and donidalorsen Q8W dosing regimens over the trial period.^{9,28} As shown in Figure 2 (please see response to Question A7), by Week 5, donidalorsen decreased PKK concentrations from Week 1 by 46% in the Q4W dosing cohort and 52% in the Q8W dosing cohort, while an increase by 2% was observed in the placebo cohort.⁹ Both donidalorsen Q4W and donidalorsen Q8W dosing regimens maintained this reduction in PKK concentrations from Week 1 at Week 25, with reductions of 73% (95% CI: 68%, 78%) in donidalorsen Q4W and 47% (95% CI: 38%, 56%) in donidalorsen Q8W cohorts.⁹ Furthermore, as shown in Figure 9, the reduction in PKK concentrations from the OASIS-HAE run-in baseline was maintained in the OASISplus OLE cohort, with reductions of [REDACTED] in donidalorsen Q4W and [REDACTED] in donidalorsen Q8W cohorts at Week 49 of OASISplus.³¹ The long-term stability between dosing regimens, despite a four-week difference in frequency, demonstrates that the marginal difference between donidalorsen Q4W and Q1M dosing frequency will have a negligible impact on the effect of donidalorsen on PKK levels over time. Consequently, no meaningful difference in efficacy or treatment outcomes is expected between the donidalorsen Q1M and Q4W dosing regimens.

Figure 9: Mean (+/- SEM) percentage change from OASIS-HAE baseline in PKK level, (On-treatment Period DY1), Full Analysis Set, OASISplus OLE cohort



Baseline is OASIS-HAE run-in Baseline, defined as the pre-dose measurement on Day 1 in OASIS-HAE. Patients who changed dosing could be plotted under both treatment groups (donidalorsen 80 mg Q4W and Q8W).

Abbreviations: PKK – Prekallikrein; Q4W – Once every four weeks; Q8W – Once every eight weeks

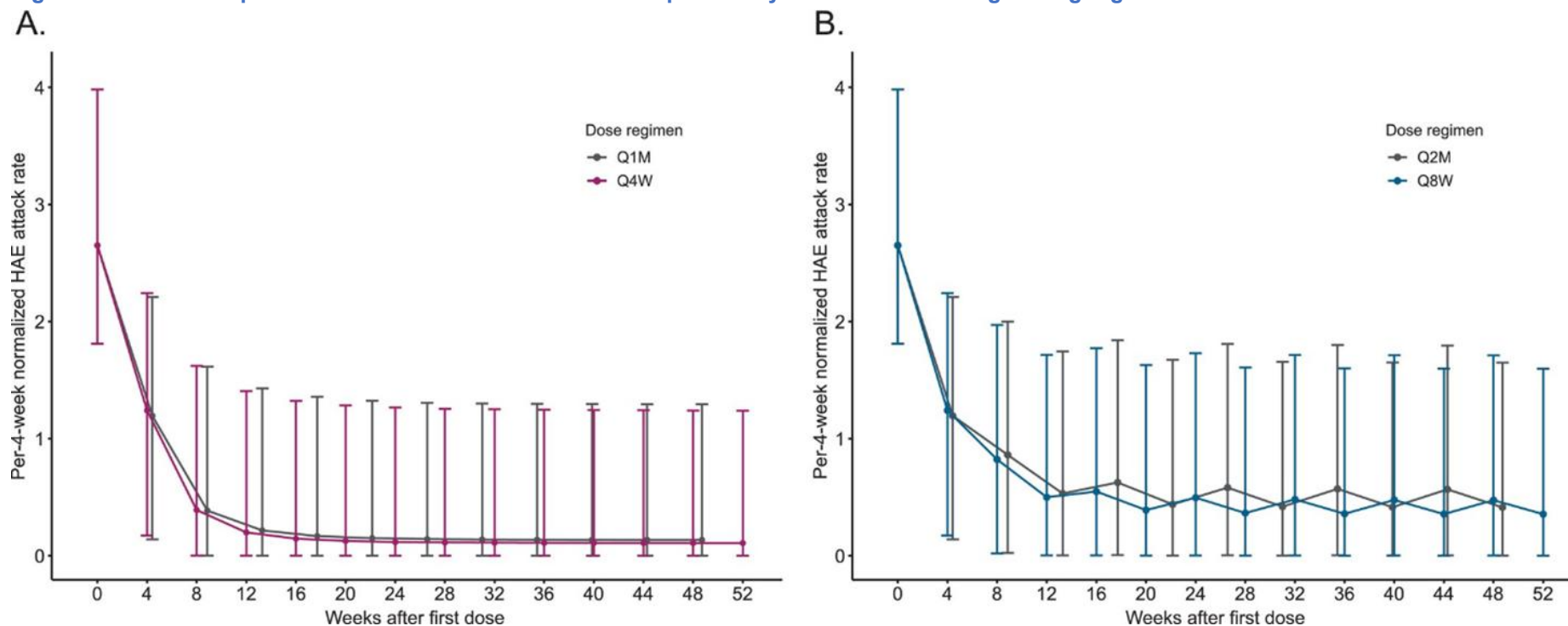
An exposure-response analysis was conducted to further characterise the relationship between PKK concentrations and HAE attack rates following treatment with donidalorsen and to predict the efficacy of potential dosing regimens.²⁸ An exposure–response model was developed using data from OASIS-HAE, in which the relationship between PKK concentrations and HAE attack rates was well characterised by a sigmoidal Emax (maximum effect) model, with baseline attack rate and baseline PKK concentration as covariates. No significant effects of age, body weight, sex, or antidrug antibodies were observed, supporting the generalisability of the exposure-response model results across the OASIS-HAE clinical trial population.²⁸

Simulations were conducted to evaluate donidalorsen 80 mg administered Q4W, Q8W, Q1M, and Q2M. Simulation of 10,000 virtual patients treated with donidalorsen Q4W or donidalorsen Q1M dosing indicated that these dosing regimens had nearly identical efficacy.²⁸ Table 60 presents the simulated HAE attack rate profiles over time for each donidalorsen dosing regimen. Simulated mean HAE attack rates per 4-weeks at steady state were 0.39 for Q4W dosing and 0.42 for Q1M dosing, corresponding to mean percentage reductions in HAE attack rates of 84.1% and 82.9% from baseline, respectively.²⁸ Simulated efficacy results were also similar between Q8W and Q2M dosing: mean HAE attack rates per 4-weeks at steady state

were 0.69 for Q8W dosing and 0.75 for Q2M dosing.²⁸ Mean percentage reductions from baseline in HAE attack rates were 72.6% for Q8W dosing and 70.2% for Q2M dosing.²⁸

These data indicate that the efficacy of donidalorsen Q1M and Q2M dosing is similar to the efficacy of donidalorsen Q4W and Q8W dosing, respectively, supporting the rationale for donidalorsen Q1M and Q2M dosing.²⁸

Figure 10: Simulated per-4-week normalised HAE attack rate profiles by donidalorsen 80 mg dosing regimen



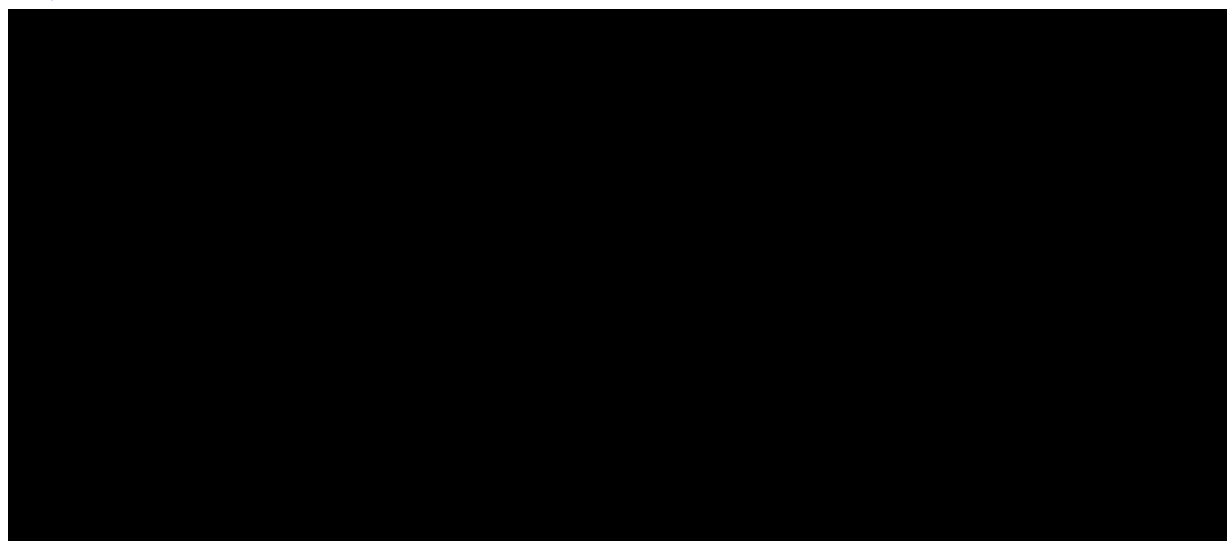
The dots represent the median, and the error bars represent the 10th and 90th percentiles.

Abbreviations: HAE – Hereditary angioedema; mg – Milligram; Q1M – Once every month; Q2M – Once every two months; Q4W – Once every four weeks; Q8W – Once every eight weeks

Source: Singh et al. 2025²⁸

In OASIS-HAE, the least squares mean (LSM) time-normalised HAE attack rate, per 4 weeks, from Week 5 to Week 25 was 0.30 (95% CI: 0.15, 0.58) for the donidalorsen Q4W group and 2.25 (95% CI: 1.59, 3.18) for the placebo group, representing a statistically significant 87% (95% CI: -93.8%, -71.9%) reduction relative to placebo ($p < 0.001$).⁹ These results reflect the expected efficacy that would be observed with donidalorsen Q1M dosing, in line with the observed reductions in plasma PKK concentrations. Furthermore, as shown in Figure 11, by the end of Week 3, a reduction of [REDACTED] in the mean rate of HAE attacks every 4 weeks compared to Week 1 was observed with donidalorsen Q4W.⁵¹ This demonstrates a meaningful treatment effect within the first dosing period of donidalorsen, before the second dose of donidalorsen is received; there is no clinical evidence to indicate that the marginal difference between donidalorsen Q4W and Q1M dosing frequency will impact the efficacy of donidalorsen in clinical practice.

Figure 11: Mean Rate (+/- SEM) (% Change from Baseline) of Investigator-confirmed HAE Attacks Standardised to Every-4-Week per Each Week from Week 1 to Week 25 Full Analysis Set, OASIS-HAE



Baseline is the OASIS-HAE run-in period, calculated as number of HAE attacks occurring during the run-in period divided by the number of days the patient contributed to the run-in period multiplied by 28 days.

Week 1 starts from Day 1 to Day 7; Week 2 starts from Day 8 to Day 14 and so on.

Abbreviations: mg – Milligram; Q4W – Once every four weeks; Q8W – Once every eight weeks; SEM – Standard error of the mean

Source: OASIS-HAE CSR⁵¹

The stability in clinical effect of donidalorsen between dosing regimens is further supported by long-term data obtained in OASISplus. In the OASISplus OLE cohort,

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all patients received donidalorsen Q4W (n=69) or donidalorsen Q8W (n=14). All patients randomised to placebo or donidalorsen Q4W dosing in the OASIS-HAE trial received donidalorsen Q4W dosing in the OASISplus OLE cohort.³⁰ Six patients randomised to Q8W dosing in the OASIS-HAE trial received donidalorsen Q4W dosing in the OASISplus OLE cohort (6/20, 30%); all other patients receiving donidalorsen Q8W dosing remained on this dose.³⁰ A schematic presenting the patient flow from OASIS-HAE for the OASISplus OLE cohort is presented in Section 2.3.2, Figure 12 of the CES. Interim data (data cut-off January 27, 2025) from the OASISplus OLE cohort show that a low attack rate was maintained throughout the study period in both donidalorsen Q4W and donidalorsen Q8W groups.³¹ At Week 53 of OASISplus, a mean reduction in HAE attack rate from Week 1 of [REDACTED] for donidalorsen Q4W and [REDACTED] for donidalorsen Q8W was observed.³¹ As shown in Figure 2 (please see response to Question A7), at Week 89 of OASISplus, a mean reduction in HAE attack rate from Week 1 of [REDACTED] was observed for patients who had received donidalorsen Q4W and donidalorsen Q8W in OASIS-HAE.³¹ At Week 89 of OASISplus, a mean reduction in HAE attack rate from Week 1 of [REDACTED] was observed for patients who had received placebo in OASIS-HAE.³¹ The convergence of efficacy between the donidalorsen Q4W and Q8W dosing regimens demonstrates the long-term stability of the clinical benefit achieved by donidalorsen and reinforces the expectation that there will be negligible difference in efficacy between Q4W and Q1M, and Q2M and Q8W dosing of donidalorsen.

Systematic literature review (Clinical and cost-effectiveness)

C2. Please provide the following Excel documents which are linked from the SLR report document but were not supplied in the reference pack:

- SLR Report Appendix B: 'Donidalorsen 2025 SLR extractions QA - v1.0_22Aug25.xlsx'
- SLR Report Appendix C: 'Donidalorsen SLR extraction grid_2Sep2025.xlsx'

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The quality assessment checklist for all extracted studies, completed as part of the SLR, is presented in the reference list of this document (Donidalorsen SLR extractions quality assessment, Otsuka, 2025).⁷⁹

The extraction grid, completed as part of the SLR, is presented in the reference list of this document (Donidalorsen SLR extraction grid, Otsuka, 2025). As explained in the company's response to Question A4, the PRISMA diagram was updated to correct a typographical error in the number of excluded studies, which does not impact the number of included studies in the SLR. The updated diagram, presented in Figure 1, shows that following the exclusion of 381 references at the full-text screening stage, 373 references were included and considered for extraction. Note, as the Company explains in their response to Question A4, many of the 373 references identified for extraction were linked to other extracted publications and therefore did not contain new information to extract. Therefore, these studies have been listed in Column K of the General Information sheet, titled 'Linked Publications', with their associated linked references. As such, the total number of studies listed in the General Information sheet in the extraction grid does not equal 373, but 211 studies. Of the 373 unique references included, 120 were full-text papers, and the remaining references were abstracts or posters (n = 253), also presented in Appendix D of the SLR report.

C3. Please explain the following discrepancies in numbers of results for the SLR as reported in different parts of the SLR report and main submission:

- SLR report section 4.1 states that “**754** references (including the grey literature searches) were assessed at second pass” and that **381** of these were excluded. The PRISMA diagram (Figure 1) indicates that **734** were assessed, and **361** excluded. The 20 grey literature records may have been missed from the PRISMA figures, however this would suggest that all 20 grey literature records were included in the review (not 11 as indicated in the final box of the PRISMA diagram, and elsewhere in the report).

- SLR report section 4.1.1 states that 457 references were screened at the full text stage for the clinical review, 215 were excluded and **243** references were included (65 full publications plus 178 abstracts). However 457 minus 215 equals **242**. The PRISMA diagram (SLR report, Figure 1) indicates that **242** references were included in the clinical review. Table 26 in Appendix D of the SLR report includes **239** references.
- The numbers of results in tables 18-22 in Appendix A of the SLR report do not align with those in the PRISMA diagram and text in section 4 of the SLR report, as shown below:

Table 18	6,333 results (line 13, before date limit added for update search)
Table 19	56 results (line 5, before date limit added for update search)
Other sources in tables 20-22	0 results
Total from tables 18-22, April 2025	6,389
Total from database searching as reported in section 4.1 text and PRISMA diagram	6,674 – 239 duplicates = 6,435

The company are grateful to the EAG for bringing to the company's attention the discrepancies between the numbers presented in the SLR report and the PRISMA diagram. The company confirm that no studies were incorrectly excluded from the

SLR and the total number of references extracted are correct. Further clarification and explanations are provided below.

Point 1

In response to the first discrepancy noted by the EAG, which was that the SLR report Section 4.1 states that “**754** references (including the grey literature searches) were assessed at second pass” and that **381** of these were excluded, while the PRISMA diagram (Figure 1 in the SLR report) indicates that **734** were assessed, and **361** excluded, the company have provided clarification to this in response to Question A4.

The original PRISMA diagram in the SLR report indicates that 734 studies were assessed at the full-text screening stage, and 361 of these were excluded; 63 did not meet the population criteria, 104 did not meet the intervention/comparator criteria, 141 did not meet the outcome criteria, 30 did not meet the study type criteria, 10 were duplicates, 11 were not in English, and 2 were unavailable. The updated PRISMA diagram in Figure 1 in the company’s response to Question A4 shows that 754 studies were assessed at the full-text screening stage; this now includes the 20 additional records identified through grey literature searches, all of which were reviewed in full at this stage. At the full-text screening stage, 381 of the 754 studies were excluded; 63 still did not meet the population criteria, 105 did not meet the intervention/comparator criteria, 154 did not meet the outcome criteria, 29 did not meet the study type criteria, 12 were duplicates, 13 were not in English, and 5 were unavailable (not available online). The company would like to highlight that this was a typographical error in the original PRISMA diagram of the number of excluded studies and their reasons for exclusion. This does not impact the number of included studies in the SLR. Please note, as indicated by the updates made to the numbers of full-text papers excluded per reason, the update to the number of full-text articles assessed for eligibility from 734 to 754, and the associated update to the number of full-text studies excluded from 361 to 381 is not purely an addition of the 20 grey literature papers onto each number for balance, as not all 20 grey literature papers were simply excluded from the review. Of the 20 grey literature papers screened, 11

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grey literature papers were included in the final review, which was presented correctly in the original PRISMA diagram, but the number of full-text papers excluded for the reasons related to outcomes, study type, duplicates, language and availability have been updated to correct the typographical error made in the original PRISMA diagram. Please see Figure 1 in the company's response to Question A4 for the updated PRISMA diagram of evidence identified in the SLR.

Point 2

The second discrepancy noted by the EAG is regarding the number of clinical references included in the SLR. The company confirm that the number of studies included for the clinical review question in the final SLR is 243. This is the number of references that were extracted, either in full as a unique study, or as linked publications to a unique study. Section 4.1.1 of the SLR report states that "457 references were screened at the full text stage for the clinical review, 215 were excluded", but the company confirm that the exclusion of 215 references was a typographical error, and the sentence should read "457 references were screened at the full text stage for the clinical review, **214** were excluded", leaving 243 references included in the final review for the clinical review question. This change does not affect the number of studies that were included or extracted in the final SLR. The company identified two studies that were generated from the database searches that were identical in content but had been identified as separate references because they were published in a separate journal. The company deemed these different references at the title/abstract screening stage, therefore including them, but excluded them at the full-text screening stage, with the reason of being duplicates. This update to exclusions therefore led to a miscount of excluded studies by one. The company confirm that 243 is the correct number of references included in the final SLR, and an update to the PRISMA diagram from 242 to 243 has been made, as presented in Figure 1 in the company's response to Question A4. An update to the text in Section 4.1.1 in the SLR report will also be made to reflect this, such that the report will state "After first pass screening 457 references (of the 754 total) were considered for secondary screening for review question one after which a total of

Clarification questions

214 references were excluded because they did not meet the selection criteria”, therefore leaving 243 references included for the clinical review question.

Regarding Table 26 in Appendix D of the SLR report, which presents 239 of the 243 references from the clinical review question, the company confirm that 239 references is the correct total for that table. The table presents the results of the 2024 SLR full-text and all abstracts (2024 and 2025) that were included in the clinical research question. Therefore, the references identified through grey literature searches relevant for clinical review, of which there are four, are not included in Table 26. Their inclusion *would* result in 243 references presented in that table, aligning with the total number of clinical references identified in the SLR, had they been included.

Point 3

In response to the third discrepancy noted by the EAG, regarding the misalignment between the total number of database searches presented in the search strategies in Appendix A of the SLR report provided in the reference pack of the donidalorsen CES, and the total number of database searches presented in the PRISMA diagram of the same SLR report, the company have provided a summary table in Table 49, to support the below explanation.

The company acknowledges that the search strategies and number of generated hits presented in the SLR report do not total 6,674 hits that were presented in the PRISMA diagram and used in the final review. This is due to misalignment between the searches that were used versus reported in the search strategy tables between the 2024 and 2025 refresh SLR. The company would like to highlight that this is a typographical error in the report and does not impact the number of studies included in the SLR at any screening or extraction stages.

The total number of database hits reported in the PRISMA in Figure 1 of the SLR report, 6,674, represents the sum of the 2024 EMBASE search (5,906), the 2024 CENTRAL search (198), the 2024 NHS HTA and EED search (6), the 2025 refresh

EMBASE search (564), the 2025 refresh CENTRAL search (3), and the 2025 refresh NHS HTA and EED search (0). The three references identified in the 2025 refresh CENTRAL search, however, were duplicates of references already identified within the database searches and therefore not included or counted in the total. The searches were combined in this way to ensure that all papers identified from the 2024 search were included, in addition to all papers identified in the 2025 search, with no overlap, which is in contrast to the combination of hits noted by the EAG (6,333 from the 2025 EMBASE search + 56 from the 2025 CENTRAL search), that did not cover the date overlap correctly.

For the full 2024 search strategy, which presents the 6,110 total 2024 hits, please refer to the company's response to Question C4.

Table 49 presents the correct totals of database generated hits which sum to 6,674, which can be viewed in conjunction with the company's response to Question C4 below.

Table 49: Number of hits informing the SLR PRISMA diagram

	Number of hits
June 2024 SLR total number of database searches	6,110 (comprised of 5,906 from EMBASE, 198 from CENTRAL, and 6 from NHS HTA and EED)
April 2025 SLR total number of database searches	564 (comprised of 564 from EMBASE + 3 from CENTRAL [all of which were considered duplicates and not included] + 0 from NHS HTA and EED)
Total	6,674

Abbreviations: EED – Economic evaluation database; HTA – Health technology assessment; NHS – National Health Service; PRISMA – Preferred reporting items for systematic reviews and meta-analyses; SLR – Systematic literature review

The 2025 search strategy presented in Appendix A of the SLR report reported two typographical errors, that the company present as resolved in Table 51, which do not affect any screening or inclusion/exclusion decisions in the SLR. The first error

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identified is in Table 18, index 14, of the SLR report and is regarding the date restriction applied to the EMBASE search in the 2025 refresh. The date restriction reported in the SLR report in the search strategy restricted the search from between 6th June 2024 and 22nd April 2025 to capture newly published evidence between the two SLR search dates. However, the search term used in the final SLR was a broader restriction of the search to filter by papers published in 2024 and 2025, and any papers that overlapped with the original 2024 search were de-duplicated and removed from the final total. Therefore, the number of hits for this search term is 564, corrected from 411. The second error is identified in Table 19, index 3 and 5, of the SLR report and corresponds to the combination search terms used. In index 3 of the search, ‘#1 AND #2’ was originally searched as ‘#1 OR #2’, therefore restricting the search more than required. This generated 156 hits and consequently restricted the hits generated in index 5. The company cannot re-run this corrected search to generate the exact number of hits it would have done when run on 22nd April 2025. However, for completeness, the company present the corrected search, run on 3rd December 2025, in Table 50. The date restricted number of hits are presented as 26, compared to 3 hits previously reported. The company would like to highlight that all 26 references have been cross-checked against the full list of 6,674 references included in the SLR, and all 26 were identified in the EMBASE search. Therefore, the references identified in the CENTRAL search were considered duplicates and removed from the total number of hits included. Although the updated search has generated more hits than originally reported, no additional references have been excluded from the SLR as a result.

Table 50: Updated CENTRAL (Cochrane Library interface) SLR search strategy (3rd December 2025)

Clinical search strategy			
Index	Description	Search terms	Hits
1	Terms for population	MeSH descriptor: [Angioedemas, Hereditary] explode all trees	184
2	Terms for population	(hereditary angioedema):ab,ti OR (hae):ab,ti	627
3	Combine terms	#1 or #2	644

Clarification questions

Clinical search strategy			
4	Interventions/comparators	Donidalorsen or Garadacimab or sebetralstat or csl312 or "pdC1-INH" or Cinryze or Haegarda or Berinert or Lanadelumab or Takhzyro or Berotralstat or Orladeyo or Danazol or Danocrine or Stanozolol or Winstrol or "Tranexamic acid" or "Epsilon aminocaproic acid" or "long-term prophylaxis" or LTP	6,438
5	Combine terms	#3 and #4	258
6	Date restriction	#5, restricted to "with Publication Year from 2024 to 2025, with Cochrane Library publication date from Jun 2024 to Apr 2025, in Trials	26

Table 51: Corrections to the 2025 SLR report search strategy tables in Appendix A

			Original 2025 SLR report		Updated 2025 SLR report	
Table number (database)	Index	Description	Search terms	Hits	Search terms	Hits
18 (EMBASE)	14	Date restriction	#13 AND [06-06-2024]/sd NOT [23-04-2025]/sd	411	#13 AND (2024:py OR 2025:py)	564
19 (CENTRAL)	3	Combine terms	#1 AND #2	156	#1 AND #2	644 (Re-run on 3 rd December 2025)
19 (CENTRAL)	5	Combine terms	#3 AND #4	56	#3 AND #4	258

Abbreviations: SLR – Systematic literature review

C4. Please provide the complete search strategy, including numbers of results, for the original searches conducted in June 2024

The company would like to highlight that Table 54 of this response presents positive values for the number of hits generated using the NHS HTA and EED database, while Table 20 in the SLR report provided within the reference pack of the CES presented zero hits for each line of search terms. The zero hits were stated in the final SLR report as a typographical error, which corresponded to zero hits being generated between the date that the initial 2024 SLR was run (June 2024) and the updated search (April 2025). The number of hits presented in Table 20 in the SLR report should therefore equal those presented in Table 54 below. This typographical error does not impact the number of papers screened within the SLR as they were assessed in the initial screening.

Clarification questions

Table 52: EMBASE, MEDLINE and MEDLINE In-Process search strategy (EMBASE interface) (6 June 2024)

Clinical search strategy			
Index	Description	Search terms	Hits
1	Population	'hereditary angioedema'/syn OR 'hereditary angioedema' OR 'hereditary angioedema':ab,ti OR 'hae':ab,ti OR 'angioedema':ab,ti OR (hereditary NEXT/3 angioedema):ab,ti	30,573
2	Interventions/ comparators	'donidalorsen'/syn OR 'garadacimab'/syn OR 'csl312'/syn OR 'sebetralstat'/syn OR 'pdC1-INH'/syn OR 'cinryze'/syn OR 'berinert'/syn OR 'haegarda'/syn OR 'lanadelumab'/syn OR 'takhzyro'/syn OR 'berotralstat'/syn OR 'orladeyo'/syn OR 'danazol'/syn OR 'danocrine'/syn OR 'stanazolol'/syn OR 'winstrol'/syn OR 'tranexamic acid'/syn OR 'epsilon aminocaproic acid'/syn OR 'long term prophylaxis'/syn OR 'long-term prophylaxis'/syn OR 'ltp'/syn	67,969
3	Study types: RCT Filter ⁸⁰	('clinical trial'/de OR 'randomized controlled trial'/de OR 'controlled clinical trial'/de OR 'multicenter study'/de OR 'Phase 3 clinical trial'/de OR 'Phase 4 clinical trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'randomi*ed controlled trial*:ti,ab OR rct:ti,ab OR 'random allocation':ti,ab OR 'randomly allocated':ti,ab OR 'allocated randomly':ti,ab OR (allocated NEXT/2 random):ti,ab OR 'single blind*:ti,ab OR 'double blind*:ti,ab OR ((treble OR triple) NEXT/1 blind*):ti,ab OR placebo*:ti,ab OR 'prospective study'/de) NOT ('case study'/de OR 'case report':ti,ab OR 'abstract report'/de OR 'letter'/de OR 'editorial'/de OR 'note'/de)	2,932,996
4	Study types: Single arm trial filter	'single arm trial':ti,ab OR singl*:ti,ab OR 'single-arm':ti,ab OR 'single arm':ti,ab	2,774,877
5	Study types: Non-RCTs	'non-randomi*ed trial'/de OR (non-randomi*ed NEXT/3 trial):ti,ab OR 'clinical trial'/de OR 'case control study' OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR (cohort NEXT/1 (study OR studies)) OR (('case control' NEXT/1 (study OR	4,863,885

Clarification questions

Clinical search strategy			
		studies)):ti,ab) OR (('follow up' NEXT/1 (study OR studies)):ti,ab) OR ((observational NEXT/1 (study OR studies)):ti,ab) OR (('cross sectional' NEXT/1 (study OR studies)):ti,ab)	
6	Combine filters	#3 OR #4 OR #5	7,934,923
7	Combine filters	#1 AND #2 AND #6 AND [humans]/lim	1,545
Cost-effectiveness, HRQoL, and cost and resource use studies search strategy			
Index	Description	Search terms	Hits
8	Economic Filter ⁸⁰	'socioeconomics'/de OR 'cost benefit analysis'/de OR 'cost effectiveness analysis'/de OR 'cost of illness'/de OR 'economic evaluation'/de OR 'cost utility analysis'/de OR 'cost control'/de OR 'economic aspect'/de OR 'financial management'/de OR 'health care cost'/de OR 'health care financing'/de OR 'health economics'/de OR 'hospital cost'/de OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimization analysis'/de OR cost NEXT/1 estimate* OR cost NEXT/1 variable* OR unit NEXT/1 cost*	1,215,378
9	Quality of life filter ⁸¹	'quality adjusted life year'/de OR 'value of life':ab,ti OR socioeconomics/de OR (qaly* OR qald* OR qale* OR qtime*):ab,ti OR (quality adjusted OR adjusted life year*):ab,ti OR 'disability adjusted life':ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwbi):ab,ti OR (multiattribute* OR multiattribute*):ab,ti OR (utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR (HSUV OR HSUVs):ab,ti OR 'health* year* equivalent*':ab,ti OR (hye OR hyes):ab,ti OR (hui OR hui1 OR hui2 OR hui3):ab,ti OR ('illness state*' OR health state*):ab,ti OR ('euro qual' OR 'euro qual5d' OR 'euro qol5d' OR eq-5d OR eq5-d OR eq5d OR euroqual OR euroqol	1,329,144

Clarification questions

Cost-effectiveness, HRQoL, and cost and resource use studies search strategy			
		OR euroqual5d OR euroqol5d):ab,ti OR (eq-sdq OR eqsdq):ab,ti OR (short form* OR shortform*):ab,ti OR (sf36* OR 'sf 36*' OR 'sf thirtysix' OR 'sf thirty six'):ab,ti OR (sf6 OR 'sf 6' OR sf6d OR 'sf 6d' OR 'sf six' OR sfsix OR sf8 OR 'sf 8' OR 'sf eight' OR sflight):ab,ti OR (sf12 OR 'sf 12' OR 'sf twelve' OR sftwelve):ab,ti OR (sf16 OR 'sf 16' OR 'sf sixteen' OR sfsixteen):ab,ti OR (sf20 OR 'sf 20' OR 'sf twenty' OR sftwenty):ab,ti OR (15D OR 15-D OR '15 dimension'):ab,ti OR ('standard gamble*' OR sg):ab,ti OR ('time trade off*' OR 'time tradeoff*' OR tto OR timetradeoff*):ab,ti OR 'ae-qol':ab,ti OR (angioedema NEXT/2 quality of life) OR (angioedema NEXT/2 qol) OR 'pedsq':ab,ti OR 'Pediatric Quality of Life Inventory':ab,ti	
10	Resource use filter	burden:ti OR resource*:ti OR ((burden* NEXT/3 (illness* OR disease* OR sickness* OR treatment* OR therap*)):ab,ti) OR ((resource* NEXT/4 (use* OR usage OR utilit*)):ab,ti) OR 'office visits':ab,ti OR 'ambulatory care'/de OR visit:ab,ti OR visits:ab,ti OR visited:ab,ti OR appointment*:ab,ti OR 'hospitalization'/de OR hospitalization*:ab,ti OR hospitalisation*:ab,ti OR hospitalised:ab,ti OR hospitalized:ab,ti OR admission*:ab,ti OR readmission*:ab,ti OR admitted:ab,ti OR readmitted:ab,ti OR 'length of stay'/de OR 'hospital stay*':ab,ti OR ((bed NEXT/3 day*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 hospital*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (stay OR stays OR stayed)):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (discharge OR discharged OR home OR homes)):ab,ti)	2,400,049
11	Burden filter	('carer' OR 'caregiver' OR care*) NEXT/2 (burden OR qol OR hrqol OR 'quality of life' OR 'quality-of-life' OR 'health-related quality-of-life' OR 'health related quality of life' OR utility OR utilit* OR 'eq-5d' OR 'sf-36' OR wellbeing OR 'well-being' OR euroqol OR qaly OR 'quality-adjusted life-year' OR disutility OR disutilit* OR daly OR 'disability-adjusted life-year')	26,788
12	Combine terms	#1 AND (#8 OR #9 OR #10 OR #11) AND [humans]/lim	4,704

Cost-effectiveness, HRQoL, and cost and resource use studies search strategy			
13	Combine terms	#7 OR #12	5,906

Table 53: CENTRAL (Cochrane Library interface) (6 June 2024)

Clinical search strategy			
Index	Description	Search terms	Hits
1	Terms for population	MeSH descriptor: [Angioedemas, Hereditary] explode all trees	167
2	Terms for population	(hereditary angioedema):ab,ti OR (hae):ab,ti	531
3	Combine terms	#1 or #2	548
4	Interventions/comparators	Donidalorsen or Garadacimab or sebetralstat or csl312 or "pdC1-INH" or Cinryze or Haegarda or Berinert or Lanadelumab or Takhzyro or Berotralstat or Orladeyo or Danazol or Danocrine or Stanozolol or Winstrol or "Tranexamic acid" or "Epsilon aminocaproic acid" or "long-term prophylaxis" or LTP	5,802
5	Combine terms	#3 and #4	198

Table 54: NHS HTA and EED search strategy (via University of York website) (6 June 2024)

Cost-effectiveness, cost and resources use and quality of life search strategy			
Index	Description	Search terms	Hits
1	Terms for population	"hereditary angioedema" or angioedema or hae	18
2	Economic filter	economics OR cost OR burden OR econ* OR health care cost OR indirect cost OR productivity	21,739
3	Combine filters	#1 AND #2 in NHSEED, HTA	6
4	QoL filter	qol OR quality of life OR patient satisfaction OR utility OR patient reported outcome OR time tradeoff OR TTO OR activities of daily living OR ADL OR social impact OR AE-QoL OR PedsQL	8,171
5	Combine terms	#1 AND #4 in NHSEED, HTA	6

Clarification questions

Table 55: ScHARRHUD search strategy (6 June 2024)

HRQoL search strategy			
Index	Description	Search terms	Hits
1	Terms for population	"hereditary angioedema" or angioedema or hae	0

Table 56: EuroQol database search strategy (6 June 2024)

HRQoL search strategy			
Index	Description	Search terms	Hits
1	Terms for population	"hereditary angioedema" or angioedema or hae	0

C5. Tables 27-32 in Appendix D of the SLR report list “results of the 2024 abstracts only”. Were any abstracts identified in the 2025 refresh search? – if so, please provide details including full references. Were all abstracts listed in Appendix D identified via the bibliographic databases or were some identified via the hand searching of conference proceedings described in section 3.3 of the SLR report?

In the 2025 refresh search of the SLR, 21 abstracts were identified. However, the company would like to highlight that Tables 27-32 in Appendix D of the SLR report do not just include the 2024 abstracts, but also report the abstracts identified in the 2025 refresh search. Appendix D therefore presents all abstracts identified in the SLR, categorised by research question, but it *does not present the full texts* from either SLR search. The use of the word “only” in the titles aimed to describe that ‘only’ abstracts are presented, not full text studies, which is how they are presented in Table 26, relating to the clinical research question. However, the company acknowledges that this wording is unclear and should explain that all abstracts across the 2024 and 2025 searches are included in Tables 27-32. The introduction of the tables in the SLR report should therefore read “Table X presents the results of the 2024 and 2025 SLR abstracts that were included in the [...] research question”. The company would like to highlight this was a typographical error in the original SLR report, which does not affect the number of abstracts included in the review, or

Clarification questions

the information extracted. For completeness, a comprehensive list of the 2025 abstracts accepted in the SLR, and for which research question they were accepted, is presented in Table 57. All abstracts presented in Table 57 are visible in Tables 27-32 in Appendix D of the SLR report in their respective tables per research question and can be easily searched using the SLR ID.

The company would like to confirm that all abstracts listed in Appendix D of the SLR report, which covers the abstracts identified in both 2024 and 2025 searches and included in the final SLR, were identified via bibliographic databases, specifically Embase and Medline. Hand searching of conference proceedings was performed prior to the first screening stage for both the 2024 and 2025 searches, as specified in Section 3.3 of the SLR report, but the searches did not identify any original references that had not been identified via the bibliographic databases. As such, all included abstracts were identified via searches in Embase and Medline.

Table 57: List of abstracts identified in the 2025 refresh SLR search (n=21)

SLR ID	Author	Study ID	Trial name	Journal	Title	Research questions
5988	Gehlen <i>et al.</i> (2024) ⁸²	NR	NR	International Archives of Allergy and Immunology	The Burden of Hereditary Angioedema in a Large Family in Brazil	Cost and resource use, BOI
5990	Braverman (2024) ⁸³	NR	NR	Value in Health	PCR37 Insights Into the Burden and Unmet Needs of Patients With Hereditary Angioedema: A Retrospective Social Media Listening Study	BOI
5991	Braverman. (2024) ⁸⁴	NR	NR	Value in Health	Clinical Meaningfulness of Improvements in Quality of Life Observed With Garadacimab Treatment in Patients Living With Hereditary Angioedema: Results From the Pivotal Phase 3 (VANGUARD) Study	Clinical, HRQoL
5992	Banerji <i>et al.</i> (2024) ⁸⁵	NCT05695248	ALPHA-STAR	Annals of Allergy, Asthma and Immunology	STAR-0215 INDUCES RAPID IMPROVEMENTS OF QUALITY OF LIFE IN HAE PATIENTS IN THE ALPHA-STAR TRIAL	Clinical, HRQoL
5993	Tachdjian <i>et al.</i> (2024) ⁸⁶	NR	NR	Annals of Allergy, Asthma and Immunology	SUSTAINED REAL-WORLD ATTACK REDUCTIONS FOLLOWING BEROTRALSTAT INITIATION AMONG PATIENTS WITH HEREDITARY ANGIOEDEMA WITH C1-INHIBITOR DEFICIENCY	Clinical
5994	Baptist <i>et al.</i> (2024) ⁸⁷	NR	NR	Annals of Allergy, Asthma and Immunology	SOCIAL DETERMINANTS OF HEALTH IN HEREDITARY ANGIOEDEMA AND THEIR IMPACT ON PATIENT OUTCOMES	Cost and resource use
5995	Keith <i>et al.</i> (2024) ⁸⁸	NCT04739059	VANGUARD	Annals of Allergy, Asthma and Immunology	LOW INCIDENCE OF GARADACIMAB IMMUNOGENICITY WITH NO IMPACT ON EFFICACY, SAFETY OR PHARMACOKINETICS: INTEGRATED ANALYSIS	Clinical
5996	Lumry <i>et al.</i> (2024) ⁸⁹	NCT05259917	KONFIDENT	Annals of Allergy, Asthma and Immunology	SUBSTANTIAL REDUCTION OF HEREDITARY ANGIOEDEMA ATTACK SYMPTOM BURDEN IN THE SEBETRALSTAT PHASE 3 KONFIDENT TRIAL	Clinical

SLR ID	Author	Study ID	Trial name	Journal	Title	Research questions
5997	Banerji <i>et al.</i> (2024) ⁹⁰	NR	NR	Annals of Allergy, Asthma and Immunology	LONGITUDINAL SURVEY OF ADULT PATIENTS WITH HEREDITARY ANGIOEDEMA RECEIVING LONG-TERM PROPHYLAXIS WITH LANADELUMAB	Clinical, HRQoL
5998	Yarlas <i>et al.</i> (2024) ⁹¹	NCT04307381	OASIS-HAE	Annals of Allergy, Asthma and Immunology	IMPACT OF DONIDALORSEN ON PATIENT-REPORTED OUTCOMES: RESULTS FROM THE PHASE 3 OASIS-HAE STUDY	Clinical, HRQoL
5999	Tachdjian <i>et al.</i> (2024) ⁹²	NCT05139810	OASIS-HAE OLE	Annals of Allergy, Asthma and Immunology	DONIDALORSEN FOR HEREDITARY ANGIOEDEMA: RESULTS FROM THE OASISPLUS OPEN-LABEL EXTENSION STUDY	Clinical
6000	Manning <i>et al.</i> (2024) ⁹³	NCT04030598	NR	Annals of Allergy, Asthma and Immunology	PHASE 2 OPEN-LABEL EXTENSION OF DONIDALORSEN IN PATIENTS WITH HEREDITARY ANGIOEDEMA: A WEEK 197 ANALYSIS	Clinical
6001	Hsu <i>et al.</i> (2024) ⁹⁴	NR	VANGUARD OLE	Annals of Allergy, Asthma and Immunology	BEING ATTACK-FREE WITH GARADACIMAB IMPROVES QUALITY OF LIFE IN PATIENTS WITH HEREDITARY ANGIOEDEMA	Clinical, HRQoL
6004	Christiansen <i>et al.</i> (2024) ⁹⁵	NR	NR	Journal of Managed Care and Specialty Pharmacy	Health care resource utilization among patients initiating berotralstat for the long-term prophylaxis of hereditary angioedema in the United States	Cost and resource use
6008	Busse <i>et al.</i> (2024) ⁹⁶	NR	NR	Value in Health	PCR267 Real-World Impact of Treated Hereditary Angioedema Attacks on Patients' Quality of Life	BOI
6009	Tachdjian <i>et al.</i> (2024) ⁹⁷	NR	NR	Value in Health	EE5 Healthcare Costs Among Commercially-Insured Patients with Hereditary Angioedema Managed with Long-Term Prophylaxis: A Retrospective US Claims Database	Cost and resource use
6011	Aygören-Pürsün <i>et al.</i> (2024) ⁹⁸	NCT04739059	VANGUARD	Allergologie	Garadacimab protects against hereditary angioedema attacks from Week 1 in pivotal Phase 3 VANGUARD study	Clinical*

SLR ID	Author	Study ID	Trial name	Journal	Title	Research questions
6012	Martinez-Saguer <i>et al.</i> (2024) ⁹⁹	NCT04739059	VANGUARD	Allergologie	Garadacimab for hereditary angioedema prophylaxis in adolescents: efficacy and safety from the phase 3 (vanguard) study and open-label extension (second interim analysis)	Clinical
6013	Magerl <i>et al.</i> (2024) ¹⁰⁰	NR	NR	Allergologie	Integrated safety and efficacy of garadacimab for hereditary angioedema prophylaxis across 3 clinical trials: phase 2, pivotal phase 3, and openlabel extension studies	Clinical
6014	Martinez-Saguer <i>et al.</i> (2024) ¹⁰¹	NR	NR	Allergologie	Health-related quality of life in adults with hereditary angioedema: Results from a multinational survey	HRQoL
6015	Magerl <i>et al.</i> (2024) ¹⁰²	NR	NR	Allergologie	Characterizing use of on-demand treatment among people living with hereditary angioedema in Germany	Cost and resource use, BOI

*Included as a linked publication associated with ID 1351

Abbreviations: BOI – Burden of illness, HAE – Hereditary angioedema; HRQoL – Health-related quality of life; NCT – National clinical trial; NR – Not reported; OLE – Open-label extension; SLR – Systematic literature review; US – United States

C6. The text accompanying table 32 in Appendix D of the SLR report states “This table does not include any of the 2025 updated search results or the re-screen papers from the 2024 SLR.” Which records were re-screened and why?

A re-screen was conducted in 2025 in conjunction with the 2025 updated search, after the initial 2024 SLR, to allow for the broadening of the inclusion criteria to be used across the five review questions. Specifically, two updates were made, which are explained further below:

- Inclusion of studies with patients with HAE Type III across all review questions
- Inclusion of studies with no active comparator for the cost-effectiveness review question

A total of 220 papers identified from the 2024 SLR were re-screened as part of the 2025 update; 220 papers were reviewed at the title/abstract stage, of which 206 were excluded at this stage. Fourteen papers were therefore screened at the full-text screening stage, and of these, nine papers were accepted in the review and extracted. Table 60 presents the nine re-screened papers that were accepted in the final SLR.

The first update made to the selection criteria in the SLR was made to the population inclusion criteria across all five review questions, which previously stated in the 2024 SLR that studies were to be included if they assessed “patients with HAE Types I and II aged 12 years old or above”. The exclusion criteria alongside this in the 2024 SLR stated that studies should be excluded if they “include any other patients/populations”, therefore excluding studies that also included patients with HAE Type III.

In the 2025 re-screen, the inclusion criteria were subsequently updated to remove the restriction to patients with HAE Type I and II only and were changed to “patients with HAE aged 12 years old or above”. In conjunction with this, the exclusion criteria were updated to exclude “studies that include any other patients/populations” or “studies of patients with HAE-nC1INH (Type III) only”. This ensured that, in line with the marketing authorisation for donidalorsen, the company were able to collate all relevant evidence for patients with HAE Type I and Type II but were not excluding

any papers that contained information about patients with HAE Type I and Type II only. The additional criteria allowed that in instances where Type III data was available in the same studies, this data could be collected too for completeness. Table 58 presents the original criteria and updated criteria together for comparison.

Table 58: Population inclusion and exclusion criteria for the 2024 and 2025 SLR screening, for all review questions

Selection criteria	Inclusion criteria	Exclusion criteria
2024 SLR (criteria used for all review questions)		
Population	Patients with HAE Types I and II aged 12 years old or above	Studies that include any other patients/populations
2025 SLR update (criteria used for all review questions)		
Population	Patients with HAE aged 12 years old or above	- Studies that include any other patients/populations - Studies of patients with HAE-nC1INH (Type III) only

Abbreviations: HAE – Hereditary angioedema; SLR – Systematic literature review

The second update was made to the criteria for review question 2 (for cost-effectiveness studies). The interventions/comparators criteria previously stated “none” as the exclusion criteria, which upon a review by the company after the 2024 SLR was conducted, was deemed unclear as it was misinterpreted to mean studies with ‘no comparators’ should be excluded, rather than ‘there are no criteria for exclusion’. As such, studies with no active comparator, such as single arm, natural history and observation studies, were not considered for inclusion because they did not satisfy this assumed ‘none’ criteria, despite likely being relevant to understand the disease burden, costs, and QoL for patients treated without any HAE interventions. The exclusion criteria were therefore updated for the 2025 re-screen and 2025 review to state “no exclusion criteria” was applicable to avoid ambiguity and ensure all relevant evidence was captured to inform the cost-effectiveness analysis. Table 59 presents the original criteria and updated criteria together for comparison

Table 59: Intervention/comparator inclusion and exclusion criteria for the 2024 and 2025 SLR screening, for review question 2 (cost-effectiveness studies)

Selection criteria	Inclusion criteria	Exclusion criteria
2024 SLR (criteria used for review question 2 [cost-effectiveness studies])		
Interventions/ comparators	Any intervention for the treatment of HAE	None
2025 SLR update (criteria used for review question 2 [cost-effectiveness studies])		
Interventions/ comparators	Any intervention for the treatment of HAE	No exclusion criteria

Abbreviations: HAE – Hereditary angioedema; SLR – Systematic literature review

Table 60: List of re-screened papers included and extracted in the 2024 re-screen review (n=9)

SLR ID	Author	Journal	Title	Research question
800	Bouillet <i>et al.</i> 2017 ¹⁰³	Allergy: European Journal of Allergy and Clinical Immunology	Hereditary angioedema: Analysis of 287 attacks treated with C1 esterase inhibitor in the French cohort cobra	Clinical
1526	Denman <i>et al.</i> 2017 ¹⁰⁴	Allergy: European Journal of Allergy and Clinical Immunology	The impact of the introduction of icatibant on A&E attendance, hospital admissions and acute treatment episodes in patients with hereditary angioedema	Cost and resource use
3469	Magliano <i>et al.</i> 2016 ¹⁰⁵	Value in Health	Cost effectiveness of icatibant for hereditary angioedema in Brazil: Challenges in the economic evaluation of orphan drugs	Cost-effectiveness
3490	Malbrán <i>et al.</i> 2017 ¹⁰⁶	Medicina (Argentina)	Treatment of hereditary angioedema due to C1 inhibitor deficiency in Argentina	BOI
4348	Piotrowicz-Wójcik <i>et al.</i> 2021 ¹⁰⁷	Journal of Clinical Medicine	Clinical characteristics and management of angioedema attacks in polish adult patients with hereditary angioedema due to C1-inhibitor deficiency	Clinical
4647	Rodríguez <i>et al.</i> 2017 ¹⁰⁸	Allergy, Asthma and Clinical Immunology	Management of hereditary angioedema: C1-inhibitor esterase and icatibant acetate self-administration for acute attacks	Cost and resource use
5215	Tachdjian <i>et al.</i> 2015 ¹⁰⁹	Allergy and Asthma Proceedings	Current characteristics associated with hereditary angioedema attacks and treatment: The home infusion based patient experience	BOI
5649	Wentzel <i>et al.</i> 2019 ¹¹⁰	World Allergy Organization Journal	Fresh frozen plasma for on-demand hereditary angioedema treatment in South Africa and Iran	Cost and resource use

SLR ID	Author	Journal	Title	Research question
5977	Craig <i>et al.</i> 2020 ¹¹¹	Allergy and Asthma Proceedings	Eastern Allergy Conference	Clinical

Abbreviations: A&E – Accident and emergency; BOI – Burden of illness; SLR – Systematic literature review

C7. Please provide the references from the SLR document either as a RIS file, compressed Endnote library, or in another format suitable for import into Endnote.

The full list of references from the SLR report are provided as a RIS file in the accompanying reference pack to this EAG clarification letter, named as 'Donidalorsen in HAE SLR Report_Full list of references_02Dec25'. The RIS file contains 388 references.

Cost-effectiveness clarifications

C8. Please confirm whether the absence of subsequent treatment records in OASIS-HAE indicates that (a) no patients received subsequent treatments during follow-up, or (b) subsequent treatment data were not collected/recorded

The absence of subsequent treatment records from the OASIS-HAE trial indicated that subsequent treatment data were not collected as part of OASIS-HAE.

C9. In the CS page 159, section 3.5.1.2 it is stated that “ it is assumed that ■■■% of patients self-administer their treatment and these patients incur a one-off 30-minute training session with a band 6 hospital nurse” and “the weighted one-off training cost per patient treated with subcutaneous therapy is £■■■■(£31.00 * ■■■)”. Can the company confirm this value was meant to be (£31.00 * ■■■).

The company acknowledges the typographical error and confirms the text should read “£■■■■(£31.00 * ■■■)”.

Appendix Question A1

A summary of the study design of OASIS-HAE and VANGAURD is presented in Table 61. The baseline attack rates in the intervention and control arms of OASIS-HAE and VANGUARD are similar: 3.6 and 3.1 attacks per month in the donidalorsen Q4W and garadacimab treatment arms, respectively. The baseline attack rate criteria and attack rate during the run-in period are presented in Table 62. The inclusion and exclusion criteria are broadly similar between OASIS-HAE and VANGUARD; criteria are presented in Table 63. The baseline characteristics are broadly similar between OASIS-HAE and VANGUARD; of summary of the baseline characteristics of patients is presented in Table 64. Overall, the clinical trial design, baseline attack rates and baseline characteristics are broadly similar between OASIS-HAE and VANGUARD.

Table 61: Comparison of OASIS-HAE and VANGUARD study designs

	OASIS-HAE⁷³	VANGUARD¹¹²
Intervention	Donidalorsen	Garadacimab
Study design	Phase 3 Randomised Placebo-controlled	Phase 3 Randomised Placebo-controlled Parallel arm
Randomisation	2:1 to either Q4W or Q8W interval; then within each dosing interval group, patients were randomly assigned again 3:1 to receive donidalorsen or placebo	3:2 to receive garadacimab or placebo
Masking/ Blinding	Double-blind	Double-blind
Loss to follow-up	0 patients	1 patient
Study duration	24-week treatment period	6-month treatment period (182 days)

Abbreviations: Q4W – Once every four weeks; Q8W – Once every eight weeks

Table 62: Comparison of OASIS-HAE and VANGUARD baseline attack rate

	OASIS-HAE⁷³	VANGUARD¹¹²
Baseline attack rate criteria	Minimum of two HAE investigator-confirmed attacks (during the 8-week screening period)	At least three HAE attacks (during 3 months before screening or over 3 consecutive months before commencing any prophylactic therapy before screening)
Time period this is measured in	8 weeks	3 months
Baseline attack rate criteria (value)	1 per month	1 per month

Treatment arm	Donidalorsen Q4W	Placebo	Garadacimab	Placebo
No. of HAE attacks per month during run-in period	3.6 (SD: 2.2)	2.9 (SD: 1.7)	3.1 (95% 2.4, 3.7)	2.5 (95% CI: 2.1, 2.9)

Abbreviations: HAE – Hereditary angioedema; SD – Standard deviation

Table 63: Comparison of OASIS-HAE and VANGUARD inclusion and exclusion criteria

	Donidalorsen	Garadacimab
Study identifier NCT number)	OASIS-HAE ⁷³ NCT05139810	VANGUARD ¹¹² NCT04656418
Inclusion criteria	Age requirements	Age requirements
	Patients aged ≥12 years	Potentially eligible patients were aged 12 years or older at screening (adolescents: ≥12 years ≤17 years, adults: >17 years)
	Diagnosis confirmation	Diagnosis confirmation
	Participants must have a documented diagnosis of HAE type I or type II base upon all of the following: Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria) Diagnostic testing result that confirms HAE type I or II based on a C1-INH functional level <40% of the normal level. Patients with functional C1-INH level of 40% to 50% of normal can be enrolled if their complement C4 concentration is below the LLN or if a known pathogenic mutation in the SERPING1 gene has been demonstrated At least one of the following: age at reported HAE onset ≤30 years, a family history consistent with HAE type I or II, or complement component 1q level within the normal range	Patients with a confirmed diagnosis of type I or type II HAE based on the following criteria: Documented clinical history consistent with HAE C1-INH functional activity of 50% or less (reference range 70–130% of normal plasma) C4 antigen concentration below the lower limit of the reference range (0.16–0.38 mg/mL)
	Attack frequency	Attack frequency
	Participants must experience a minimum of 2 HAE attacks (confirmed by the Investigator) during the 8-week screening period	Patients must have had at least three HAE attacks during the 3 months before screening (or over 3 consecutive months before commencing any prophylactic therapy before screening)
	Other criteria	Other criteria
	Willingness to Participate: Participants must be willing to complete the PRO assessments throughout the study	Access to Medication: Eligible patients were required to willingly stop using long-term prophylactic HAE treatments (e.g. C1-INH replacement therapy, androgens, antifibrinolytics, or other small molecule medications),

	Donidalorsen	Garadacimab
Study identifier NCT number)	OASIS-HAE ⁷³ NCT05139810	VANGUARD ¹¹² NCT04656418
	Access to Medication: Participants must have access to, and the ability to use, acute medication(s) to treat angioedema attacks	allowing for a washout period of at least 2 weeks before the start of the run-in period Routine HAE prophylactic treatments were prohibited during the run-in period and the 6-month treatment period; on-demand therapies were permitted as per patient treatment plans
Exclusion criteria	Concurrent diagnosis of any other type of recurrent angioedema, including acquired, idiopathic angioedema or HAE with normal C1-INH (also known as HAE Type III) Any clinically significant abnormalities in screening laboratory values that would render a participant unsuitable for inclusion in the study Treatment with another investigational drug or biological agent within 1 month or 5 half-lives, whichever is longer, of Screening Participated in a prior ISIS 721744 study Exposure to any of the following medications: Angiotensin-converting enzyme (ACE) inhibitors or any oestrogen containing medications with systemic absorption within 4 weeks prior to Screening Chronic prophylaxis with Takhzyro, Haegarda, Cinryze and Ruconest or Orladeyo within 5 half-lives prior to Screening Oligonucleotides (including small interfering ribonucleic acid [siRNA]) within 4 months of Screening if single dose received, or within 12 months of Screening if multiple doses received. This exclusion does not apply to vaccines Recent history (3 years) of, or current drug or alcohol abuse	Patients were excluded in cases of concomitant diagnosis of other forms of angioedema (e.g., idiopathic, acquired, HAE with normal C1-INH), preplanned major surgeries, and use of monoclonal antibodies within 3 months before the run-in period, garadacimab (in previous trials), or oestrogen-containing medications.

Abbreviations: ACE - Angiotensin-converting enzyme; C1-INH - C1-esterase inhibitor; HAE – Hereditary angioedema; PRO – Patient-reported outcome; SD – Standard deviation

Table 64: Comparison of OASIS-HAE and VANGUARD baseline characteristics

	OASIS-HAE ⁷³		VANGUARD ¹¹²	
	Donidalorsen 4-week group	Placebo	Garadacimab 200 mg	Placebo
Study size, N	45	22	39	25
Age years (range)	Mean (SD) [range]: 39.6 (15.23) [12,68]	Mean (SD) [range]: 35.4 (11.03) [21,59]	Median (SD) [range]: 43.3 (17.5) [12-69]	Median (SD) [range]: 37.8 (12.8) [14-62]
Years No. / % in each age group	12–17 yr: 4 (8.9%) 18–39 yr: 19 (42.2%) 40–64 yr: 21 (46.7%) ≥65 yr: 1 (2.2%)	12–17 yr: 0 18–39 yr: 15 (68.2%) 40–64 yr: 7 (31.8%) ≥65 yr: 0	≤ 17: 18 (46%). >17 to ≤40: 18(46%) >40: 3 (8%)	≤ 17: 12 (48%); >17 to ≤40: 11(44%); >40: 2 (8%)
Male: N (%)	17 (37.8%)	14 (63.6%)	15 (38%)	11 (44%)
BMI	Mean (SD): 28.03 (6.738)	Mean (SD): 28.88 (9.216)	Median (SD): 27.9 (6.0)	Median (SD): 28.4 (7.6)
Ethnicity: N (%)	White: 42 (93.3%) Asian: 1 (2.2%) Black or African American: 1 (2.2%) American Indian or Alaska Native: 0 Multiple: 0 Other: 1 (2.2%)	White: 18 (81.8%) Asian: 0 Black or African American: 1 (4.5%) American Indian or Alaska Native: 2 (9.1%) Multiple: 1 (4.5%) Other: 0	Asian (Japanese): 4 (10%) Black or African American; 0 Native Hawaiian or Other Pacific Islander: 1 (3%) White: 33 (85%) Other: 1 (3%)	Asian (Japanese): 2 (8%) Black or African American: 1 (4%) Native Hawaiian or Other Pacific Islander: 0 White: 22 (88%) Other; 0
HAE type: N (%)	Type I: 42 (93.3%) Type II: 3 (6.7%)	Type I: 20 (90.9%) Type II: 2 (9.1%)	Type I: 34 (87%) Type II: 5 (13%)	Type I: 22 (88%) Type II: 3 (12%)
Previous family history of HAE: N (%)	Yes: 41 (91.1%) No: 4 (8.9%)	Yes: 17 (77.3%) No: 5 (22.7%)	Yes: 34 (87%)	Yes: 23 (92%)
History of HAE types of attacks experienced: N (%)	Peripheral: 43 (95.6%) Abdominal: 43 (95.6%) Laryngeal: 22 (48.9%)	Peripheral: 20 (90.9%) Abdominal: 20 (90.9%) Laryngeal:12 (54.5%)	History of laryngeal attacks: 21 (54%) Primary location of HAE attacks in the last 3 months prior to screening: Cutaneous (extremities): 30 (77%)	History of laryngeal attacks: 17 (68%) Primary location of HAE attacks in the last 3 months prior to screening: Cutaneous

	OASIS-HAE ⁷³		VANGUARD ¹¹²	
	Donidalorsen 4-week group	Placebo	Garadacimab 200 mg	Placebo
			Abdomen: 30 (77%) Cutaneous(head/face/lip/neck): 13 (33%) Genitourinary: 6 (15%) Cutaneous (trunk): 5 (13%) Cutaneous (genitourinary): 2 (5%) Throat/larynx/tongue: 3 (8%) Groin and testicles: 1 (3%) Hands: 0 Peripheral: 1 (3%)	(extremities): 20 (80%) Abdomen: 18 (72%) Cutaneous (head/face/lip/neck): 8 (32%) Genitourinary: 2 (8%) Cutaneous – trunk: 2 (8%) Cutaneous (genitourinary): 4 (16%) Throat/larynx/tongue: 2 (8%) Groin and testicles: 0 Hands: 1 (4%) Peripheral: 0
Previous prophylactic treatment: N (%)	Any Predefined Prophylactic Therapy Use Yes: 6 (13.3%) No: 39 (86.7%)	Any Predefined Prophylactic Therapy Use Yes: 5 (22.7%) No: 17 (77.3%)	Tranexamic acid: 2 Berotralstat dihydrochloride: 4 Lanadelumab: 1	Tranexamic acid: 1 Berotralstat dihydrochloride: 3 Lanadelumab: 0
Previous prophylactic C1-INH treatment: N (%)	48.9%	31.8%	6	2
Number of HAE attacks prior to screening: N (%)	No. of HAE attacks in the 12 months before screening, mean (SD): 45.7 (43.0) No. of HAE attacks during run-in period, mean (SD): 3.6 (2.2)	No. of HAE attacks in the 12 months before screening, mean (SD): 29.1 (21.1) No. of HAE attacks during run-in period, mean (SD): 2.9 (1.7)	Number of hereditary angioedema attacks during the 3 months before screening or at the start of prophylaxis: 8.6 (6.3-10.9) During the run-in period: 3.1 (2.4-3.7)	Number of hereditary angioedema attacks during the 3 months before screening or at the start of prophylaxis: 9.3 (6.4 -12.2) During the run-in period 2.5 (2.1-2.9)

Abbreviations: BMI – Body mass index; C1-INH - C1-esterase inhibitor; HAE – Hereditary angioedema; SD – Standard deviation

Appendix Question A21

Mean number of moderate or severe HAE attacks per month

Goodness-of-fit statistics

Table 65 shows that the residual deviance (██████) for the NMA conducted for this outcome is very close to the total number of data points (█). This indicates that the model fits the observed data well, as a residual deviance approximately equal to the number of data points suggests the model explains the data accurately with little evidence for misfit to the data in the network.⁵⁶ The effective number of parameters, pD, (██████) is also very close to the total number of data points, indicating the model fits suitably well.

Table 65: Goodness-of-fit statistics – mean number of moderate or severe HAE attacks per month

Parameter	Value
Residual deviance	██████
pD	██████
Number of data points	██████

Abbreviations: HAE – Hereditary angioedema; pD – effective number of parameters.

Tau

In Table 66 the median value of tau (██████) suggests there is moderate heterogeneity in treatment effects across studies. The wide 95% credible interval (██████ to ██████) reflects the uncertainty in this estimate, likely due to limited data to estimate this parameter across the network.

Similarly to the outcome of mean number of HAE attacks per month, the estimated tau strongly supports the use of the company's base-case RE model.

Table 66: Between-study heterogeneity – mean number of moderate or severe HAE attacks per month

Parameter	Value
Median value for tau	██████
95% CrI	██████████████

Abbreviations: CrI – Credible interval, HAE – Hereditary angioedema.

SUCRA and rank probabilities

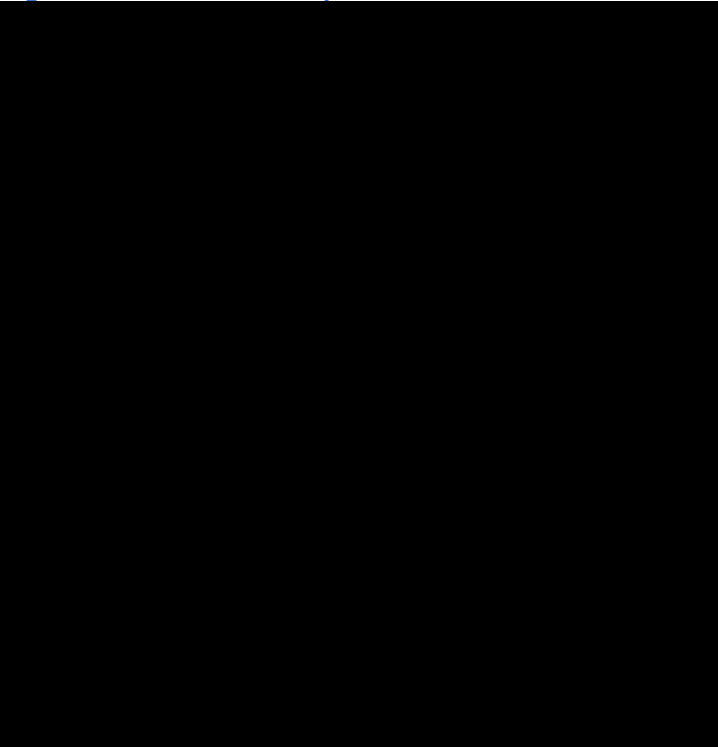
As presented in Table 67, donidalorsen Q4W and donidalorsen Q8W have the [REDACTED] and [REDACTED] highest SUCRA values, respectively. Figure 12 presents the posterior rank plot where the bold bars represent the 66% CrI and the thin bars represent the 95% CrI. Therefore, while lanadelumab Q2W and lanadelumab Q4W achieved numerically higher rankings than donidalorsen Q4W and donidalorsen Q8W, respectively, credible intervals overlap between treatments, indicating comparable efficacy across active treatments.

Table 67: SUCRA – mean number of moderate or severe HAE attacks per month

Treatment	SUCRA
Donidalorsen Q4W	[REDACTED]
Donidalorsen Q8W	[REDACTED]
Lanadelumab Q2W	[REDACTED]
Lanadelumab Q4W	[REDACTED]
Placebo	[REDACTED]

Abbreviations: HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks; SUCRA – Surface under the cumulative ranking curve.

Figure 12: Posterior rank plot – mean number of moderate or severe HAE attacks per month



Abbreviations: HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

R-hat values

The R-hat values presented in Table 68 are all [REDACTED] to two decimal places, indicating that the MCMC chains in the NMA have converged successfully and the resulting treatment effect estimates are robust.

Table 68: Treatment effect R-hat value per treatment versus donidalorsen Q4W – mean number of moderate or severe HAE attacks per month

Treatment	R-hat
Donidalorsen Q8W	[REDACTED]
Lanadelumab Q2W	[REDACTED]
Lanadelumab Q4W	[REDACTED]
Placebo	[REDACTED]

Abbreviations: HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

Overall, the performance metrics indicate that the NMA model fits the observed data for the outcome of mean number of moderate or severe HAE attacks well and provides robust estimates, aligning with the outcome for mean number of HAE attacks per month. The goodness-of-fit demonstrated the NMA model fits the observed data well, tau supported the choice of a RE model over a FE model, the Clarification questions

posterior rank plot showed donidalorsen Q4W to have comparable efficacy with lanadelumab Q2W and the R-hat values confirmed MCM chain convergence ensuring reliability of the treatment effects.

Proportion of patients achieving ≥50% reduction in HAE attacks from baseline

Goodness-of-fit statistics

Table 69 shows that the residual deviance () for the NMA conducted for this outcome is close to the total number of data points (). This indicates that the model fits the observed data well, as a residual deviance approximately equal to the number of data points suggests the model explains the data accurately with little evidence for misfit to the data in the network.⁵⁶ The effective number of parameters, pD,() is also close to the total number of data points, indicating the model fits suitably.

Table 69: Goodness-of-fit statistics – proportion of patients achieving ≥50% reduction in HAE attacks from baseline

Parameter	Value
Residual deviance	
pD	
Number of data points	

Abbreviations: HAE – Hereditary angioedema; pD – effective number of parameters.

Tau

In Table 70 the median value of tau () suggests there is moderate heterogeneity in treatment effect across studies. The wide 95% credible interval (,) reflects the uncertainty in this estimate, likely due to limited data to estimate this parameter across the network.

Similarly to the outcome of mean number of HAE attacks per month, the estimated tau strongly supports the use of the company’s base-case RE model.

Table 70: Between-study heterogeneity – proportion of patients achieving ≥50% reduction in HAE attacks from baseline

Parameter	Value
Median value for tau	██████
95% CrI	██████████

Abbreviations: CrI – Credible interval, HAE – Hereditary angioedema.

SUCRA and rank probabilities

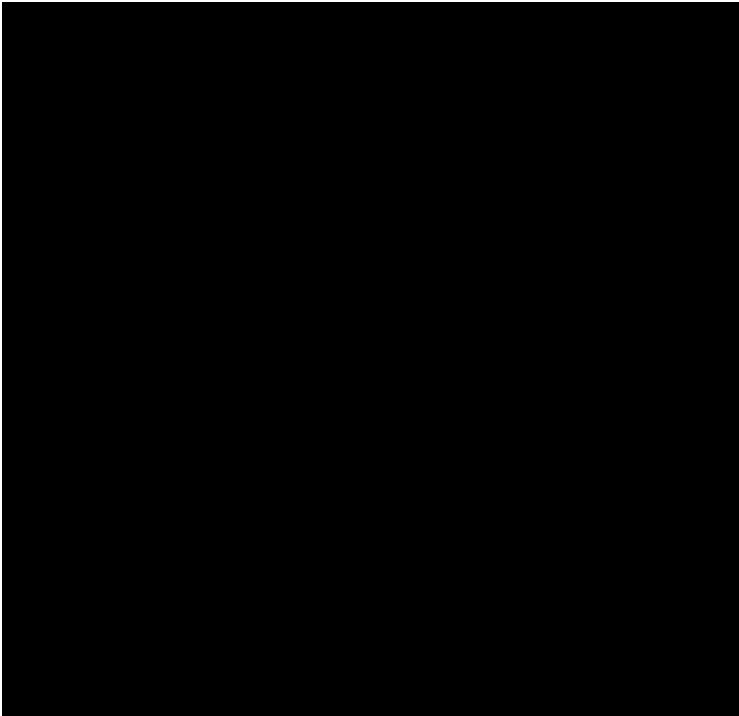
As presented in Table 71, donidalorsen Q4W and donidalorsen Q8W have the ██████ and ██████ highest SUCRA values, respectively. Figure 13 presents the posterior rank plot which does not show credible interval overlap between donidalorsen Q4W and donidalorsen Q8W and lanadelumab Q4W or lanadelumab Q2W, indicating that both lanadelumab regimens are more effective than donidalorsen Q4W and donidalorsen Q8W. Additionally, while donidalorsen Q4W and donidalorsen Q8W achieved numerically higher rankings than berotralstat, credible intervals overlap between treatments, indicating comparable efficacy across active treatments.

Table 71: SUCRA - proportion of patients achieving ≥50% reduction in HAE attacks from baseline

Treatment	SUCRA
Donidalorsen Q4W	██████
Berotralstat	██████
Donidalorsen Q8W	██████
Lanadelumab Q2W	██████
Lanadelumab Q4W	██████
Placebo	██████

Abbreviations: HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks; SUCRA – Surface under the cumulative ranking curve.

Figure 13: Posterior rank plot – proportion of patients achieving ≥50% reduction in HAE attacks from baseline



Abbreviations: HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

R-hat values

The R-hat values presented in Table 72 are all [REDACTED] to two decimal places, indicating that the MCMC chains in the NMA have converged successfully and the resulting treatment effect estimates are robust.

Table 72: Treatment effect R-hat value per treatment versus donidalorsen Q4W – proportion of patients achieving ≥50% reduction in HAE attacks from baseline

Treatment	R-hat
Berotrastat	[REDACTED]
Donidalorsen Q8W	[REDACTED]
Lanadelumab Q2W	[REDACTED]
Lanadelumab Q4W	[REDACTED]
Placebo	[REDACTED]

Abbreviations: HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

Overall, the performance metrics indicate that the NMA model fits the observed data for the outcome of proportion of patients achieving ≥50% reduction in HAE attacks from baseline well and provides robust estimates, aligning with the outcome for mean number of HAE attacks per month. The goodness-of-fit demonstrated the NMA

Clarification questions

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model fits the observed data well, tau supported the choice of a RE model over a FE model and the R-hat values confirmed MCMC chain convergence ensuring reliability of the treatment effects. However, the SUCRA values and the posterior rank plot provide less favourable results for donidalorsen Q4W and donidalorsen Q8W in this outcome, suggesting both lanadelumab regimens are more effective.

Proportion of patients achieving ≥70% reduction in HAE attacks from baseline

Goodness-of-fit statistics

Table 73 demonstrates the residual deviance () for the NMA conducted for this outcome is very close to the total number of data points (). This indicates that the model fits the observed data well, as a residual deviance approximately equal to the number of data points suggests the model explains the data accurately with little evidence for misfit to the data in the network.⁵⁶ The effective number of parameters, pD, () is also very close to the total number of data points, indicating the model fits suitably well.

Table 73: Goodness-of-fit statistics – proportion of patients achieving ≥70% reduction in HAE attacks from baseline

Parameter	Value
Residual deviance	
pD	
Number of data points	

Abbreviations: HAE – Hereditary angioedema; pD – effective number of parameters.

Tau

In Table 74 the median value of tau () suggests there is moderate heterogeneity in treatment effects across studies. The wide 95% credible interval (,) reflects the uncertainty in this estimate, likely due to limited data to estimate this parameter across the network.

Similarly to the outcome of mean number of HAE attacks per month, the estimated tau strongly supports the use of the company’s base-case RE model.

Table 74: Between-study heterogeneity – proportion of patients achieving ≥70% reduction in HAE attacks from baseline

Parameter	Value
Median value of tau	██████
95% CrI	██████████

Abbreviations: CrI – Credible interval, HAE – Hereditary angioedema.

SUCRA and rank probabilities

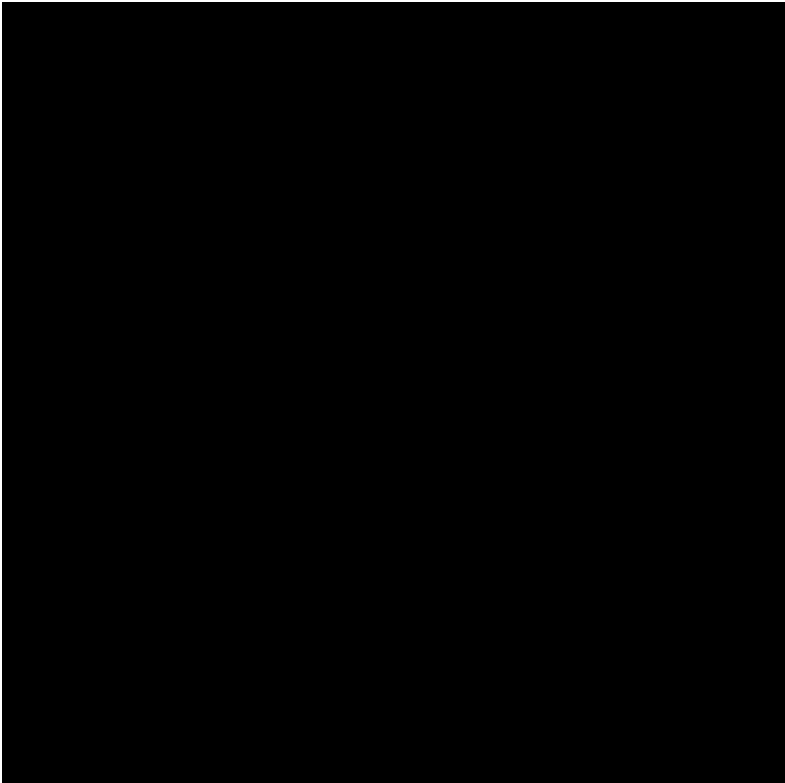
As presented in Table 75, donidalorsen Q4W and donidalorsen Q8W have the ██████ and ██████ highest SUCRA values, respectively. Figure 14 presents the posterior rank plot which shows donidalorsen Q4W and donidalorsen Q8W ranked ██████ and ██████, respectively. This difference in ranking suggests that although donidalorsen Q4W frequently ranks near the top (reflected by its high SUCRA), the single most probable rank from the posterior distribution places it third. While lanadelumab Q2W and lanadelumab Q4W achieved numerically higher rankings than donidalorsen Q4W and donidalorsen Q8W, credible intervals overlap between treatments, indicating comparable efficacy across active treatments.

Table 75: SUCRA - proportion of patients achieving $\geq 70\%$ reduction in HAE attacks from baseline

Treatment	SUCRA
Donidalorsen Q4W	██████
Berotrastat	██████
Donidalorsen Q8W	██████
Lanadelumab Q2W	██████
Lanadelumab Q4W	██████
Placebo	██████

Abbreviations: HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks; SUCRA – Surface under the cumulative ranking curve.

Figure 14: Posterior rank plot – proportion of patients achieving ≥70% reduction in HAE attacks from baseline



Abbreviations: HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

R-hat values

The R-hat values presented in Table 76 are all [REDACTED] to two decimal places, indicating that the MCMC chains in the NMA have converged successfully and the resulting treatment effect estimates are robust.

Table 76: Treatment effect R-hat value per treatment versus donidalorsen Q4W – proportion of patients achieving ≥70% reduction in HAE attacks from baseline

Treatment	R-hat
Berotrastat	[REDACTED]
Donidalorsen Q8W	[REDACTED]
Lanadelumab Q2W	[REDACTED]
Lanadelumab Q4W	[REDACTED]
Placebo	[REDACTED]

Abbreviations: HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

Overall, the performance metrics indicate that the NMA model fits the observed data for the outcome of proportion of patients achieving ≥70% reduction in HAE attacks

from baseline considerably well and provides robust estimates, aligning with the outcome for mean number of HAE attacks per month. The goodness-of-fit demonstrated the NMA model fits the observed data well, tau supported the choice of a RE model over a FE model, the posterior rank plot showed donidalorsen Q4W to have comparable efficacy with lanadelumab Q2W and lanadelumab Q4W and the R-hat values confirmed MCMC chain convergence ensuring reliability of the treatment effects.

Proportion of patients achieving $\geq 90\%$ reduction in HAE attacks from baseline

Goodness-of-fit statistics

Table 77 shows that the residual deviance (■■■■) for the NMA conducted for this outcome is very close to the total number of data points (■). This indicates that the model fits the observed data well, as a residual deviance approximately equal to the number of data points suggests the model explains the data accurately with little evidence for misfit to the data in the network.⁵⁶ The effective number of parameters, pD, (■■■■) is also very close to the total number of data points, indicating the model fits suitably well.

Table 77: Goodness-of-fit statistics – proportion of patients achieving $\geq 90\%$ reduction in HAE attacks from baseline

Parameter	Value
Residual deviance	8.270
pD	8.269
Number of data points	8.000

Abbreviations: HAE – Hereditary angioedema; pD – effective number of parameters.

Tau

In Table 78 the median value of tau (■■■■) suggests there is moderate heterogeneity in treatment effects across studies. The wide 95% credible interval (■■■■, ■■■■) reflects uncertainty due to limited data or variability in effect estimates across studies.

Similarly to the outcome of mean number of HAE attacks per month, the estimated tau strongly supports the use of the company's base-case RE model.

Table 78: Between-study heterogeneity – proportion of patients achieving $\geq 90\%$ reduction in HAE attacks from baseline

Parameter	Value
Median value for tau	██████████
95% CrI	████████████████████

Abbreviations: CrI – Credible interval, HAE – Hereditary angioedema.

SUCRA and rank probabilities

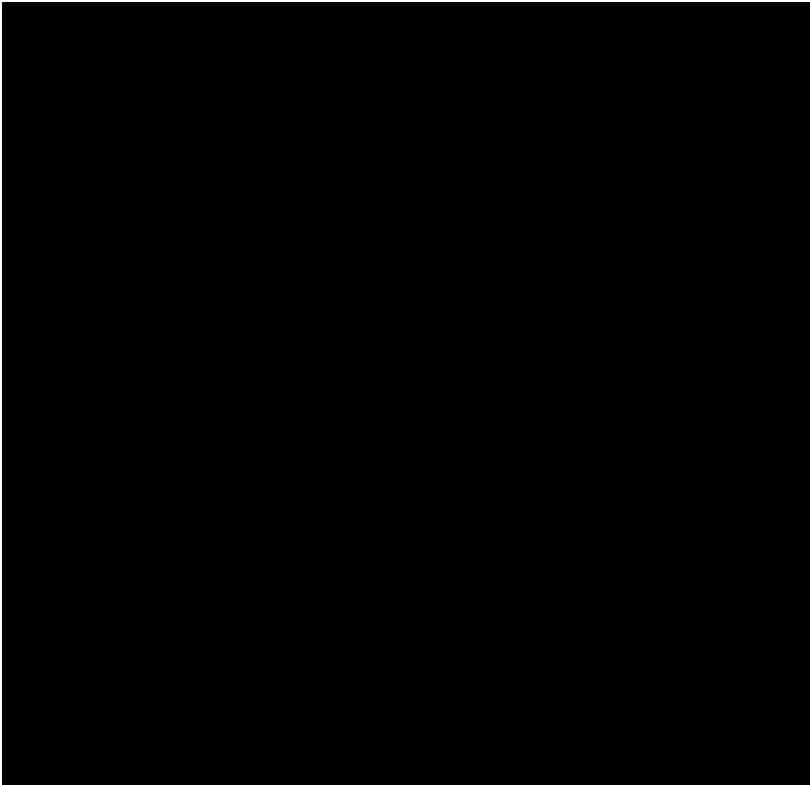
As presented in Table 33, donidalorsen Q4W and donidalorsen Q8W have the third and fifth highest SUCRA values, respectively. Figure 15 presents the posterior rank plot which shows donidalorsen Q4W, donidalorsen Q8W and berotralstat all rank joint fourth. While lanadelumab Q2W and lanadelumab Q4W achieved numerically higher rankings than donidalorsen Q4W, donidalorsen Q8W and berotralstat, credible intervals overlap between treatments, indicating comparable efficacy across active treatments.

Table 79: SUCRA - proportion of patients achieving $\geq 90\%$ reduction in HAE attacks from baseline

Treatment	SUCRA
Donidalorsen Q4W	██████████
Berotralstat	██████████
Donidalorsen Q8W	██████████
Lanadelumab Q2W	██████████
Lanadelumab Q4W	██████████
Placebo	██████████

Abbreviations: HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks; SUCRA – Surface under the cumulative ranking curve.

Figure 15: Posterior rank plot – proportion of patients achieving ≥90% reduction in HAE attacks from baseline



Abbreviations: HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

R-hat values

The R-hat values presented in Table 80 are all [REDACTED] to two decimal places, indicating that the MCMC chains in the NMA have converged successfully and the resulting treatment effect estimates are robust.

Table 80: Treatment effect R-hat value per treatment versus donidalorsen Q4W – proportion of patients achieving ≥90% reduction in HAE attacks from baseline

Treatment	R-hat
Berotrastat	[REDACTED]
Donidalorsen Q8W	[REDACTED]
Lanadelumab Q2W	[REDACTED]
Lanadelumab Q4W	[REDACTED]
Placebo	[REDACTED]

Abbreviations: HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

Overall, the performance metrics indicate that the NMA model fits the observed data for the outcome of proportion of patients achieving ≥90% reduction in HAE attacks

from baseline considerably well and provides robust estimates, aligning with the outcome for mean number of HAE attacks per month. The goodness-of-fit demonstrated the NMA model fits the observed data well, tau supported the choice of a RE model over a FE model, the posterior rank plot showed donidalorsen Q4W to have comparable efficacy with lanadelumab Q2W and lanadelumab Q4W and the R-hat values confirmed MCMC chain convergence ensuring reliability of the treatment effects.

Mean number of HAE attacks requiring on-demand medication

Goodness-of-fit statistics

Table 81 shows that the residual deviance (██████) for the NMA conducted for this outcome is very close to the total number of data points (██). This indicates that the model fits the observed data well, as a residual deviance approximately equal to the number of data points suggests the model explains the data accurately with little evidence for misfit to the data in the network.⁵⁶ The effective number of parameters, pD, (██████) is also very close to the total number of data points, indicating the model fits suitably well.

Table 81: Goodness-of-fit statistics – mean number of HAE attacks requiring on-demand medication

Parameter	Value
Residual deviance	██████
pD	██████
Number of data points	██████

Abbreviations: HAE – Hereditary angioedema; pD – effective number of parameters.

Tau

In Table 82 the median value of tau (██████) suggests there is moderate heterogeneity in treatment effects across studies. The wide 95% credible interval (██████ to ██████) reflects the uncertainty in this estimate, likely due to limited data to estimate this parameter across the network.

Similarly to the outcome of mean number of HAE attacks per month, the estimated tau strongly supports the use of the company's base-case RE model.

Table 82: Between-study heterogeneity – mean number of HAE attacks requiring on-demand medication

Parameter	Value
Median value for tau	██████
95% CrI	██████████

Abbreviations: CrI – Credible interval, HAE – Hereditary angioedema.

SUCRA and rank probabilities

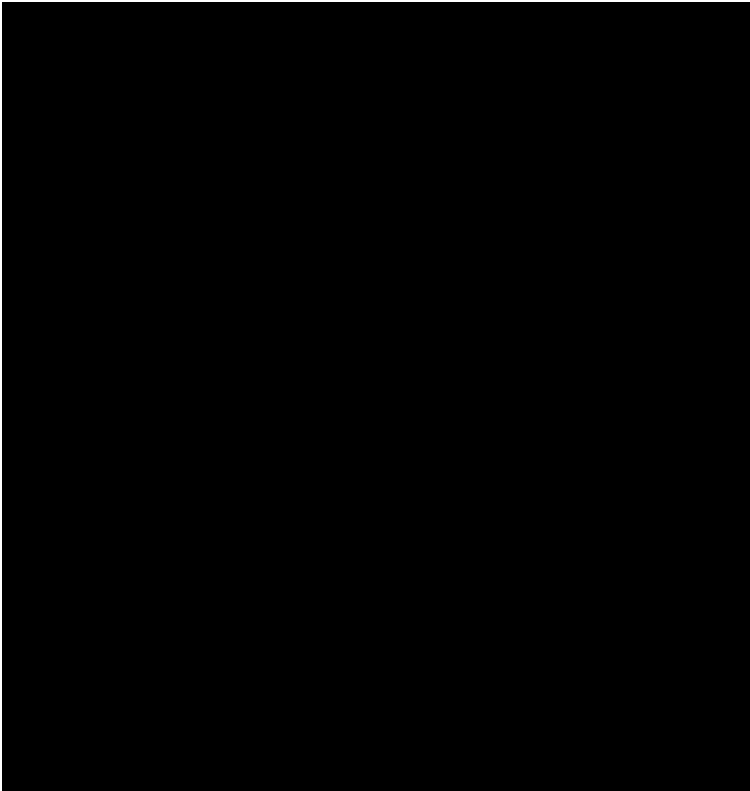
As presented in Table 83, donidalorsen Q4W and donidalorsen Q8W have the ██████ and ██████ highest SUCRA values, respectively. Figure 16 presents the posterior rank plot, which also shows donidalorsen Q4W and donidalorsen Q8W as rank ██████ and ██████, respectively. While lanadelumab Q2W and lanadelumab Q4W achieved numerically higher rankings than donidalorsen Q4W and donidalorsen Q8W, credible intervals overlap between treatments, indicating comparable efficacy across active treatments.

Table 83: SUCRA – mean number of HAE attacks requiring on-demand medication

Treatment	SUCRA
Donidalorsen Q4W	██████
Donidalorsen Q8W	██████
Lanadelumab Q2W	██████
Lanadelumab Q4W	██████
Placebo	██████

Abbreviations: HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks; SUCRA – Surface under the cumulative ranking curve.

Figure 16: Posterior rank plot – mean number of HAE attacks requiring on-demand medication



Abbreviations: HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

R-hat values

The R-hat values presented in Table 84 are all [REDACTED] to two decimal places, indicating that the MCMC chains in the NMA have converged successfully and the resulting treatment effect estimates are robust.

Table 84: Treatment effect R-hat value per treatment versus donidalorsen Q4W – mean number of HAE attacks requiring on-demand medication

Treatment	R-hat
Donidalorsen Q8W	[REDACTED]
Lanadelumab Q2W	[REDACTED]
Lanadelumab Q4W	[REDACTED]
Placebo	[REDACTED]

Abbreviations: HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

Overall, the performance metrics indicate that the NMA model fits the observed data for the outcome of mean number of HAE attacks requiring on-demand medication considerably well and provides robust estimates, aligning with the outcome for mean number of HAE attacks per month. The goodness-of-fit demonstrated the NMA

model fits the observed data well, tau supported the choice of a RE model over a FE model, the posterior rank plot showed donidalorsen Q4W to have comparable efficacy with lanadelumab Q2W and lanadelumab Q4W and the R-hat values confirmed MCMC chain convergence ensuring reliability of the treatment effects.

Mean change from baseline in AE-QoL score

Goodness-of-fit statistics

Table 85 shows that the residual deviance () for the NMA conducted for this outcome is very close to the total number of data points (8). This indicates that the model fits the observed data well, as a residual deviance approximately equal to the number of data points suggests the model explains the data accurately with little evidence for misfit to the data in the network.⁵⁶ The effective number of parameters , pD, () is also very close to the total number of data points, indicating the model fits suitably well.

Table 85: Goodness-of-fit statistics – mean change from baseline in AE-QoL score

Parameter	Value
Residual deviance	
pD	
Number of data points	

Abbreviations: AE-QoL – Angioedema quality of life questionnaire; HAE – Hereditary angioedema; pD – effective number of parameters.

Tau

The median and 95% Crls for tau, presented in Table 86, are all , indicating that there is effectively no between-study heterogeneity for this outcome. In other words, the observed variation in treatment effects can be entirely explained by within-study sampling error. While these results suggest a FE model would be more appropriate given the lack of between-study heterogeneity, the RE model is used to remain consistent with the modelling approach applied across all outcomes, ensuring a uniform methodology.

Table 86: Between-study heterogeneity – mean change from baseline in AE-QoL score

Parameter	Value
Median value for tau	██████
95% CrI	██████████

Abbreviations: AE-QoL – Angioedema quality of life questionnaire; CrI – Credible interval, HAE – Hereditary angioedema.

SUCRA and rank probabilities

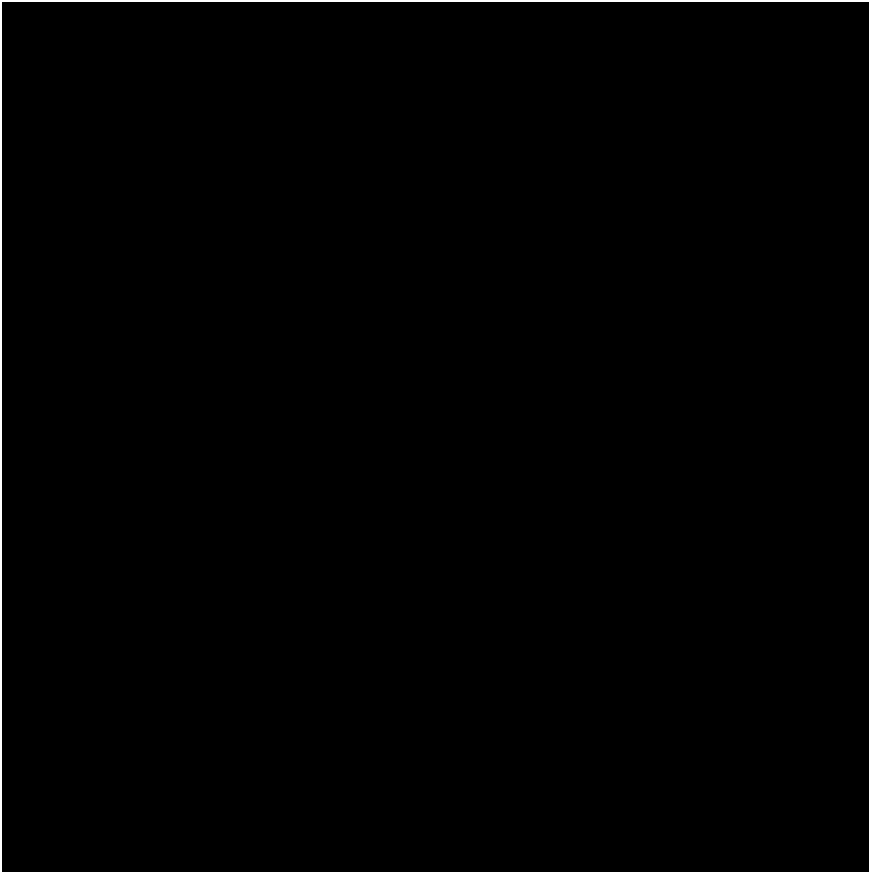
As presented in Table 87, donidalorsen Q4W and donidalorsen Q8W have the ██████ and ██████ highest SUCRA values, respectively. Figure 17 presents the posterior rank plot, which also shows donidalorsen Q4W and donidalorsen Q8W as rank ██████ and ██████, respectively. While donidalorsen Q4W achieved a numerically higher ranking than donidalorsen Q8W, both lanadelumab regimens and berotralstat, credible intervals overlap between treatments, indicating comparable efficacy across active treatments.

Table 87: SUCRA – mean change from baseline in AE-QoL score

Treatment	SUCRA
Donidalorsen Q4W	██████
Berotralstat	██████
Donidalorsen Q8W	██████
Lanadelumab Q2W	██████
Lanadelumab Q4W	██████
Placebo	██████

Abbreviations: AE-QoL – Angioedema quality of life questionnaire; HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks; SUCRA – Surface under the cumulative ranking curve.

Figure 17: Posterior rank plot – mean change from baseline in AE-QoL score



Abbreviations: AE-QoL – Angioedema quality of life questionnaire; HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

R-hat values

The R-hat values presented in Table 88 are all [REDACTED] to two decimal places, indicating that the MCMC chains in the NMA have converged successfully and the resulting treatment effect estimates are robust.

Table 88: Treatment effect R-hat value per treatment versus donidalorsen Q4W – mean change from baseline in AE-QoL score

Treatment	R-hat
Donidalorsen Q8W	[REDACTED]
Lanadelumab Q2W	[REDACTED]
Lanadelumab Q4W	[REDACTED]
Placebo	[REDACTED]

Abbreviations: AE-QoL – Angioedema quality of life questionnaire; HAE – Hereditary angioedema; Q2W – Once every 2 weeks; Q4W – Once every 4 weeks; Q8W – Once every 8 weeks.

Overall, the performance metrics indicate that the NMA model fits the observed data for the outcome of mean change from baseline in AE-QoL score considerably well

and provides robust estimates, aligning with the outcome for mean number of HAE attacks per month. The goodness-of-fit demonstrated the NMA model fits the observed data well, the posterior rank plot showed donidalorsen Q4W to have numerically superior efficacy than both lanadelumab regimens, the R-hat values confirmed MCMC chain convergence ensuring reliability of the treatment effects. However, tau indicated that a FE model would be most appropriate, but to remain consistent with the modelling approach applied across all outcomes the RE model approach was maintained.

Appendix Question A22

[REDACTED]

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Appendix Question A23

Mean number of moderate or severe HAE attacks per month

Median rate ratios for the mean number of moderate or severe HAE attacks per month and 95% CrIs from the steady state NMA are shown in Table 89 and Figure 18. No statistically significant differences were observed for the mean number of moderate or severe HAE attacks per month, as informed by the mean rate ratios, in treatment with donidalorsen Q4W compared to donidalorsen Q8W, lanadelumab Q2W or lanadelumab Q4W. Treatment with donidalorsen Q4W was associated with [REDACTED]. The results for donidalorsen Q4W showed a [REDACTED] [REDACTED] regimens, however, as stated above, this difference was not statistically significant.

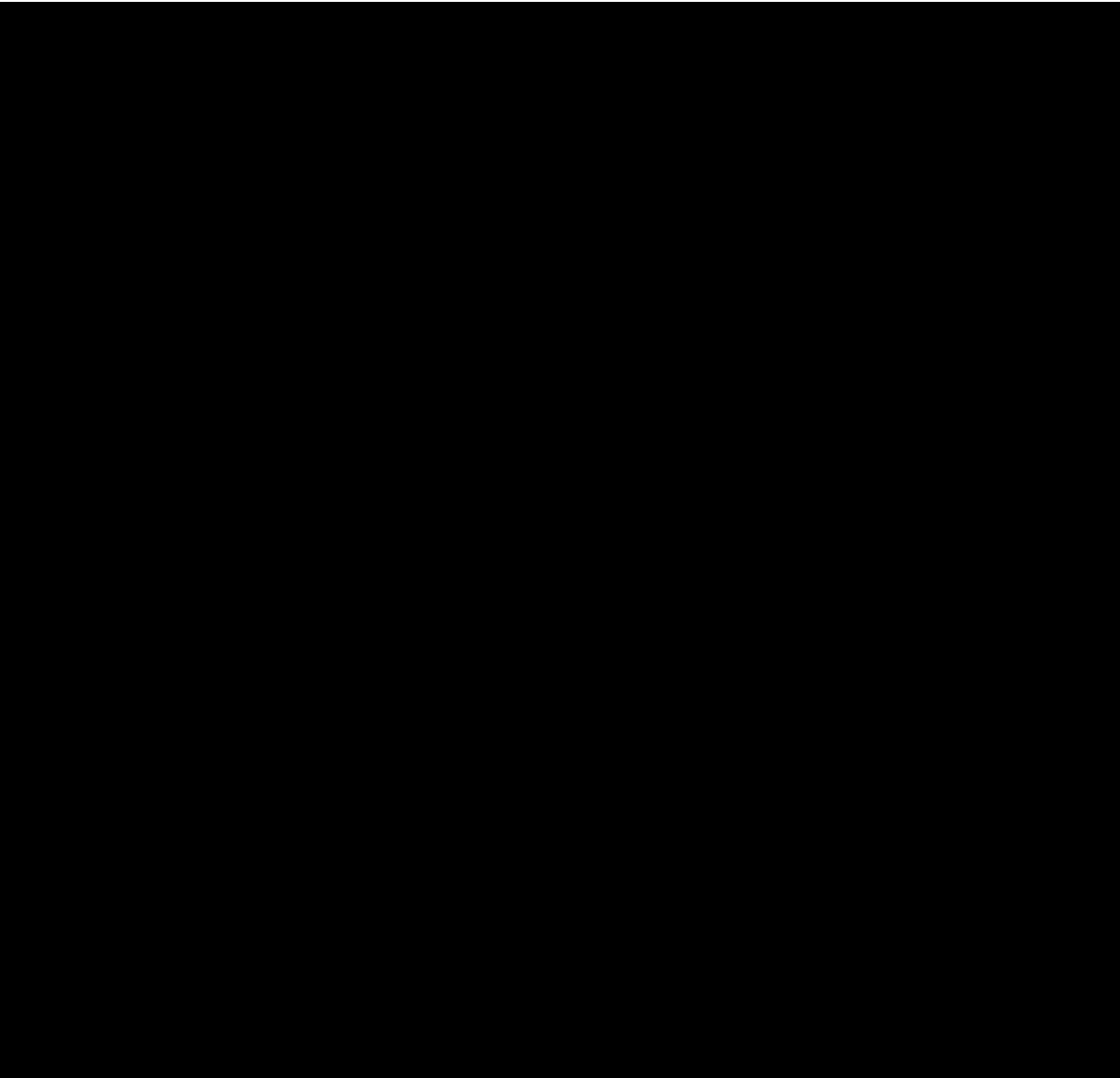
The wide and overlapping CrIs observed in the forest plot presented in Figure 18, demonstrate that there is no statistically significant difference between the median rate ratios for donidalorsen Q4W and comparators.

Table 89: Median rate ratios and 95% CrIs for SS mean number of moderate or severe HAE attacks per month

Treatment	Median rate ratio (95% CrI)
Donidalorsen_Q8W	[REDACTED]
Lanadelumab_Q2W	[REDACTED]
Lanadelumab_Q4W	[REDACTED]
Placebo	[REDACTED]

Abbreviations: CrI – Credible interval; HAE – Hereditary angioedema; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks; SS – Steady state.

Figure 18: Forest plot of median rate ratios and 95% Crls – endpoint: SS mean number of moderate or severe HAE attacks per month treatment effects



Abbreviations: Crls – credible intervals; HAE – Hereditary angioedema; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks; RE – Random effects; SS – Steady state.

Mean number of HAE attacks requiring on-demand medication

Median rate ratios for the mean number of HAE attacks requiring on-demand medication per month and 95% Crls from the steady state NMA are shown in Table 90 and Figure 19. No statistically significant differences were observed for the mean number of moderate or severe HAE attacks per month, as informed by the mean rate ratios, in treatment with donidalorsen Q4W compared to donidalorsen Q8W, lanadelumab Q2W or lanadelumab Q4W. Treatment with donidalorsen Q4W was associated with

[REDACTED]. The results for donidalorsen Q4W showed a [REDACTED] [REDACTED] regimens, however, as stated above, this difference was not statistically significant.

The wide and overlapping CrIs observed in the forest plot presented in Figure 18, demonstrate that there is no statistically significant difference between the median rate ratios of donidalorsen Q4W and LTP comparators.

A

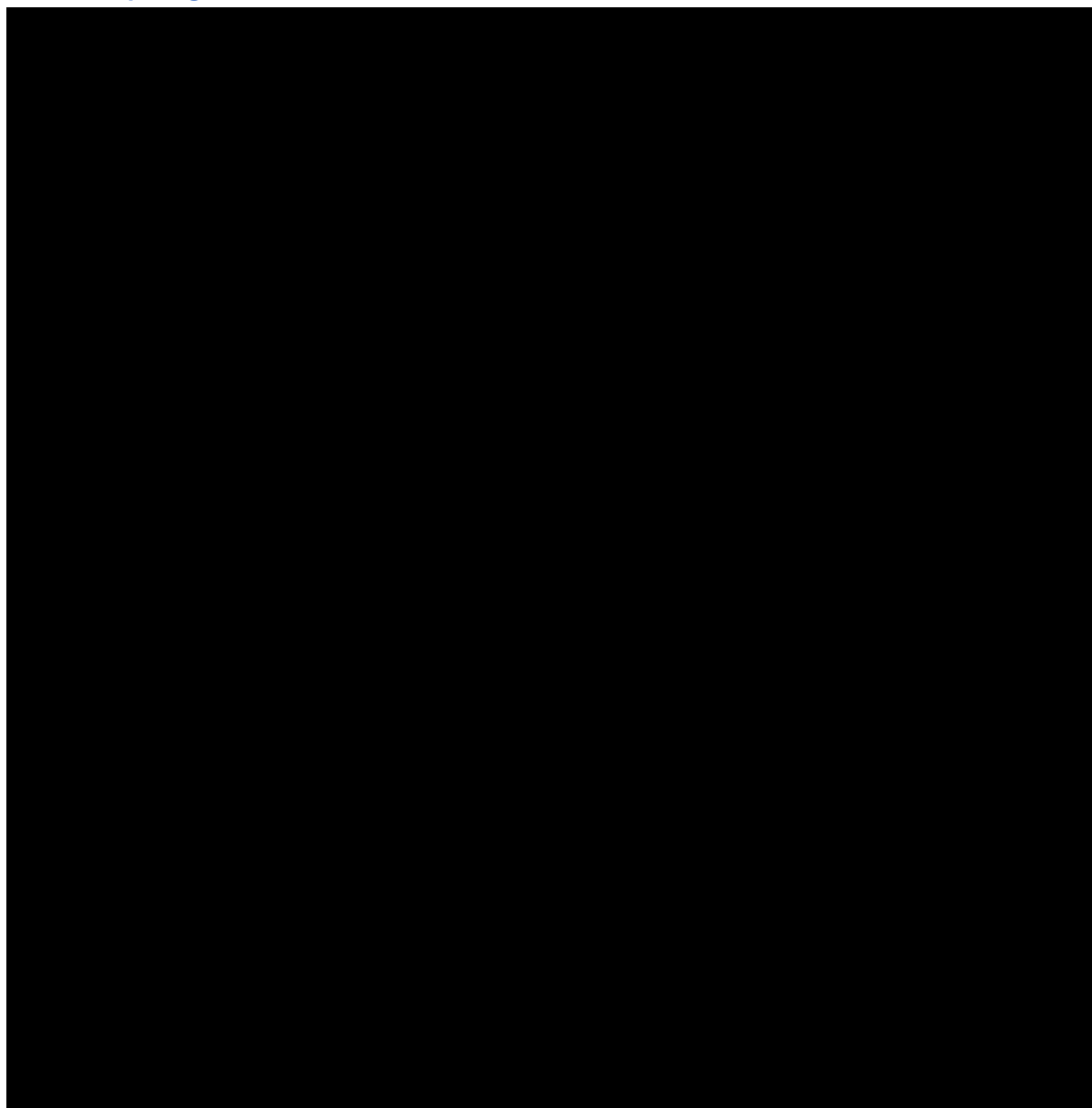
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Table 90: Median rate ratios and 95% CrIs for SS mean number of HAE attacks that require on-demand medication

Treatment	Median rate ratio (95% CrI)
Donidalorsen_Q8W	[REDACTED]
Lanadelumab_Q2W	[REDACTED]
Lanadelumab_Q4W	[REDACTED]
Placebo	[REDACTED]

*95% CrI does not include 1 and is therefore considered statistically significant
Abbreviations: CrI – Credible interval; HAE – Hereditary angioedema; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks; SS – Steady state.

Figure 19: Forest plot of median rate ratios and 95% Crls – endpoint: SS Mean number of HAE attacks requiring on-demand medication treatment effects



Abbreviations: Crls – credible intervals; HAE – Hereditary angioedema; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks; RE – Random effects; SS – Steady state.

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Single Technology Appraisal

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	Angela Metcalfe	
2. Name of organisation	HAE UK	
3. Job title or position	CEO	
4a. Brief description of the organisation (including who funds it). How many members does it have?	HAE UK is a patient advocacy and support group. There is the CEO and a part time executive officer and a board of 8 Trustees. We represent approximately 700 patients and carers with a diagnosis of HAE of all types	
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	Unrestricted grants in the financial year ended September 2024 (last audited accounts) to HAE UK BioCryst Pharmaceuticals £20,150	
4c. Do you have any direct or indirect links	No	

Patient organisation submission

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	By being the CEO of HAE and advocating for and supporting patients

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Hereditary Angioedema produces intense and excruciatingly painful swellings in the abdomen, peripherals (hands and feet), in the face causing temporary blindness when eyelids swell, and can cause death by asphyxiation if swelling occurs in the laryngeal area. Attacks are brought on by a number of factors including anxiety (good and bad), trauma – anything from cutting a finger to being in an accident – and also other illness such as the common cold. Attacks are highly unpredictable and last from anything between 24 and 72 hours, with a post recovery time of 48 to 72 hours. Carers also live with the anxiety of the unpredictability of attacks and in many cases are trained to administer medications which the patient would not be able to do. HOWEVER no two patients are the same with each individual experiencing difference frequency and severity of attacks. These attacks are debilitating often leading to prolonged after effects post attack meaning 'normal' life takes days to resume and QoL is severely affected

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The current restrictions dictated by commissioning guidance mean some patients are missing out on receiving medication/treatment that would achieve an overall zero attack rate. NOTE breakthrough attacks can happen at any time even on Long Term Prophylaxis. Care is delivered through specialist Immunology Service which has a severe shortage of both consultants and specialist nurses. This leads to appointments not being as frequent as they should be. Additionally, GPs often don't know anything about HAE so diagnosis can go round and round in circles, sometimes for 10 years or more, before a patient is correctly diagnosed by an immunologist.
8. Is there an unmet need for patients with this condition?	100% yes. Not all patients can access the most appropriate treatment for their own HAE due to commissioning restrictions. Every single patient is different and experiences frequency, severity and location of attack different to any other patient. There is an extreme unmet need for psychological intervention which would help patients to hopefully manage anxiety (both good and bad) which therefore reduces potential attack rate. BUT if a patient cannot access a medication just because of commissioning guidance this can increase anxiety and therefore attack rate.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	It is a sub cutaneous injection which is therefore much less invasive than intravenous injection. Patients can be trained to self administer, as can a family member or carer or friend, thereby negating the patient having to attend hospital/A&E for treatment. Potentially, once a patient is past the initial introduction period of this treatment, it also should mean them only have to have an injection once a month, instead of potentially two IV treatments a week. That greatly impacts on anxiety and QoL as it is far less invasive to be treated monthly rather than twice weekly.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	None – unless the commissioning guidance is restrictive

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No. Every single patient is different so each patient needs to be assessed and treatment given according to their HAE. The variety of treatments is required – due to current clinical commissioning guidance – to thereby suit each individual. There are different guidances in the devolved nations.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• This gives patients another choice of medications to control HAE • Every patient is different so the choice of medications is needed in order to effectively treat HAE • LTP therapy is the preferred mechanism of treatment for many, but not for all. Breakthrough attacks will still happen for which other on-demand/rescue therapies will be needed but if the efficacy of Donidalorsen is that it achieves a zero attack rate under normalised QoL then it is of high benefit to those patients for whom it works • This particular treatment targets the pre-kalikrein pathway and therefore inhibits the bradykinin pathway that causes attacks. A once a month injection of LTP to 'clear' this pathway can only be beneficial in many patients.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Patient organisation submission

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our [privacy notice](#).

Single Technology Appraisal

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	██████████ (completing sections 1-5c), ██████████ (completing sections 6 onwards)
2. Name of organisation	British Society for Immunology Clinical Immunology Professional Network
3. Job title or position	██████████ – Programme Manager, ██████████ – Consultant Clinical Immunologist
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes – ██████████ A specialist in the treatment of people with this condition? Yes – ██████████
5a. Brief description of the organisation (including who funds it).	The BSI-CIPN is a professional network hosted within the British Society for Immunology, a learned society. The BSI-CIPN is an integrated and impactful professional network for individuals working within clinical immunology. The network includes over 200 professionals working in the clinical immunology field, including clinical immunologists, allergists, healthcare scientists, pharmacists and specialist nurses. The BSI-CIPN is funded through the British Society for Immunology, which has a range of income streams which can be viewed in our 2024 annual report here. The BSI-CIPN also has some ringfenced funding as a result of a merger with the UK Primary Immunodeficiency Network in 2022.

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	No to positions and other interests. All funding detailed below is between 30/10/2024 and 30/10/2025 ----- Otsuka Invoice date: 02 September 2025 Purpose: Sponsorship of BSI-CIPN Conference Amount (gross): £50,400 (not yet paid) Invoice date: 17 Oct 2025 Purpose: Registration for BSI-CIPN Conference Amount (gross): £630 (not yet paid) ----- CSL Behring Invoice date: 24 July 2025 Purpose: Funding for BSI-CIPN Nursing Excellence Programme 2025/26 Amount (gross): £40,081 Invoice date: 22 July 2025 Purpose: Platinum sponsorship of BSI-CIPN Conference Amount (gross): £50,400 Total CSL Behring: £90,481 ----- ----- Takeda UK

Invoice date: 5 November 2024
Purpose: Sponsorship of BSI-CIPN Conference
Amount (gross): £59,394

Total Takeda: £59,394

BioCryst

Invoice date: 30 September 2025
Purpose: Grant, BSI-CIPN Clinical Immunology Workforce Policy report
Amount (gross): £6000 (not yet paid)

Invoice date: 03 September 2025
Purpose: Webinar
Amount (gross): £4800

Invoice date: 03 September 2025
Purpose: Webinar
Amount (gross): £4800

Invoice date: 04 December 2024
Purpose: Webinar
Amount (gross): £1800

Total BioCryst: £11,400

Pharming

Invoice date: 11 October 2024

	Purpose: Sponsorship of BSI-CIPN Conference Amount (gross): £35,000 Invoice date: 27 August 2025 Purpose: Sponsorship of BSI-CIPN Conference Amount (gross): £42,000 <i>Total Pharming: £77,500</i> -----
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent recurrent swelling (angioedema) attacks in hereditary angioedema. Episodes of swelling occur in hereditary angioedema, and can be life threatening if affecting the airway, or result in morbidity and functional disability if affecting limbs or abdomen.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction in frequency and severity of attacks. There is no consensus agreement as to what the minimum amount of frequency and/or severity reduction would be considered clinically significant. The previous NICE assessment on berotralstat used a 50% reduction in attack frequency (without accounting for severity) to allow continuation of treatment. A lower reduction in attack frequency can be clinically significant as well.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Although there are now more treatments available for patients with hereditary angioedema, there remains unmet needs in these patients. Patients with attack frequencies below the NICE approved thresholds for other treatments do not have access to modern licensed prophylactic therapies for HAE and only have access to treatments like androgens (not licensed for any indication in the UK, with potential long-term side effects) or tranexamic acid (ineffective in most patients) for prophylaxis. Additionally, children/adolescents often have lower attack frequencies compared to adults and are less likely to be eligible for modern licensed therapies, but where the disease can still have significant impact, affecting school attendance and educational attainment.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Treatment consists of on-demand therapy for acute attacks, and prophylaxis for prevention of attacks. On-demand therapy options include icatibant and C1 inhibitor.

	Modern licensed long-term prophylaxis options include C1 inhibitor, lanadelumab, berotralstat, and garadacimab. Criteria for access to treatment is determined by NICE TAs or NHSE commissioning policies. Other options include androgens (mostly danazol) and tranexamic acid, which are unlicensed or of uncertain efficacy.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Criteria for access to treatment for the modern licensed therapies are determined by NICE TAs and NHSE commissioning policies. NHSE has an algorithm which summaries most of these therapies. The most recent published international guidelines are the 2021 WAO/EAACI guidelines for HAE. These guidelines recommend aiming for complete control of disease and normalising patient lives. The guidelines do not use an attack frequency criterion for determining when LTP should be used, and so NHSE commissioning policy and NICE TA supersede the guidelines in relation to when LTP can be offered.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Access to medicines is determined by NHSE commissioning policies and NICE TAs, resulting in a defined population of patients currently eligible for these LTP medications. Care of patients with HAE rests with specialised immunology/allergy centres commissioned by NHSE.
9c. What impact would the technology have on the current pathway of care?	This will depend on what access criteria will end up being for the new technology. There are no approved modern licensed therapies available to HAE patient with fewer than 2 attacks per month – approval for usage in this group of patients would help address an unmet need. If only approved for 2 or more attacks per month, this technology will offer an additional option for patients where the other currently available technologies are either ineffective or unsuitable. The technology also potentially allows a longer licensed dosing interval, which could improve the burden of treatment for HAE patients.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will be used for long-term prophylaxis, so will be used in the same way as the other long-term prophylaxis therapies. Access criteria will determine which patients will be eligible to have treatment with this technology.

10a. How does healthcare resource use differ between the technology and current care?	This will depend on the access criteria for the technology. For patients with 2 or more attacks per month, the technology will offer patients another therapeutic option to the available treatments. For patients with fewer than 2 attacks per month, there are no other approved modern licensed therapies available. For this group of patients, if the technology improves disease control, this will result in reduced need for on-demand therapy and potentially fewer visits to the emergency department.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialised immunology services.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific investment is required to introduce the technology.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	This will depend on the access criteria for the technology. For patients with fewer than 2 attacks per month, there are no approved modern licensed therapies. For this group of patients, the technology would be expected to provide more clinically meaningful benefits compared with current available options, particularly if current available options are ineffective or not tolerated.
11a. Do you expect the technology to increase length of life more than current care?	The technology is unlikely to significantly increase length of life more than current care.
11b. Do you expect the technology to increase health-related quality of life more than current care?	This will depend on the access criteria for the technology. For patients with fewer than 2 attacks per month, there are no available modern licensed therapies at all. For this group of patients, the technology is likely to result in the most increase in HRQoL. For patients who are currently eligible for modern licensed prophylactic therapies, the potential increased dosing interval could improve health-related quality of life by reducing treatment burden.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would not be expected to be more or less effective in any subgroups of people with HAE.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	This will depend on what medication the patient is currently using and its effectiveness. If the patient is using IV injections or frequent injectable on-demand therapies, then the technology will be easier for patients compared to current care.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This will most likely depend on access criteria, similar to the other medications that have NICE TAs or NHSE commissioning policies. Additional testing is unlikely to be necessary.
15. Do you consider that the use of the technology will result in any	N/A

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This will depend on the access criteria for the technology. For patients with fewer than 2 attacks per month, there are no approved effective licensed prophylactic therapies at all in England. For this group of patients, the technology is likely to result in the most increase in HRQoL as there is no approved effective licensed LTP options available.
16a. Is the technology a 'step-change' in the management of the condition?	The technology is a highly effective LTP agent given as a subcutaneous injection every 4-8 weeks. There are two other LTP agents given subcutaneously, with licensed intervals between 2 weeks to 1 month. The technology would be considered as a slight improvement in terms of administration compared to current therapies in the current management (if as effective for an individual at an 8-week interval), rather than a major step-change. It should be noted that the approved licensed LTP agents are restricted to patients with at least 2 or more attacks per month, so this treatment is a potential "step-change" in management for patients who do not meet the criteria for access to the approved licensed LTP agents, who have a significant burden of disease.

	The technology utilises a different therapeutic approach (LICA) compared to existing technologies. This is potentially useful where current technologies are ineffective in an individual patient.
16b. Does the use of the technology address any particular unmet need of the patient population?	This will depend on the access criteria for the technology. For patients with fewer than 2 attacks per month, there are no commissioned effective licensed therapies. For this group of patients, there is a significant unmet need.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Treatment side effects from the trial data suggest that it was generally well-tolerated, so should not have significant impact on management of the condition.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Patients in the clinical trials all have hereditary angioedema, and the technology was used for prevention of angioedema attacks. The technology would be used for prevention of angioedema attacks in UK practice as well, although the access criteria will determine which patients would be eligible to be treated with the technology.
18a. If not, how could the results be extrapolated to the UK setting?	N/A

18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Attack frequency, use of rescue medication, attack severity, quality of life, safety. These were measured in the trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	We are not aware of any.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	We are not aware of any.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance (TA) 606 and TA738?	There is published data on the comparator treatments since the publication of NICE TA606 and TA738, showing the real-world experience with those therapies.
21. How do data on real-world experience compare with the trial data?	There is no published real-world experience of this technology in the UK.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Children and young people often have fewer HAE attacks compared to adults, as attack frequency often increases with age. Access criteria based purely on attack frequency may disadvantage children and young people, who can be significantly affected despite having attack frequencies below current access criteria.
22b. Consider whether these issues are different from issues with current care and why.	The issues relating to children and young people also affect current care.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• There remains an unmet need for long-term prophylaxis for people with HAE (although improved compared to before), as current access criteria limit the use of effective licensed therapies, resulting in a group of patients that would benefit from LTP, but are unable to access it. • Depending on what access criteria is approved for the technology, this could meet some of the unmet need. • Children and young people are a particular group of patients with more limited access to treatment options. • The new technology also utilises a different therapeutic approach and will have a role in patients who do not respond to current approved technologies. •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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- Your response should not be longer than 13 pages.

About you

1. Your name	Dr [REDACTED]
2. Name of organisation	The Royal College of Pathologists
3. Job title or position	Consultant Immunologist
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation with charitable status concerned with all matters relating to the science and practice of pathology. It is a body of its Fellows, Diplomates, Affiliates and trainees, supported by the staff who are based at the College's London offices. The College is a charity with over 13,000 members worldwide. The majority of members are doctors and scientists working in hospitals and universities in the UK. The College oversees the training of pathologists and scientists working in 17 different specialties, which include cellular pathology, haematology, clinical biochemistry and medical microbiology.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	no
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent recurrent swelling (angioedema) attacks in hereditary angioedema. Episodes of swelling occur in hereditary angioedema, and can be life threatening if affecting the airway, or result in morbidity and functional disability if affecting limbs or abdomen.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction in frequency and severity of attacks. There is no consensus agreement as to what the minimum amount of frequency and/or severity reduction would be considered clinically significant. The previous NICE assessment on berotralstat used a 50% reduction in attack frequency (without accounting for severity) to allow continuation of treatment. A lower reduction in attack frequency can be clinically significant as well.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Although there are now more treatments available for patients with hereditary angioedema, there remains unmet needs in these patients. Patients with attack frequencies below the NICE approved thresholds for other treatments do not have access to modern licensed prophylactic therapies for HAE and only have access to treatments like androgens (not licensed for any indication in the UK, with potential long-term side effects) or tranexamic acid (ineffective in most patients) for prophylaxis. Additionally, children/adolescents often have lower attack frequencies compared to adults and are less likely to be eligible for modern licensed therapies, but where the disease can still have significant impact, affecting school attendance and educational attainment.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Treatment consists of on-demand therapy for acute attacks, and prophylaxis for prevention of attacks. On-demand therapy options include icatibant and C1 inhibitor. Modern licensed long-term prophylaxis options include C1 inhibitor, lanadelumab, berotralstat, and garadacimab. Criteria for access to treatment is determined by NICE TAs or NHSE commissioning policies. Other options include androgens (mostly danazol) and tranexamic acid, which are unlicensed or of uncertain efficacy.

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Criteria for access to treatment for the modern licensed therapies are determined by NICE TAs and NHSE commissioning policies. NHSE has an algorithm which summaries most of these therapies. The most recent published international guidelines are the 2021 WAO/EAACI guidelines for HAE. These guidelines recommend aiming for complete control of disease and normalising patient lives. The guidelines do not use an attack frequency criterion for determining when LTP should be used, and so NHSE commissioning policy and NICE TA supersede the guidelines in relation to when LTP can be offered.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Access to medicines is determined by NHSE commissioning policies and NICE TAs, resulting in a defined population of patients currently eligible for these LTP medications. Care of patients with HAE rests with specialised immunology/allergy centres commissioned by NHSE.
9c. What impact would the technology have on the current pathway of care?	This will depend on what access criteria will end up being for the new technology. There are no approved modern licensed therapies available to HAE patient with fewer than 2 attacks per month – approval for usage in this group of patients would help address an unmet need. If only approved for 2 or more attacks per month, this technology will offer an additional option for patients where the other currently available technologies are either ineffective or unsuitable. The technology also potentially allows a longer licensed dosing interval, which could improve the burden of treatment for HAE patients.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will be used for long-term prophylaxis, so will be used in the same way as the other long-term prophylaxis therapies. Access criteria will determine which patients will be eligible to have treatment with this technology.
10a. How does healthcare resource use differ between the technology and current care?	This will depend on the access criteria for the technology. For patients with 2 or more attacks per month, the technology will offer patients another therapeutic option to the available treatments. For patients with fewer than 2 attacks per month, there are no other approved modern licensed therapies available. For this group of patients, if the technology improves disease control, this will result in reduced need for on-demand therapy and potentially fewer visits to the emergency department.
10b. In what clinical setting should the technology be	Specialised immunology services.

used? (For example, primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific investment is required to introduce the technology.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	This will depend on the access criteria for the technology. For patients with fewer than 2 attacks per month, there are no approved modern licensed therapies. For this group of patients, the technology would be expected to provide more clinically meaningful benefits compared with current available options, particularly if current available options are ineffective or not tolerated.
11a. Do you expect the technology to increase length of life more than current care?	The technology is unlikely to significantly increase length of life more than current care.
11b. Do you expect the technology to increase health-related quality of life more than current care?	This will depend on the access criteria for the technology. For patients with fewer than 2 attacks per month, there are no available modern licensed therapies at all. For this group of patients, the technology is likely to result in the most increase in HRQoL. For patients who are currently eligible for modern licensed prophylactic therapies, the potential increased dosing interval could improve health-related quality of life by reducing treatment burden.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would not be expected to be more or less effective in any subgroups of people with HAE.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals	This will depend on what medication the patient is currently using and its effectiveness. If the patient is using IV injections or frequent injectable on-demand therapies, then the technology will be easier for patients compared to current care.

than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This will most likely depend on access criteria, similar to the other medications that have NICE TAs or NHSE commissioning policies. Additional testing is unlikely to be necessary.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	N/A
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This will depend on the access criteria for the technology. For patients with fewer than 2 attacks per month, there are no approved effective licensed prophylactic therapies at all in England. For this group of patients, the technology is likely to result in the most increase in HRQoL as there is no approved effective licensed LTP options available.

16a. Is the technology a 'step-change' in the management of the condition?	The technology is a highly effective LTP agent given as a subcutaneous injection every 4-8 weeks. There are two other LTP agents given subcutaneously, with licensed intervals between 2 weeks to 1 month. The technology would be considered as a slight improvement in terms of administration compared to current therapies in the current management (if as effective for an individual at an 8-week interval), rather than a major step-change. It should be noted that the approved licensed LTP agents are restricted to patients with at least 2 or more attacks per month, so this treatment is a potential "step-change" in management for patients who do not meet the criteria for access to the approved licensed LTP agents, who have a significant burden of disease. The technology utilises a different therapeutic approach (LICA) compared to existing technologies. This is potentially useful where current technologies are ineffective in an individual patient.
16b. Does the use of the technology address any particular unmet need of the patient population?	This will depend on the access criteria for the technology. For patients with fewer than 2 attacks per month, there are no commissioned effective licensed therapies. For this group of patients, there is a significant unmet need.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Treatment side effects from the trial data suggest that it was generally well-tolerated, so should not have significant impact on management of the condition.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Patients in the clinical trials all have hereditary angioedema, and the technology was used for prevention of angioedema attacks. The technology would be used for prevention of angioedema attacks in UK practice as well, although the access criteria will determine which patients would be eligible to be treated with the technology.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important	Attack frequency, use of rescue medication, attack severity, quality of life, safety. These were measured in the trials.

outcomes, and were they measured in the trials?	
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	We are not aware of any.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	We are not aware of any.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance (TA) 606 and TA738?	There is published data on the comparator treatments since the publication of NICE TA606 and TA738, showing the real-world experience with those therapies.
21. How do data on real-world experience compare with the trial data?	There is no published real-world experience of this technology in the UK.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Children and young people often have fewer HAE attacks compared to adults, as attack frequency often increases with age. Access criteria based purely on attack frequency may disadvantage children and young people, who can be significantly affected despite having attack frequencies below current access criteria.
22b. Consider whether these issues are different from issues with current care and why.	The issues relating to children and young people also affect current care.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• There remains an unmet need for long-term prophylaxis for people with HAE (although improved compared to before), as current access criteria limit the use of effective licensed therapies, resulting in a group of patients that would benefit from LTP, but are unable to access it. • Depending on what access criteria is approved for the technology, this could meet some of the unmet need. • Children and young people are a particular group of patients with more limited access to treatment options. • The new technology also utilises a different therapeutic approach and will have a role in patients who do not respond to current approved technologies. •

Thank you for your time.

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Single Technology Appraisal

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	Dr Matthew Buckland
2. Name of organisation	NHS England (NHSE) Clinical Reference Group (CRG) in Immunology and Allergy
3. Job title or position	Consultant Immunologist

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? No Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? No Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? Yes An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	CRG – NHSE
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes – there is an NHSE clinical pathway for the management of HAE including attack frequency and when prophylaxis is appropriate. There are also society guidelines e.g. EAACI and WAO
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway by NHSE was achieved by consensus and based on evidence and commissioning criteria and is widely accepted as appropriate by professionals across the NHS. There are instances where attack severity may be as important as frequency and this is not accounted for in the current pathway.
8. What impact would the technology have on the current pathway of care?	This would likely be an additional option for non-responsive patients or may add a further option at a lower attack threshold depending on how the medication is positioned by the company.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	Not currently available as this is a new medicine and no EAMS. It would add to existing therapies that are in use locally.
10. Will the technology be used (or is it already used) in the same way	This would add to current standard of care in the same care pathway(s)

as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	This is a subcutaneous therapy, so would have the same implications for healthcare resource as currently available long term prophylaxis options.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This should be secondary care in specialist centres (Immunology) only with a sufficient case load of patients with HAE.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment is likely to be needed other than pharmacy time in setting up homecare agreements.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Testing would not be used for starting or stopping – the rules are based on patient attack frequency diaries and use of acute rescue therapies.
11. What is the outcome of any evaluations or audits of the use of the technology?	This has been subject to Phase 1-3 clinical trials with favourable phase 3 outcomes (placebo controlled with investigator normalisation of attacks outcome).

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
12b. Consider whether these issues are different from issues with current care and why.	N/A

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Single Technology Appraisal

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Monday, 16 February 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

Clinical expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Part 1: Treating hereditary angioedema and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	ANTHONY DORR
2. Name of organisation	BARTS HEALTH NHS TRUST
3. Job title or position	CONSULTANT IMMUNOLOGIST
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with hereditary angioedema? ☒ A specialist in the clinical evidence base for hereditary angioedema or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for hereditary angioedema? (For example, to stop progression, to improve mobility, to	The main aim of treatment of hereditary angioedema (HAE) is normalisation of patients' lives and improving quality of life. What this entails is specific to each patient, however, most patients and physicians would agree that the most

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cure the condition, or prevent progression or disability)	significant part of this is freedom from attacks of angioedema,, and balancing this with both low treatment and psychological burdens associated with the condition. The current internationally accepted view is that this can only be achieved through the use of effective long-term prophylaxis (LTP).
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	The natural course of HAE is variable and some patients may have periods without attacks and periods where frequency and/or severity is worsened, which is largely unpredictable, although emotional and physical stresses, medication, and hormonal changes are known factors. A reduction in the frequency and/or severity of HAEs by around 50% would be a robust marker for a significant treatment response over a prolonged period to account for this potential variability. In addition, any sustained response perceived by patients who have been refractory to other treatments would also demonstrate clinical efficacy.
10. In your view, is there an unmet need for patients and healthcare professionals in hereditary angioedema?	Yes. At present, excluding paediatric patients who have far fewer treatment options, adolescent and adult patients have limited access to first-line options for HAE LTP compared to some other developed nations. Treatment is either in the form of daily oral medication or 2-4 weekly injections with variable responses for individual patients. Whilst the most recent medications are available in the UK, the thresholds for accessing these are based predominantly on attack frequency, which fails to capture the true impact of uncontrolled disease on patients' quality of life. The long-term commitment to these treatments also carries a significant treatment burden for patients. Whilst this landscape is changing, there remains a need for multiple effective LTP options with a low treatment burden.
11. How is hereditary angioedema currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Currently, hereditary angioedema management is guided by the NHSE HAE algorithm (https://www.england.nhs.uk/wp-content/uploads/2025/02/hereditary-and-acquired-angioedema-algorithms.pdf), which is essentially an amalgam of the current NICE commissioning and technology appraisals for berotralstat, lanadelumab and C1 esterase inhibitor. Notably, the most recent addition to the HAE LTP landscape in the UK, garadacimab, has not yet been incorporated, although is now commissioned (https://www.nice.org.uk/guidance/ta1101/resources/garadacimab-for-preventing-recurrent-attacks-of-hereditary-angioedema-in-people-12-years-and-

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What impact would the technology have on the current pathway of care?	over-pdf-2973530385039301). The current pathways are well-defined, but there is a widely held view amongst clinicians that these are too prescriptive and the current criteria for treatment disenfranchises certain patients with severe, albeit less frequent attacks, given that in England the minimum threshold for first line LTP is 2 HAE attacks per month. Donidalorsen was also studied in the OASISplus trial (Riedl <i>et al. J Allergy Clin Immunol Pract</i> . 2025 Sep;13(9):2381-2389.e3.), which was an open label trial where 65 patients were switched from existing LTP (berotralstat, lanadelumab, C1-INH) and outcomes including attack rate, quality of life, control test scores and participant preference were studied over 16 weeks. Results showed improved HAE attack rate and improved quality of life and control measures with a patient preference for donidalorsen for a variety of reasons. Although this study was likely subject to selection bias, it would indicate that a subset of patients poorly controlled on existing therapies would benefit from treatment with donidalorsen. Garadacimab was not available to patients at the time of this trial. In the current pathway, donidalorsen would appear offer a viable option for LTP-naïve patients, but also as an alternative to patients on existing LTP.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? - How does healthcare resource use differ between the technology and current care? - In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) - What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology in question will be used to prevent the emergence of HAE attacks similarly to current LTP options. The main way in which this will differ from current options is a reduction in treatment burden. The minimum dosing interval between injections for donidalorsen is 4-weekly, with the option to increase to 8-weekly for patients who are well-controlled as demonstrated in the OASIS-HAE trial (Riedl <i>et al. N Engl J Med</i> . 2024 Jul 4;391(1):21-31). This will be the longest dosing interval for any HAE LTP treatment and appears to be efficacious with a favourable side effect profile. The other novelty in this case, is the use of antisense RNA technology, which has not been used in HAE previously outside of clinical trials. Donidalorsen will be prescribed by specialist physicians in centres commissioned for the treatment of hereditary angioedema, where patients would

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	initially be trained and then self-administer at home with a homecare medicine delivery framework. Assuming the use of a pre-filled syringe/injector (as a standard in other modern LTPs), patients will require on-site training from clinical nurse specialists and then transferring to homecare, which will be an essential component in on-going treatment provision.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	I do not expect the technology to increase length of life more than current care and this would not be a normal aim of novel HAE LTP. Whilst there have been no controlled head-to-head clinical trials with current treatments (which is expected), donidalorsen was superior to placebo in a phase 3 double-blinded controlled trial. The reduction in time normalised angioedema attacks, moderate and severe attacks, use of rescue medication and AE-QoL and AECT scores, as well as a number of exploratory end-points demonstrated efficacy comparable to phase 3 trials of the current LTP offerings. This was broadly true for both 4-weekly and 8-weekly dosing intervals. If this is born out in real-world settings then this would improve quality of life for patients given the reduced treatment burden from reduced dosing intervals. Additionally, the OASISplus trial showed benefits in patients who were not previously fully controlled on berotralstat, lanadelumab and C1-INH as I have described above. Taken together, it is therefore feasible that donidalorsen would increase health-related quality of life more than current care at least in certain patients.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Efficacy would be expected to be comparable across populations with hereditary angioedema type 1 and type 2. Given baseline attack rates were 1-2 a month in both donidalorsen treatment groups in the OASIS-HAE trial this real-world population would be expected to derive similar benefit to the trial population. Additionally, patients with 1 attack a month would likely benefit, particularly as they have no current commissioned first line LTP treatments.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	Despite this being a first-drug-in-class with a novel mechanism of action in the sphere of HAE, I do not anticipate this would be easier or more difficult for

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current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	patients or healthcare professions versus current care. From my experience, mechanism of action does not appear to be a barrier to patients outside of blood products or gene therapy. The half-life of donidalorsen is approximately a month, which is longer than the next longest half-life seen in current LTP options (around 19 days for garadacimab), so may require forward planning for patients who plan to become pregnant, but this is not significantly different than with garadacimab.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As with other LTP treatments in HAE, this is likely to be based around the number of attacks a month. If ineffective, the treatment should be stopped, but formal stopping criteria are not necessary and should be based on clinical judgement.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	A generally reduced dosing interval of 4-8 weekly vs. current options would reduce treatment burden, which would be expected to improve quality of life and may not be captured.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	This is the first use of antisense RNA technology in the treatment of HAE and the first with the potential to increase dosing to 8-weekly in certain patients, reducing the associated treatment burden. In this way it represents a step-change and addresses the unmet need of the requirement to frequent treatment. Moreover, it allows treatment options in patients who may have failed other treatment modalities, which is an ever-present need, especially in patients who do not have access to all options due to their attack rate.
19. How do any side effects or adverse effects of the technology affect the management of the condition	The main adverse effects are headache and injection site reactions. The headaches are likely non-specific. The injection site reactions are expected for a

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and the patient's quality of life?	subcutaneous injection and consistent with results from other parenteral LTP trials in hereditary angioedema. In needle-phobic patients this may represent a challenge and negatively impact their perception of the treatment and subsequent engagement, which remains an issue with LTP in the form of C1 esterase inhibitor, lanadelumab and garadacimab. However, I would not anticipate this being an issue for the vast majority of patients who are used to injections and in the OASISplus study, the majority patients found donidalorsen more tolerable than other injectables (lanadelumab and C1-INH).
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The OASIS-HAE trial generally reflects UK practice in that patients with type 1 and type 2 hereditary angioedema who have 1-2 attacks a month should be considered for long-term prophylaxis, although only patients with at least 2 attacks per month would be eligible for current first line LTP options in England. The most important outcomes of trials would be the effect of the treatment on attack frequency, severity, use of rescue medication, attack free periods, quality of life and of course safety. These were all measured in the OASIS-HAE trial. [REDACTED] [REDACTED] [REDACTED] [REDACTED]
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA606, TA738, TA1101?	There are numerous clinical trials (open-label and paediatric) and real-world studies for lanadelumab since its NICE approval in 2019 demonstrating efficacy in the populations studied: Banerji <i>et al.</i> <i>Allergy</i>. 2022 Mar;77(3):979-990. Hahn <i>et al.</i> <i>J Drugs Dermatol</i>. 2020 Oct 1;19(10):978-983.

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Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

	laboni <i>et al. Allergy Asthma Clin Immunol.</i> 2021;17:78. Fain <i>et al. Allergy Asthma Clin Immunol.</i> 2022;18(1):30. Martinez-Saguer <i>et al. J Dtsch Dermatol Ges.</i> 2022;20:1127–9. Abuzakouk <i>et al. World Allergy Organ J.</i> 2022;15(7):100664. Dorr <i>et al. Allergy.</i> 2023 May;78(5):1369-1371. Maurer <i>et al. J Allergy Clin Immunol Pract.</i> 2024 Jan;12(1):201-211.e6. Buttgereit <i>et al. Front Immunol.</i> 2024 May 10;15:1405317. Magerl <i>et al. J Allergy Clin Immunol Pract.</i> 2025 Feb;13(2):378-387. Bernstein <i>et al. Adv Ther.</i> 2025 Jun 12. 6. Similarly, there are numerous open label and real-world studies for berotralstat: Srinivasan <i>et al. Front Immunol.</i> 2024 Jan 22;15:1339421. Kiani-Alikhan <i>et al. J Allergy Clin Immunol Pract.</i> 2024 Mar;12(3):733-743.e10. Riedl <i>et al. Ann Allergy Asthma Immunol.</i> 2024 Apr;132(4):505-511.e1 Farkas <i>et al. Ann Allergy Asthma Immunol.</i> 2025 Sep;135(3):311-319.e6. Elbashir <i>et al. Allergy.</i> 2025 Oct 14. There is also on-going garadacimab OLE: Reshef <i>et al. Allergy.</i> 2025 Feb;80(2):545-556.
23. How do data on real-world experience compare with the trial data?	I am not aware of any real-world donidalorsen data.
24. [EAG key issue 1] Is garadacimab a treatment that is commonly used in the UK? If not, do you expect it to be widely used in the future? Would it be used for ≥ 2 attacks per month and / or ≥ 8 attacks per month?	Garadacimab is not currently commonly used in the UK, but will be in the very near future. I expect it will be used mainly for patients with ≥ 2 attacks per month, but also a proportion of patients with ≥ 8 attacks per month who will likely switch from their existing prophylaxis, especially if this is 2-weekly lanadelumab or C1 twice-weekly esterase inhibitor concentrate partly due to favourable dosing but also likely favourable efficacy and cost.

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25. [EAG key issue 2] Is it appropriate to assume that donidalorsen has equal efficacy to berotralstat, lanadelumab, C1-INH and garadacimab?	Yes, the OASIS-HAE trial outcomes are broadly consistent with those for berotralstat, lanadelumab, C1-INH and garadacimab.
26. [EAG key issue 3] Is the use of androgens and tranexamic acid during the OASIS-HAE trial consistent with previous HAE trials? Is this a concern?	The use of danazol in the OASIS-HAE trial is not typical for HAE LTP trial. Washout/exclusionary periods were used in phase 3 trials for lanadelumab, berotralstat and garadacimab. However, the proportion of patients on danazol was very similar in placebo and the 4-weekly donidalorsen group and one would assume that a concurrent LTP would have masked differences between donidalorsen treatment and placebo groups. In view of this, I do not think this is a significant concern.
27. [EAG key issue 4] Is berotralstat subject to stopping rules in the UK? If so, what are they?	Yes. Berotralstat is supposed to be stopped if the number of attacks per month does not reduce by at least 50% after 3 months, although how long after these 3 months is debatable and there would appear to be some physician discretion in real-world practice.
28. [EAG secondary issue 3] Are the company's extrapolations of long-term HAE attack rates appropriate?	Extrapolation of the trial data using average attack rate from week 5 to 25 seems plausible. This excludes baseline results, incorporates attack rate variability, and does not rely on a single time point as would be the case for a last observation carried forward approach. The extrapolation of long-term HAE rates is therefore appropriate.
29. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	This treatment has not been studied in pregnant or breast feeding individuals or those at extremes of age, and these treatments are not recommended in the former group. Self-administration may be challenging patients with conditions that affect their manual dexterity or sight, consistent with other injectable therapies. In these cases peer/carer or homecare support has been used to facilitate treatment in the past. I therefore do not think this treatment will be prohibitively exclusionary or adversely affect groups protected by equality legislation.

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belief, sex, and sexual orientation or people with any other shared characteristics.

Please state if you think this evaluation could

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Clinical expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The overarching goal of hereditary angioedema (HAE) treatment is achieving normalisation of patients' lives with minimal treatment and psychological burden, which is currently only possible through effective long-term prophylaxis (LTP).

Access to first-line LTP in England remains limited and overly dependent on attack frequency thresholds, leaving some significantly affected patients without suitable options, particularly if patients have failed an LTP treatment.

Donidalorsen offers a novel and meaningful advance by reducing treatment burden through 4- to 8-weekly dosing with efficacy in trials comparable to existing LTPs and expected benefits for patients with 1–2 attacks per month.

Its safety profile is consistent with other injectable therapies, with headache and injection-site reactions as the main adverse effects, and it should be delivered via specialist centres with homecare support.

Trial outcomes align with UK practice, and while no controlled real-world comparator data exist, donidalorsen appears to address an unmet need in those who have failed other treatments and provides an additional option combined with the potential for reduced dosing.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Clinical expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

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Single Technology Appraisal

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Monday, 16 February 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

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Part 1: Treating hereditary angioedema and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Matthew Buckland
2. Name of organisation	NHS England Immunology and Allergy CRG
3. Job title or position	Consultant Immunologist/Clinical Representative CRG Member
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with hereditary angioedema? ☐ A specialist in the clinical evidence base for hereditary angioedema or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for hereditary angioedema?	Acute therapy is life saving for laryngeal oedema or bowel obstruction with abdominal angioedema and for peripheral swellings improves quality of life and function. Prophylactic therapy aims to reduce or eliminate attacks (in number

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(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	and severity) to allow the individual to lead a normal life and avoid the need for acute attack therapy.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A reduction in attack frequency or severity by 50% or more for a prophylactic therapy. For an acute therapy a reduction in attack duration and severity compared to placebo.
10. In your view, is there an unmet need for patients and healthcare professionals in hereditary angioedema?	There is an ongoing unmet need in HAE. There are now 3 routinely licensed novel prophylactic therapies, an oral prophylactic (Berotrlastat), and two monoclonal antibody based treatments (Lanadelumab and Garadacimab). The former has lower efficacy and limited by side effect profile and the latter are effective in up to 70% of patients leaving a significant group without effective prophylaxis. C1 esterase inhibitor is licensed and commissioned for prophylaxis but has a high treatment burden and cost.
11. How is hereditary angioedema currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would the technology have on the current pathway of care?	The NHS CRG in Immunology and Allergy have created a summary algorithm for the treatment of HAE including both on demand acute therapy and prophylaxis (https://www.england.nhs.uk/wp-content/uploads/2025/02/hereditary-and-acquired-angioedema-algorithms.pdf). The is based on national and international consensus and the current available licensed therapies and their specific licensed indications. The care pathway is therefore well defined as above within the framework of currently licensed therapies. An additional oral option for acute therapy is currently available as an EAMS prior to NICE consideration. There is little difference of opinion between healthcare professionals as to the best treatment for HAE as this remains evidence based. Where there is variation in consensus this relates to whether no attacks (as per the EAACI/WAO guidance) is an appropriate target for long term prophylaxis as opposed to leaving people with a lower ongoing attack frequency. The technology under consideration would add an option for patients who are intolerant of or the 30% for each medicine who are not responsive to the therapy available and as a new option for initial prophylaxis. For Lanadelumab the

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	threshold for treatment is higher (although of lower efficacy) than Garadacimab and so many patients cannot access this treatment as 2 or more attacks per week are required, as opposed to two or more attacks per month for Berostralstat and Garadacimab, which is a more reasonable threshold. The current era of targeted prophylactic therapies is relatively new, with less than a decade of routine use. The age of availability has been extended down to 2 years and the antibody based therapies as in other therapeutic areas can develop inhibitors over time as although fully humanised, they can form non-native immune complexes or have binding regions, alternative glycosylation all of which can result in inhibitor formation and loss of efficacy. With so few medicines available that may result in complete loss of options for some patients and with extended use we are seeing more treatment failures. Over a whole lifetime (2yrs and up whenever needed) the probability of treatment failure for an individual is high and alternatives are needed to ensure lifelong therapeutic options. Whilst C1 esterase inhibitor remains a prophylactic option for patients with frequent attacks the burden of therapy (at least twice a week subcutaneous or intravenous) and cost of therapy is high and with very low patient and carer or physician acceptability. The addition of Donidalorsen would provide an attractive primary option for therapy as some may be dosed only 8QW and an alternative for patients ineligible, intolerant to or who have failed other HAE prophylaxis. For patients on the 4 weekly dosing interval it compares favourably with e.g. Gardacimab (noting that approximately 50% of Lanadelumab patients require fortnightly injections) and since data is available for safe continuation at 8 weeks for some patients with Donidalorsen this would be a significant reduction in treatment burden for the patient, homecare costs and ancillaries and presumably cost of the medicine for the NHS. Given the data from the 4 year phase 2 open label extension trial, it is likely that up to 30% of patients initiated on Donidalorsen may have meaningful (83%) reduction in attack frequency and approximately 70% could be expected to have no attacks for a year (on Q4W and Q8W dosing) which would reduce healthcare

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	associated acute costs, acute therapy costs, reduction in time lost to education, carer support and the workplace.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology would “slot in” to the existing framework of patient care with initiation usually being hospital based for the first dose of therapy and homecare delivery thereafter. Monitoring would be per the established clinical schedule with no modification likely. The healthcare resource would not differ other than for patients who have no current options their healthcare utilisation (acute and outpatients and for acute therapies) would be expected to drop. For patients needing i.v. C1 esterase prophylaxis due to no options the drop in need for home i.v. nursing twice a week, a high cost drug and twice weekly or more therapy is a significant reduction in care input. This is a specialist clinic only therapy. Training of patients needed for initiation of therapy, but as per current therapies. A homecare setup is needed with time for pharmacy/procurement to setup homecare delivery contracts to get the medicine to the patient (the use of homecare avoids NHS dispensing in hospital which incurs a VAT charge).
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Acute laryngeal attacks of HAE carry a mortality risk and all new therapeutic options that reduce attack frequency and severity have the potential to prolong life. As above – when prophylaxis may be life long and a need for managing treatment failure, over a patients lifetime the new technology availability may well extend life. The company provide healthcare QoL in patients previously treated with prophylaxis and this suggests increased HR-QoL in patients on the new technology (https://doi.org/10.1016/j.jaip.2025.06.018)

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Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This is a treatment for patients with bradykinin mediated angioedema. It is primarily targeted at patients with C1 esterase inhibitor deficiency, but not exclusively, since rarer forms of genetically evidenced HAE (e.g FXII gain of function) also have angioedema due to excess bradykinin and they would equally benefit. There would be no appropriate use of this medicine in the wider population and a confirmed diagnosis of HAE would be needed for prescribing.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	For patients on Q4W dosing this is equivalent to the recently approved Garadacimab for patients and healthcare providers and differs to Berostralstat as that is tablet (but with a daily treatment burden and food restriction). The burden of C1 esterase prophylaxis is much higher (2x weekly iv. Or subcut therapy). For patients on Q8W dosing the burden would be lower for healthcare and patients alike. The technology as an oligonucleotide therapy does not have any significant interactions and the only factors affecting acceptability would be that it is injectable (for those with needle phobia) or with hypersensitivity to the excipients. In general since acute therapy to date (apart from the unapproved by NICE Sebetralstat) is injectable, we find that needle phobic patients prefer prophylaxis with a low frequency/burden to acute and frequent injections for attacks when management of the attack and its complications makes it harder to initiate plans for the management of the needle phobia. No additional tests or monitoring are required.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Is envisaged that this would fit in the current framework for starting i.e. there must be an attack "burden" threshold, which is now established at 2 per month for other therapies and is a reasonable threshold above which QoL and patient safety is significantly impacted. Stopping is based on response and usually less than 50% reduction in attack frequency OR severity is required. The latter is important since 2 laryngeal attacks a month falling to one arguably has a greater impact in many patients than 2 non-dominant hand swellings.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The HR QoL benefits are particularly bad at capturing the impact on children >12 years of age currently and their carers. The impact is on schooling, peer relationships, sport, wider health, self esteem and on carers ability to live without

Clinical expert statement

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Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	fear of their child being unwell or being called away from home or the workplace to support acute attacks. The treatment regimen is low burden and therefore has potential to reduce this compared to standard of care.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	As per the narrative above, this is a novel form of inhibitor of the pathway that leads to HAE attacks. It moves away from the complications of oral inhibitors of kallikrein that have significant GI side effects and have interactions via the cytochrome metabolism pathways with other drugs. Monoclonal antibody options have variably high efficacy but are prone to inhibitor formation over time. An antisense oligonucleotide represents a novel mechanism and pathway that avoids the limitations of current therapy and meets the needs of those needing to start therapy for the first time as first line, who are intolerant of or who have failed to respond to current options or for whom inhibitors have formed and therefore treatment options have been lost.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Patients who have reactions due to intolerance or hypersensitivity to the excipients in the medication would not be able to continue. This would remove a new therapeutic option but not otherwise adversely affect future management assuming new treatments become available.
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? - Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials have been conducted in centres including the UK and in keeping with current clinical practice although the patients required only one attack in the 2 months preceding enrolment to be eligible, however the mean attack frequency was approximately 4 (3.6) in the period which would equate to 2 or more attacks per month as per standard current initiation frequency in the UK. The most important outcomes of OASIS-HAE the OASIS-Plus and related phase 2 extension studies is the reduction in attack frequency of 60-87% and the improvement in HR-QoL

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	In the extension studies there were no additional AEs that have not previously been described.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No – the trial data is comprehensive.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA606, TA738, TA1101?	No
23. How do data on real-world experience compare with the trial data?	The open label extension study gives the best realworld data and compares favourably to the placebo controlled trials.
24. [EAG key issue 1] Is garadacimab a treatment that is commonly used in the UK? If not, do you expect it to be widely used in the future? Would it be used for ≥ 2 attacks per month and / or ≥ 8 attacks per month?	Garadacimab has been approved in Q4 2025 for routine prophylaxis in the UK and availability through supply chain has been slow so currently it is not commonly used in the UK. Its use is likely to increase. It is used for 2 or more attacks per month as per the NICE guidance and Blueteq.
25. [EAG key issue 2] Is it appropriate to assume that donidalorsen has equal efficacy to berotralstat, lanadelumab, C1-INH and garadacimab?	Direct comparison of efficacy is difficult. If you compare the clinical trials it is more effective than Berotralstat and Landelumab Q2W and at Q4W dosing likely equivalent to Garadacimab and the data is less clear on comparison with Garadacimab at Q8W for the new technology vs Q4W for Garadacimab.
26. [EAG key issue 3] Is the use of androgens and tranexamic acid during the OASIS-HAE trial consistent with previous HAE trials? Is this a concern?	The use of Tranexamic acid and androgens usually excluded from other trials is more reflective of ongoing practice in some parts of the world or where patients have failed targeted therapies and have few/no other options. It is not cause for concern and gives data on tolerability and side effects for concomitant therapy use. Concomitant Danazol use was equal in placebo vs Q4W (5%) and slightly higher in the Q8W group (13%).
27. [EAG key issue 4] Is berotralstat subject to stopping rules in the UK? If so, what are they?	Berotralstat is required to be stopped at 3 months if there has not been a 50% reduction in attack frequency. This is a Blueteq/commissioning requirement.
28. [EAG secondary issue 3] Are the company's extrapolations of long-term HAE attack rates appropriate?	Data not supplied/available for comment.

Clinical expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

29. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.

Please state if you think this evaluation could

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

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[Find more general information about the Equality Act and equality issues here.](#)

The main consideration is if made available if this will be equal to all patients with hereditary angioedema.

Currently treatment algorithms favour Type 1 and Type 2 HAE (C1 esterase inhibitor deficiency). The incidence of these is about 1:50,000 of population. By contrast the rarer e.g. FXII, Plasminogen, AGPT, etc HAE at 1:500,000 or less of the population benefit equally from these therapies when bradykinin is the primary mediator, but despite genetic confirmation of diagnosis may be excluded at the commissioning phase. Ensuring that this is available for "HAE" and not specifying the subtype ensures access to all eligible patients.

As ever access for children remains a concern, the expedition of a PIP to ensure access at lower ages when needed is essential.

Finally access should be equitable across attack frequency and types. Currently value judgements on high attack burden exists for e.g. Lanadelumab, but arguably 2 abdominal attacks or laryngeal attacks which are life threatening a month carry a high morbidity. All attacks affecting work or school and ability to enjoy life without fear are important. Equity should be given so that if this medication is approved that it can be used a) first line and b) at 2 or more attacks a month as a maximum threshold to be equitable with other therapies that may or may not be suitable for **all** patients.

I do not think this evaluation will directly exclude those with a protected characteristic.

I do not think recommendations should have an impact on the wider population and equality legislation as the disease is defined by a genetic inherited basis.

I do not think there will be an adverse impact on disabled people.

Clinical expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There remains a high unmet need in HAE.

HAE is a lifelong condition and treatment options are needed that can span a whole lifetime

Newer treatments with lower treatment burdens (e.g. less frequent dosing) are required

Older generation therapies have unacceptable side effects or lower efficacy and newer targeted and more potent therapies are needed

Treatment aims should be for zero attacks and new treatments should be offered when patients still suffer debilitating or life threatening HAE related symptoms

Thank you for your time.

Your privacy

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Clinical expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Single Technology Appraisal

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with hereditary angioedema or caring for a patient with hereditary angioedema. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

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Patient expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Part 1: Living with this condition or caring for a patient with hereditary angioedema

Table 1 About you, hereditary angioedema, current treatments and equality

Patient expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

1. Your name	██████████
2. Are you (please tick all that apply)	☐ A patient with hereditary angioedema? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with hereditary angioedema? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	HAEUK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing

Patient expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with hereditary angioedema? If you are a carer (for someone with hereditary angioedema) please share your experience of caring for them	First presentation of HAE aged 14. Until the development of modern drug therapies had to rely on rest and analgesia for abdominal pain. Episode frequency approx eight per annum. Had to take a positive attitude to deal with everyday life. Had one episode of upper airway swelling which was nearly fatal. The introduction C1 esterase inhibitor concentrate and icatibant were game changers. Danazol as long term prophylaxis has been questionable but C1 and icatibant have improved life enormously.
7a. What do you think of the current treatments and care available for hereditary angioedema on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	As above. The thing is that frequency of attacks varies enormously from one patient to another and response to icatibant can be variable from one patient to another. Also the dose of icatibant from one attack to another can vary. The biggest breakthrough is in LTP for frequent attacks where lanadelumab has brought great improvement by reducing frequency. I find it difficult to say if there is variability in NHS care. Personally my care has been very good. I think these views are in line with other patients I have met through HAEUK

Patient expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

8. If there are disadvantages for patients of current NHS treatments for hereditary angioedema (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Self administration of iv C1 is a problem for many patients requiring a trip to A&E. Serious side effects seem to be uncommon. Self administration of sc drugs does not seem to be a problem in adults
9a. If there are advantages of donidalorsen over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does donidalorsen help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	From the information that I can access it appears the donidalorsen has superior efficacy compared to existing LTP drugs for HAE. For example donidalorsen reduces frequency by 97% compared to lanadelumab where the reduction in frequency is 74%. Clearly for patients who have very frequent attacks or poor outcomes from existing drugs the quality of life will be hugely improved. This is the most important advantage of donidalorsen. Effective LTP in HAE has to be the overall aim in HAE treatment. The advantages overcome poor response to existing drugs and the need for iv C1 and the associated problems. In this respect donidalorsen would seem to be the best of the bunch.
10. If there are disadvantages of donidalorsen over current treatments on the NHS please describe these. For example, are there any risks with donidalorsen? If you are concerned about any potential side effects you have heard about, please describe them and explain why	As with all drugs there are potential side effects but with current knowledge none are serious. Reported side effects include inflammation at the injection site, upper respiratory tract infection and headache. administration is by sc injection which in the majority of cases should not present a problem.

Patient expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

11. Are there any groups of patients who might benefit more from donidalorsen or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	The group of patients with the maximum gain from donidalorsen will be those with frequent attacks. These patients have many real life problems holding them back. I cannot think of any patient who would not benefit. In reality all HAE patients would benefit. Issues around mobility, dexterity or cognitive impairment could be overcome
12. Are there any potential equality issues that should be taken into account when considering hereditary angioedema and donidalorsen? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equality issues can be found in the NICE equality scheme Find more general information about the Equality Act and equality issues here.	No
13. [EAG key issue 1] Is garadacimab a treatment that is commonly used in the UK? If not, do you expect it to be widely used in the future?	Garadacimab is approved by NICE. I do not know if it is commonly used

Patient expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

14. [EAG key issue 4] Is berotralstat subject to stopping rules in the UK? If so, what are they?	As far as I known berotralstat is not being withdrawn.
15. Are there any other issues that you would like the committee to consider?	

Patient expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
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Patient expert statement

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

External Assessment Group (EAG) Report

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Produced by	Centre for Evidence and Implementation Science, University of Birmingham
Authors	Mubarak Patel, Research Fellow II (Statistician), University of Birmingham Christiana Anyebe, Research Associate, University of Birmingham Mubarak Patel, Research Fellow II (Clinical Effectiveness Reviewer), University of Birmingham Angela Mwape, Research Fellow, University of Birmingham Anna Brown, Information Specialist, University of Birmingham Mandy Maredza, Research Fellow II, University of Birmingham
Correspondence to	Dr Mandy Maredza, m.maredza@bham.ac.uk
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None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Mandy Maredza led the project and conducted the review of the cost-effectiveness evidence.

Mubarak Patel (statistician) conducted the review of the statistical analysis and performed additional statistical analysis

Mubarak Patel (clinical effectiveness reviewer) and Angela Mwape conducted the review of the clinical evidence.

Christiana Anyebe conducted the review of the cost-effectiveness evidence.

Anna Brown conducted the review of the literature search.

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Table of Abbreviations

AAS	Angioedema activity score
AE	Adverse events
AECT	Angioedema Control Test
AE-QoL	Angioedema Quality of Life Questionnaire
AgD	Aggregate data
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
C1-INH	C1-inhibitor
CEM	Cost-effectiveness model
CI	Confidence interval
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CUA	Cost-utility analysis
DSU	Decision Support Unit
EAG	External assessment group
FAS	Full analysis set
HAE	Hereditary angioedema
HCRU	Health care resource use
HRQoL	Health related quality of life
HTA	Health technology appraisal
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
IRT	Interactive response technology
ITC	Indirect treatment comparator
IV	Intravenous
kg	Kilogram
LSM	Least mean squares
LTP	Long term prophylaxis
MCID	Minimal clinically important difference
MHRA	Medicines and Healthcare products Regulatory Agency
mg	Milligrams
N/A	Not applicable
NHS	National Health Service
NHS(E)	National Health Service (England)
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported

OLE	Open label extension
OWSA	One-way sensitivity analysis
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q1M	Once every month
Q2M	Once every two months
Q2W	Once every 2 weeks
Q4W	Once every four weeks
Q8W	Once every eight weeks
QD	Once daily
QoL	Quality of life
RR	Rate ratio
RCT	Randomised controlled trial
RoB2	Risk of bias 2
SAE	Serious adverse events
SC	Subcutaneous injection
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
STA	Single technology appraisal
STP	Short term prophylaxis
SUCRA	Surface under the cumulative curve
TA	Technology appraisal
TEAE	Treatment-emergent adverse events
TEM	Treatment effect modifiers

1 Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of EAG's key issues

Table 1: Summary of key issues

ID[6457]	Summary of issue	Impact on results	Report sections
1	Exclusion of garadacimab as a comparator in the population experiencing ≥ 2 hereditary angioedema attacks (HAE) per month	Large	2.3; Table 5
2	Concomitant use of androgens and tranexamic acid in OASIS-HAE in some patients (■) which may have potentially improved overall treatment efficacy of donidalorsen	Unknown	3.2
3	Assumption of equal efficacy across treatments	Large	3.6.6; 5.2.3
4	Berotrastat stopping rule not implemented in the company's base case and cost-utility scenario analysis which does not reflect its recommended use in clinical practice	Large	4.2.5; 4.2.7

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- Whether garadacimab is included as a comparator in the population experiencing ≥ 2 HAE attacks per month
- Whether treatment effectiveness is modelled using median rate ratios derived from the network meta-analysis or by assuming equal efficacy across treatments
- Whether a stopping rule for berotrastat is implemented to reflect its recommended use in clinical practice

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Reduction in the frequency of HAE attacks, which adversely affects the quality of life of patients and carers, compared with berotralstat (≥ 2 attacks per month) and C1-INH (≥ 8 attacks per month) in the company's cost-utility scenario analysis
- In the company's base case, equal efficacy is assumed across treatments; therefore, no incremental QALY benefits are accrued.

Overall, the technology is modelled to affect costs by:

- Ongoing treatment acquisition costs and potential cost reductions associated with reduced dosing frequency in patients who are well controlled (for example, attack-free for at least 3 months), affecting long-term prophylaxis costs relative to comparators.
- Reduced frequency of HAE attacks, leading to lower acute treatment costs and associated healthcare resource use

The modelling assumptions that have the greatest effect on the ICER are:

- Inclusion of garadacimab as a comparator in the population experiencing ≥ 2 HAE attacks per month.
- Assumption of differential efficacy across treatments rather than equal efficacy.
- Implementation of a stopping rule for berotralstat.

1.3 EAG's key issues

Issue [1]: Exclusion of garadacimab as a relevant comparator

Report section	2.3
Description of issue and why the EAG has identified it as important	Garadacimab was not included as a comparator in the company's clinical or economic analyses, despite expert clinical opinion indicating that it is likely to be widely adopted as a long-term prophylactic treatment in UK clinical practice. Its exclusion limits the relevance of the comparative evidence and introduces uncertainty regarding the relative cost effectiveness of donidalorsen in the evolving treatment landscape
What alternative approach has the EAG suggested?	The EAG updated the company's NMA to include garadacimab in both the clinical and economic analyses
What is the expected effect on the cost-effectiveness estimates?	ICER lies in the [REDACTED] quadrant indicating garadacimab may be [REDACTED] but also [REDACTED] than donidalorsen.
Could any additional evidence or analyses be provided to resolve this key issue?	The company could address this issue by providing a network meta-analysis that includes garadacimab as a comparator, enabling more precise estimation of relative treatment effects. The EAG's analysis was constrained by reliance on the company's NMA outputs and the lack of access to individual patient data, which limited the ability to fully explore alternative modelling approaches.

Issue 2: Assumption of equal efficacy justified from NMA results

Report section	3.6.6
Description of issue and why the EAG has identified it as important	The company assumed equal efficacy between active treatments based on overlapping credible intervals from the NMA. The NMA shows substantial differences in point estimates across treatments, indicating heterogeneity in treatment effects. This is important because the equal-efficacy assumption was used to justify a cost-comparison analysis rather than a cost-utility analysis.
What alternative approach has the EAG suggested?	The EAG prefers a probabilistic cost-utility analysis informed by the rate ratios obtained from the NMA. If equal efficacy is claimed, it should be supported by posterior pairwise contrasts showing effects close to unity within a prespecified equivalence margin, alongside clinical justification.
What is the expected effect on the cost-effectiveness estimates?	Moving to a cost-utility framework would allow differences in treatment effectiveness to be reflected in QALYs. This may improve the cost-effectiveness of more efficacious but more expensive treatments relative to cheaper, less effective options, meaning the company's base-case results are likely biased in favour of lower-cost treatments.
Could any additional evidence or analyses be provided to resolve this key issue?	Demonstrate equivalence within a defined margin. Formal equivalence or non-inferiority analyses would be required but are unlikely to be feasible given the sparse network and wide uncertainty.

Issue [3]: Concomitant use of androgens and tranexamic acid in OASIS-HAE trial

Report section	3.2
Description of issue and why the EAG have identified it as important	A small number of participants in the OASIS-HAE trial received androgens or tranexamic acid during the study period. Clinical expert opinion indicated that this is not consistent with previous HAE trials. As both treatments are known to reduce HAE attack rates, their use may bias estimates of treatment effect. No sensitivity analyses were presented to explore the impact of this concomitant medication use.
What alternative approach has the EAG suggested?	Sensitivity analyses with these small numbers of participants removed from the analysis in the NMA. The EAG could not explore this due to lack of access to individual patient-level data for donidalorsen.
What is the expected effect on the cost-effectiveness estimates?	Unknown and cannot be fully quantified without sensitivity analyses excluding these participants from the analysis.
Could any additional evidence or analyses be provided to resolve this key issue?	Sensitivity analyses with these small numbers of participants removed from the analysis in the NMA.

Issue [4]: Exclusion of Berotralstat stopping rule in the model

Report section	4.2.5
Description of issue and why the EAG has identified it as important	The company did not implement a stopping rule for berotralstat in either the base-case cost-comparison or cost-utility scenario analyses, citing the equal-efficacy assumption for the former. The EAG clinical expert advised that this does not reflect UK clinical practice, where berotralstat is discontinued if HAE attacks are not reduced by at least 50% after 3 months. Previous appraisals have identified the stopping rule as a key driver of cost effectiveness.
What alternative approach has the EAG suggested?	The EAG implemented a berotralstat stopping rule in its base-case cost-utility analysis, which does not assume equal efficacy across long-term prophylaxis treatments.
What is the expected effect on the cost-effectiveness estimates?	The impact on cost effectiveness is [REDACTED]. Applying the stopping rule changes the results from donidalorsen [REDACTED] berotralstat to an ICER of [REDACTED], primarily due to a reduction in berotralstat acquisition costs.
Could any additional evidence or analyses be provided to resolve this key issue?	Exploratory analyses using real-world evidence for berotralstat and/or alternative modelling assumptions that explicitly account for the stopping rule.

1.4 Secondary issues identified by the EAG

Issue [1]: Baseline imbalance in disease severity

Report section	3.2 and 3.6.3.3
Baseline imbalance in disease severity	Baseline attack rates were higher in the donidalorsen treatment arms compared with placebo, particularly in the Q4W group. This imbalance introduces uncertainty in the magnitude of the treatment effect, particularly in a small sample-sized trial. Furthermore, baseline attack rates also differed for other LTPs where a baseline attack rate was reported.
What alternative approach have the EAG suggested?	For the comparison with other LTPs, a pooled baseline attack rate for all LTPs where a baseline attack rate is available (berotralstat and lanadelumab) for the ≥ 2 attack per month population was used as provided by the company post clarification. The EAG could not explore the effect of differing baseline attack rates between donidalorsen treatment arms compared with placebo.
What is the expected effect on the cost-effectiveness estimates?	No change in the company's base case cost-comparison analysis due to equal efficacy assumption. The ICER marginally improves in favour of donidalorsen when pooled baseline attack rates are used in the cost-utility scenario analysis. Effect of differing baseline attack rates between donidalorsen treatment arms compared with placebo unknown.
Could any additional evidence or analyses be provided to resolve this issue?	None

Issue [2] Limited generalisability to NHS practice

Report section	3.2
Baseline imbalance in disease severity	The trial population was predominantly White and recruited largely outside the UK, with limited representation of UK patients. Differences in clinical practice patterns, access to on-demand therapy, and patient characteristics may limit the applicability of results to NHS settings.
What alternative approach has the EAG suggested?	Provide additional real-world evidence from UK HAE data to support assessment of the generalisability of trial outcomes imbalance
What is the expected effect on the cost-effectiveness estimates?	Unknown
Could any additional evidence or analyses be provided to resolve this issue?	Additional real-world evidence from UK HAE data to support assessment of the generalisability of trial outcomes imbalance

Issue [3]: Extrapolation of long-term attack rates beyond 24 weeks

Report section	Section 4.2.5
Baseline imbalance in disease severity	Long-term HAE attack rates were assumed to remain constant after week 25 and calculated as an average from the time the treatment is assumed to reach full treatment effect up to week 24. The company did not explore alternative extrapolation methods despite limited long-term evidence. Previous NICE appraisals have shown that long-term extrapolation assumptions materially affect the ICER.
What alternative approach has the EAG suggested?	Exploration of alternative long-term extrapolation methods (e.g. zero-inflated or Poisson regression models that account for attack-free periods), where feasible. The EAG could not undertake these due to lack of individual level data.
What is the expected effect on the cost-effectiveness estimates?	Uncertain but potentially large, as changes to long-term attack rate assumptions may materially affect QALYs, costs, and the ICER.
Could any additional evidence or analyses be provided to resolve this issue?	Access to individual patient data or longer-term follow-up data to support alternative extrapolation approaches and sensitivity analyses.

1.5 Company's modelling errors identified by the EAG

The EAG did not identify any modelling errors in the CS.

1.6 Summary of EAG's preferred assumptions and resulting ICER

The company's base case is a cost-comparison analysis; therefore, no change in ICER relative to the base case is presented in the table below. The exception is the preferred assumption relating to key issue 4 (berotralstat stopping rule), which the company considers can only be meaningfully assessed within a cost-utility framework. To aid interpretation, total costs and total QALYs are presented to illustrate the impact of alternative assumptions on the company's base-case cost-comparison results.

Table 2: Summary of EAG's preferred assumptions and ICER –donidalorsen vs. comparators, ≥ 2 HAE attacks per month population

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (change from company base case)
Company's base case (cost-comparison analysis)					
Donidalorsen	██████	N/A	-	N/A	N/A
Berotralstat	██████	N/A	██████	N/A	N/A
Garadacimab	N/A	N/A	N/A	N/A	N/A
Key Issue 1: Exclusion of garadacimab as comparator					
Donidalorsen	██████	██	█	-	-
Berotralstat	██████	██	██████	N/A	N/A
Garadacimab	██████	██	██████	N/A	N/A
Key Issue 2: Assumption of equal efficacy ^a					
Donidalorsen	██████	██████	-	-	-
Berotralstat	██████	██████	██████	██████	██████

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (change from company base case)
Garadacimab	N/A	N/A	N/A	N/A	N/A
Key Issue 4: Exclusion of Berotralstat stopping rule ^b					
Donidalorsen	██████	██████			
Berotralstat	██████	██████	██████	██████	██████
Garadacimab	N/A	N/A	N/A	N/A	N/A
Secondary issue 1: Baseline imbalance in disease severity^c					
Donidalorsen	██████	N/A	-	N/A	N/A
Berotralstat	██████	N/A	██████	N/A	N/A
Garadacimab	██████	N/A	██████	N/A	N/A
EAG's preferred base case deterministic					
Donidalorsen	██████	██████	██████	██████	██████
Berotralstat	██████	██████	██████	██████	██████ ^d
Garadacimab	██████	██████	██████	██████	██████ ^d
EAG's preferred base case probabilistic					
Donidalorsen	██████	██████	██████	██████	██████
Berotralstat	██████	██████	██████	██████	██████ ^d
Garadacimab	██████	██████	██████	██████	██████ ^d

^aMedian rate ratios based on EAG updated NMA and efficacy assumed to vary by treatment, ^b

Berotralstat is ██████ in the company's base case cost-utility scenario analysis, ^c Explored using pooled baseline attack rates, ^d EAG preferred base case ICER presented (not the change in ICER from company base case) as latter is a cost-comparison analysis, N/A; Not applicable because not included in company's base case cost-comparison analysis

Table 3: Summary of EAG's preferred assumptions and ICER –donidalorsen vs. comparators, ≥8 HAE attacks per month population

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (change from company base case)
Company's base case (cost-comparison analysis)					
Donidalorsen	██████	N/A		N/A	N/A
Lanadelumab	██████	N/A	██████	N/A	N/A
C1-INH	██████	N/A	██████	N/A	N/A
Key Issue 2: Assumption of equal efficacy ^a					
Donidalorsen	██████	██████			
Lanadelumab	██████	██████	██████	██████	██████ ^b
C1-INH	██████	██████	██████	██████	██████ ^b
EAG Preferred base case deterministic					
Donidalorsen	██████	██████			
Lanadelumab	██████	██████	██████	██████	██████ ^b
C1-INH	██████	██████	██████	██████	██████ ^b
EAG Preferred base case probabilistic					
Donidalorsen	██████	██████			
Lanadelumab	██████	██████	██████	██████	██████ ^b
C1-INH	██████	██████	██████	██████	██████ ^b

^aMedian rate ratios based on EAG updated NMA EAG preferred base case and efficacy assumed to vary by treatment, ^b ICER presented (not the change in ICER from company base case) as latter is a cost-comparison analysis, N/A; Not applicable because not included in company's base case cost-comparison analysis

1.7 Outline of confidential comparator or subsequent treatment prices

The EAG has provided a confidential appendix to accompany this report. The cPAS appendix replicates the company and EAG analyses presented in this report but

applying the confidential prices for comparator LTPs and where relevant, on-demand treatments. Additional detail of this information can be found in section 5.4.

2 Background

This report critiques the company submission for donidalorsen subcutaneous injection for preventing hereditary angioedema attacks (HAE) in people 12 years and over.

2.1 Critique of the company's description of underlying health problem

The company discusses the disease pathophysiology, risk factors, symptoms, and burden of HAE in CS sections 1.3.1 to 1.3.3. The EAG notes that many of the references cited by the company are secondary sources of evidence, such as overviews. HAE is described as a very rare, debilitating genetic condition characterised by recurrent, unpredictable episodes of swelling. The prevalence in the UK has been estimated at approximately 1 in 59,000, based on a national survey.¹

Disease pathology and risk factors

The pathophysiology of HAE reported by the company in CS section 1.3.1 is consistent with the description in the cited reference,² although the EAG notes this is a secondary reference. HAE is a rare genetic condition which affects 1/50,000 individuals and is mostly caused by autosomal dominant mutations in the serpin family G member 1 (SERPING1) gene, resulting in deficient or dysfunctional C1-esterase inhibitor (C1-INH) protein and consequent dysregulation of the kallikrein–bradykinin pathway.³ The kallikrein–bradykinin pathway is a plasma protease cascade initiated by Factor XII (a blood protein), leading to the generation of bradykinin.⁴ When C1-INH is deficient or dysfunctional, this pathway becomes overactive, resulting in excessive bradykinin production and increased vascular permeability.⁵ The resulting fluid extravasation into subcutaneous or submucosal tissues causes the swelling (or angioedema) observed in acute HAE attacks.³ A summary of the kallikrein–bradykinin pathway underlying HAE-related swelling is presented in CS Figure 1, which is reproduced from external sources.^{6, 7} The CS describes three types of HAE; Type I and Type II HAE are collectively termed HAE-C1-INH. Type I is characterised by low plasma levels of C1-INH, while Type II is characterised by normal levels of dysfunctional C1-INH.⁴ The CS reports that Type I

HAE accounts for 80–85% of cases and Type II for 15–20%.⁸ The EAG notes that published estimates vary and that the largest genetic series reports Type II disease in approximately 15% of cases, with the remainder representing Type I HAE, suggesting that small differences in reported proportions reflect natural variability rather than true epidemiological differences.⁹ The EAG notes that the broader ranges cited in the CS appear to derive from secondary clinical reviews rather than primary genetic datasets. Type III, or HAE-nl-C1-INH, is defined by the absence of SERPING1 mutations.³ Type III is rare and affects less than 1% of patients, and presents with diagnostic challenges as patients typically show normal plasma levels and normal functional activity of C1-INH and C4.³ The CS reports that more than 700 SERPING1 variants are associated with Type I and Type II HAE, citing Maurer et al.¹⁰ The EAG notes that this value originates from the primary mutation-update study cited in the paper by Ponard et al.⁹ and that the CS cites a secondary guideline rather than the primary source directly. The EAG notes that the company trial (OASIS-HAE) explicitly excluded patients with a Type III HAE diagnosis,¹¹ and the CS therefore focuses exclusively on Type I and Type II HAE (HAE-C1-INH).

The CS describes the onset of Type I/II HAE as typically occurring in childhood, with approximately 50% of patients being symptomatic by age 10 and a mean onset of 8–12 years. This is consistent with the evidence cited,^{12–14} although the specific age distribution varies between studies. The EAG notes that Campos et al.¹² is a narrative overview drawing on heterogeneous international paediatric cohorts rather than primary epidemiological data, while Busse et al.¹³ is a US guideline. The study by Jolles et al.,¹⁴ a UK national audit included 376 patients drawn from 14 centres across England, Scotland and Wales, comprising mainly adults with a small paediatric subset. The paediatric dataset was limited in size, which the authors acknowledge, and only 29–37 children contributed to analyses depending on the outcome. In addition to age of onset, cited sources^{12–14} highlight other triggers of attacks which include upper airway infections, mechanical trauma, emotional stress, and hormonal influences such as menstruation, ovulation and puberty. Medication exposures, particularly oestrogen-containing therapies, and environmental or physical factors such as heat, cold, physical exertion and dental or surgical procedures may provoke swelling episodes. The EAG also notes that these hormonal factors predominantly affect female patients and influence disease activity

rather than the risk of developing HAE. The EAG clinical expert further advised that, due to hormonal differences, female patients may experience a higher frequency or severity of attacks compared to male patients, particularly during periods of hormonal fluctuations. The EAG clinical expert also highlighted that in addition to hormonal factors, emotional stress was also a trigger for an attack.

Symptoms of HAE

HAE is characterised by recurrent swelling episodes that affect the subcutaneous and/or submucosal tissues of the extremities, larynx, face, abdomen, and genitals.^{5, 8} The company describes the symptoms of HAE as burdensome, dependent on the location of attack in CS Figure 1; this figure is reproduced from external sources.¹⁵⁻²⁰ While the company provides a broad overview of the symptoms associated with HAE, much of the evidence cited is derived from secondary sources,^{8, 16, 20} narrative accounts,^{17, 19, 21} and a patient-recall survey,¹⁸ which may overestimate the symptom burden based on location. The EAG notes that mortality rates referenced by the company are largely based on pre-modern treatment eras and may not reflect current outcomes. For example, the company accurately reports findings from Bork et al.²² on historical mortality associated with laryngeal HAE attacks (32.7% mortality), the EAG notes that these data are derived from cohorts in which 90% of fatal cases occurred before the diagnosis of HAE-C1-INH, and largely reflect an era without access to modern acute therapies, home treatment or long-term prophylaxis (LTP). Evidence from Farkas¹⁹ asserts that the 30–50% mortality often quoted in the literature applies specifically to undiagnosed or improperly managed cases, rather than contemporary, well-managed patients. The company accurately reports the attack frequency and timing data from Mendivil et al.²³ (mean 12.5 attacks in 6 months; 47% experiencing an attack within 7 days). However, the EAG notes that the data comes from a specialist-care cohort with over one-third of participants not receiving long-term prophylaxis. As the study does not assess treatment effectiveness, the company's implication that high attack rates persist despite LTP is not supported by the underlying evidence.^{19, 22, 24} The company does not consistently distinguish between untreated and treated patients when reporting symptom burden, potentially overstating disease severity in those receiving modern prophylactic

therapy. Additionally, reliance on narrative accounts and anecdotal patient quotes limits the robustness and generalisability of the symptom burden described.

Burden and impact on healthcare-resource use of HAE

The company describes the physical and mental burden of symptoms in Health-related quality of life (HRQoL) of patients, and the impact on socioeconomic burden due to ongoing needs. This information is supported by primary data from surveys and qualitative accounts that highlight anxiety, depression, fear of attacks and impacts on work, social functioning and family life.^{17, 25-29} The EAG notes that the spontaneous, recurrent attacks of swelling in HAE patients are often painful and potentially life-threatening, particularly when laryngeal oedema occurs.^{17, 23, 26-28} Additionally, the abdominal pain experienced during attacks can be excruciating, rated as above 10 on the pain scale by one participant,¹⁷ and was considered severe by 52% of patients in a European multinational study.²³ The unpredictable nature of these attacks is a core component of the disease burden, leading to constant stress, anxiety, and depression for both patients and their families.^{17, 23, 27, 28} The CS reports that in a survey,²⁷ nearly half of patients reported some degree of anxiety, and 24% reported symptoms consistent with depression. The EAG notes that this a US based survey of recruited individuals engaged with specialist care and patient organisations. Similarly, the multinational European survey by Mendivil et al.²³ reports moderate to severe anxiety and depression in 38% and 17% of participants, respectively. The EAG notes that this sample was enriched for patients with ongoing disease activity as 62% were on LTP, yet many still reported high attack rates. Although the company states that anxiety and depression are “largely not impacted by attack frequency”, Mendivil et al.²³ actually report that worse Hospital Anxiety and Depression Scale (HADS) scores are associated with poorer quality of life (QoL) and higher disease activity, and that Angioedema Control Test (AECT), Angioedema Quality of Life questionnaire (AE-QoL) and the Work Productivity and Activity Impairment questionnaire (WPAI) scores were all worse with higher attack burden. Furthermore, a study by Manning,³⁰ despite being conducted in the US, highlights continued anxiety associated with parenteral on-demand treatment, which can cause patients to delay treatment by an average of 3.7 hours or opt not to treat up to one in four attacks. The company also presents evidence on the socioeconomic and carer

burden of HAE.^{23, 24, 26, 31} The EAG notes that the data demonstrate substantial constraints on patients' ability to work, study and perform daily activities, with high rates of absenteeism, presenteeism and lost productivity reported across studies. However, the EAG notes that some figures cited by the company (for example, 69.1% of patients being unable to consider certain jobs) do not appear in the cited paper by Aygören-Pürsün et al.²⁶ In that study, approximately 40% of patients reported being prevented from applying to certain jobs, while 51% reported that HAE hindered their educational and/or career advancement. The EAG therefore considers that citing a figure of 69.1% may overstate the occupational limitations directly supported by the published evidence.

2.2 Critique of the company's overview of current service provision

The EAG agree that HAE has no cure, however, established standards of care (SoC) are prescribed in accordance with disease activity, with attack frequency being a key driver of treatment choice, alongside attack severity, treatment burden, contraindications, and patient preference.³² Management includes avoidance of known triggers, on-demand treatment for acute attacks, and the use of short-term (STP) or long-term prophylaxis (LTP).³³ Trigger avoidance alone is insufficient due to the unpredictable nature of attacks. Short-term prophylaxis is used prior to known risk events, while LTP is administered routinely to reduce attack frequency and the need for acute treatment.^{33, 34} The CS provides a rationale for its focus on LTP as per the final scope and does not discuss STP further. However, the company discusses on-demand treatments as part of the management of acute HAE attacks citing the NHSE treatment algorithm.³²

On-demand therapies commissioned in England and Wales include subcutaneous icatibant, a bradykinin B2 receptor antagonist, and intravenous therapies including ruconest, a recombinant C1-esterase inhibitor, and plasma derived C1-esterase inhibitors such as berinert and cinryze.³³⁻³⁶ Other on-demand treatments include oral formulations such as sebetralstat, a plasma kallikrein inhibitor currently undergoing NICE technology appraisal.³⁷

In England and Wales, the use of licensed LTPs is governed by commissioning policies issued by the National Health Service (NHS) England and National Institute for Health and Care Excellence (NICE) technology appraisals.³² The CS also states that attack frequency is an important factor in treatment choice and shared decision-making, which is consistent with NHS England commissioning pathways. The EAG clinical expert also agrees that attack frequency is a key determinant of LTP prescription, although other factors such as treatment burden, route of administration, and patient preference also play an important role. The CS summarises in Table 3, current UK commissioned LTP SoC options in the UK including berinert, cinryze, lanadelumab, and berotralstat.^{32, 38, 39} The EAG notes that garadacimab, a recently NICE-recommended LTP, is not included in the company's Table 3. While the company states that garadacimab was not considered as established standard of care at the time of submission, the EAG notes that garadacimab received a positive NICE recommendation on 8th October 2025, prior to receipt of the appraisal on 31st October 2025. The EAG sought clarification on the company's consideration of garadacimab (Clarification Question A1). In response, the company stated that the recommendation was issued 22 days before submission and that implementation was ongoing, with limited use at the time. The company also added that, the phase III pivotal trial for garadacimab, VANGUARD, did not include any sites in the UK. However, EAG clinical expert advice indicated that the exclusion of garadacimab represents a major omission, as implementation is already underway in some centres, particularly where local commissioning processes, pharmacy pathways, and logistics are well established, although uptake has been slower in other hospitals due to logistical and administrative delays. Furthermore, the EAG clinical expert advised that, by the time this appraisal is considered by the committee, garadacimab is likely to dominate the market share for LTP in patients experiencing two or more HAE attacks per months. Therefore, the EAG considers the evidence (Phase III pivotal trial for garadacimab, VANGUARD) as reflected in the positive NICE recommendation and also undertook additional work to evaluate the VANGUARD trial (Section 3.7).⁴⁰ The EAG therefore considers garadacimab to be part of the current UK treatment pathway and includes it in Table 4 (Additional information see Sections 2.2, 2.3, 3.1, 3.7.1). The EAG notes that the NHSE algorithm states that attenuated androgens (such as danazol and oxandrolone) and

antifibrinolytics (such as tranexamic acid) are used as LTP in selected patients. However, due to limited clinical evidence and safety considerations, these are not recommended as first-line options for patients newly starting prophylaxis, but may be considered if clinically appropriate.³² EAG clinical expert advice further indicated that the evidence base for antifibrinolytics is poor and that androgens, although still used in some patients, are associated with well-documented adverse effects.⁴¹

The EAG note that subcutaneous berinert is excluded from the CS Table 3 as a SoC LTP, with the rationale outlined in the company decision problem (CS Table 1), namely its lack of routine commissioning in UK clinical practice, and further support from company's clinical expert opinion. This position is supported by EAG clinical expert advice, which indicated that subcutaneous berinert is rarely used in clinical practice, with cost and local availability representing key barriers, and that lanadelumab has been widely adopted in eligible patients during the period when subcutaneous berinert might otherwise have been considered. The company also includes intravenous berinert as an off-label standard-of-care LTP in Table 4.

Table 4: Current UK commissioned LTP SoC options in the UK

Treatment/Class	Administration	Dosing Frequency	NHSE/NICE Eligibility Criteria
Garadacimab (factor XIIa (FXIIa) inhibitor monoclonal antibody)	Subcutaneous (SC) injection	Once monthly	Recommended for patients aged ≥ 12 years with ≥ 2 attacks per month.
Berotrastat (plasma kallikrein inhibitor)	Oral capsule	Once daily (QD)	Recommended for patients aged ≥ 12 years with ≥ 2 attacks per month. Treatment should be stopped if attack frequency does not reduce by $\geq 50\%$ after 3 months.
Lanadelumab (plasma kallikrein inhibitor)	Subcutaneous (SC) injection	Every 2 weeks (Q2W), potentially reducing to every 4 weeks Q4W	Commissioned for people aged ≥ 12 years who meet criteria for preventative therapy, typically those with ≥ 2 clinically significant attacks per week (8 per month) and who have failed, are intolerant of, or have contraindications to oral prophylaxis.
Intravenous C1-esterase inhibitor (prophylaxis; e.g., cinryze, berinert)	Intravenous (IV) infusion	Multiple times per week (e.g., twice weekly)	Commissioned for patients who fail or are intolerant of oral prophylaxis and experience ≥ 2 clinically significant attacks per week (8 per month).

The CS cites evidence to support general limitations and unmet need of current LTP options for HAE, including treatment burden and ongoing disease activity.^{42, 43} The systematic review by Longhurst et al. (2024) demonstrates that a substantial proportion of patients receiving LTP do not achieve an attack-free status, with attack-free rates generally below 45% for most available LTPs, and that attacks continue to occur across all anatomical sites, including laryngeal attacks. In addition, the CS cites a discrete-choice experiment by Villa et al.⁴³ which shows that patients place greatest importance on reductions in attack frequency, followed by avoidance of gastrointestinal side effects, mode of administration, and less frequent dosing, indicating a preference for treatments that minimise administration burden. The EAG notes that while this study captures patient preferences for treatment attributes, it does not directly assess adherence, discontinuation, or real-world treatment persistence. Similarly, although intravenous and subcutaneous C1-esterase inhibitor therapies require regular parenteral administration and most breakthrough attacks during LTP require on-demand treatment, the cited evidence does not explicitly evaluate administration burden or adherence as clinical outcomes. The EAG therefore considers that statements as cited in the CS regarding “frequent and invasive administration” and adherence challenges are partly interpretative and extend beyond the direct findings of the cited literature. The EAG also considers that some statements in the CS overstate the absence of alternative LTPs by conflating commissioning eligibility thresholds with the availability of clinically effective treatments. For example, while the EAG acknowledge the limitations of berotralstat, including gastrointestinal tolerability concerns and the stopping rule,^{38, 44} the EAG disagrees with the assertion that berotralstat is the only standard-of-care long-term prophylactic option for patients experiencing ≥ 2 attacks per month. Other clinically effective long-term prophylactic therapies are available, including the recently commissioned garadacimab, as well as lanadelumab and intravenous C1-esterase inhibitor therapies, although these are subject to higher commissioning thresholds or additional eligibility criteria.³²

The CS states that donidalorsen is a first-in-class, RNA-targeted PKK inhibitor, intended for the

■ In CS Figure 9, donidalorsen is positioned as an alternative to berotralstat, IV C1-

INHs or lanadelumab for HAE in people 12 years and over, with eligibility defined as two or more attacks per month (alongside berotralstat) or eight or more attacks per month (alongside IV C1-INHs and lanadelumab). The company highlight several benefits of donidalorsen in comparison to existing SoC. These include a reduced dosing regimen

([REDACTED]), minimal in-hospital visits for patients who can self-administer treatment subcutaneously at-home using an auto-injector pen, and extended storage stability of up to six weeks when kept in the original carton at temperatures below 30 °C. In contrast, the company note that lanadelumab pre-filled syringes may be stored unrefrigerated at temperatures below 25 °C for up to two weeks, while C1-esterase inhibitor treatments require reconstitution using aseptic technique and intravenous administration within three hours. Furthermore, the company highlights that donidalorsen addresses an unmet equality need for patients who, based on their religion, may decline treatment options derived from human plasma, such as IV cinryze and berinert, and positions donidalorsen as a treatment that is not derived from human plasma. The EAG requested that the company provide real-world evidence to support the equality considerations relating to patients who may decline plasma-derived products for religious or ethical reasons (clarification question A3). In response, the company did not provide any real-world data but instead stated that its equality considerations regarding human plasma-derived C1-INH were based on the existence of certain religious groups who may decline plasma-derived therapies, such as C1-INHs, due to their beliefs. However, the EAG notes that none of the cited evidence specifically addresses these equality considerations.⁴⁵ Instead, the cited source is a UK statutory legislation that defines religion or belief, and it does not relate to plasma-derived therapies or the treatment of HAE.

2.3 Critique of the company's definition of decision problem

The decision problem in the CS has some differences to the final NICE scope (see Table 5). The key difference being the omission of a relevant comparator. The omitted comparator in the company's decision problem is garadacimab, a recently NICE-recommended long-term prophylactic treatment for hereditary angioedema. Garadacimab is commissioned for people aged 12 years and over with two or more attacks per month, directly overlapping with the target population for donidalorsen. Its exclusion limits the completeness of the comparative clinical and economic analyses and may bias results in favour of donidalorsen by not reflecting the full range of currently available standard-of-care options as described in Sections 2.2, 2.3, 3.1 and 3.7.1.

Table 5: Summary of decision problem

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People 12 years and over with hereditary angioedema	People 12 years and over with hereditary angioedema	N/A	The population in the decision problem matches the final NICE scope and the anticipated marketing authorisation. The characteristics of the population generally reflects the patient population in England and Wales who may be eligible for long-term prophylactic (LTP) treatment under NHS England commissioning arrangements
Intervention	Donidalorsen	Donidalorsen	N/A	The intervention in the company's submission matches the intervention in the scope. Donidalorsen 80 mg is a ribonucleic acid (RNA)-targeted antisense oligonucleotide that binds to prekallikrein messenger ribonucleic acid in the liver, thereby reducing the production of prekallikrein and interrupting the cascade that leads to the overproduction of bradykinin which causes vasodilation and increased vascular permeability, leading

				to angioedema. Donidalorsen has received marketing authorisation from the European Medicines Agency (EMA) and undergoing Medicines and Healthcare products Regulatory Agency (MHRA) assessment through [REDACTED] with an anticipated licence date of [REDACTED].
Comparator(s)	Established clinical management for preventing hereditary angioedema attacks, which may include: • C1-esterase inhibitors (this includes Cinryze, Berinert and Ruconest) • Attenuated androgens • Antifibrinolytics • Lanadelumab for people eligible for preventative C1-esterase inhibitor treatment in line with NHS England's commissioning policy • Berotralstat Garadacimab (subject to NICE evaluation)	Established clinical management for preventing hereditary angioedema attacks, which may include: • Plasma-derived, intravenous C1-esterase inhibitors (this includes IV Cinryze, IV Berinert) • Lanadelumab for people eligible for preventative C1-esterase inhibitor treatment in line with NHS England's commissioning policy Berotralstat	The comparators considered relevant to this appraisal are berotralstat, lanadelumab, and C1-INHs (IV Cinryze and IV Berinert). SC Berinert, Ruconest, attenuated androgens, and antifibrinolytics have not been included as comparators in the decision problem for the reasons outlined below. Only IV Berinert is considered an appropriate comparator to donidalorsen; SC Berinert is not a comparator as no plasma-derived SC C1-INH therapies are reimbursed in the UK for	The EAG considers the company's inclusion of comparators: berotralstat, lanadelumab, and intravenous plasma-derived C1-esterase inhibitors (IV Cinryze and IV Berinert) as treatments commissioned for long-term prophylaxis in England and Wales for defined patient groups. The EAG agrees with the exclusion of subcutaneous berinert, as no plasma-derived subcutaneous C1-esterase inhibitor products are reimbursed in the UK for long-term prophylaxis, and EAG clinical expert feedback indicated that any historical use has largely been replaced by lanadelumab.

			LTP.¹⁸ This exclusion is further supported by clinical expert opinion, sought as part of clinical validation meetings held in September 2025; clinical experts noted that any use of SC Berinert has been largely replaced with lanadelumab.¹⁹ Ruconest is predominantly used as an on-demand therapy for the treatment of acute attacks and is therefore not considered to be an appropriate comparator for donidalorsen. The marketing authorisation of Ruconest states that: “<i>Ruconest is indicated for treatment of acute angioedema attacks in adults, adolescents, and children (aged 2 years and above) with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency</i>”.²⁰ Furthermore, Ruconest is neither recommended by NICE nor commissioned by NHS England for use	The EAG also agrees that Ruconest is not an appropriate comparator. Ruconest is predominantly used as an on-demand therapy for the treatment of acute hereditary angioedema attacks and is not licensed, recommended by NICE, or commissioned by NHS England for long-term prophylaxis. NHS England commissioning policies for C1-esterase inhibitor prophylaxis specifically refer to plasma-derived products, whereas ruconest is a recombinant C1-esterase inhibitor. This distinction has been reflected in previous NICE technology appraisals (TA606 and TA738). The EAG agrees that attenuated androgens are not appropriate comparators. Although androgens were historically used off-label for prophylaxis, they are not licensed or recommended by NICE for long-term prevention of hereditary angioedema attacks. NHS England guidance states that androgens are not

			as an LTP.^{20–22} The NHS commissioning policy for C1-INH treatment specifically discusses plasma derived C1-INHs, in contrast to Ruconest which is a recombinant treatment.^{20–22} This has been established in previous technology appraisals for lanadelumab and berotralstat (TA606 and TA738).^{9,18} Androgens are not licensed as LTP, nor are they recommended by NICE for the long-term prevention of HAE attacks. Although off-label use of androgens such as danazol was historically considered standard of care for prophylaxis in HAE, since the availability of licensed and commissioned treatments in England has improved, androgens are no longer considered as treatment option when patients are initiated on an LTP or require an alternative LTP.	recommended as first-line prophylaxis for patients newly starting long-term treatment and should generally be continued only in established patients where clinically appropriate. In addition, androgens are associated with significant safety concerns and are not recommended for use in people under 18 years of age, which is relevant given the anticipated licence population for donidalorsen. Danazol has also been discontinued in the UK, and current guidance advises against initiating new patients on androgen therapy. Similarly, the EAG agrees with the exclusion of antifibrinolytics, such as tranexamic acid. These agents are not licensed for long-term prophylaxis in hereditary angioedema, and international guidelines do not recommend their use due to limited evidence of efficacy. Tranexamic acid is generally indicated for short-term use only.

			An algorithm of commissioned treatment options for the management of HAE, published by NHS England, states <i>“Some adult patients are treated with androgens as oral prophylactic treatment. However, evidence is limited and accessing treatment is difficult, so this is not recommended as first line for patients newly starting on prophylaxis. Where existing patients are established on androgen therapy, this may continue if considered clinically appropriate; if established patients do cease treatment with androgen therapy, then review the need for any prophylaxis. An individualised assessment to withdrawal of androgens and commencing new prophylaxis should be taken. If a historical attack frequency is documented, it can be</i>	The EAG disagrees with the exclusion of garadacimab as a comparator. Garadacimab received a positive NICE recommendation shortly before submission and is commissioned for people aged 12 years and over with two or more hereditary angioedema attacks per month, directly overlapping with the population for donidalorsen. In accordance with NICE methods, it should therefore be included as a relevant comparator. (See section 1.3) EAG clinical expert advice also supports the inclusion of garadacimab, as it is expected to be used in the same treatment line and clinical setting as donidalorsen. Clinical experts consider its exclusion to be a major omission, given that garadacimab is recommended by NICE and available for use across England and Wales. Experts further highlighted that implementation is already underway in routine practice, with some hospitals having begun prescribing garadacimab, particularly

			<i>used as the basis for selecting other prophylaxis treatment options.</i>²³ Additionally, clinical expert feedback in berotralstat TA738 stated that patients under the age of 18 should not be treated with androgens. Therefore, androgens are not considered to be an appropriate comparator for donidalorsen, for which patients aged 12 years and above are included in the anticipated licence. Androgens are also associated with adverse androgenic and anabolic effects, drug interactions and contraindications.⁹ Furthermore, danazol has been discontinued in the UK and current treatment directives state not to start new patients on androgens.^{23,24} Similarly, anti-fibrinolytics were historically considered standard of care but these are not indicated as LTPs for	where local logistics and commissioning processes are well established, although uptake has been slower in other centres. In addition, the EAG clinical expert advised that garadacimab is expected to capture a substantial proportion of the long-term prophylaxis market share, as it was approved earlier than donidalorsen and is likely to be adopted ahead of newer entrants into the treatment pathway.

			patients with HAE and the marketing authorisation for tranexamic acid specifically indicates “short term use”.^{24,25} In addition, WAO and EAACI guidelines do not recommend anti-fibrinolytics due to the limited efficacy data available.²⁶ Following recent NICE guidance in October 2025, garadacimab is recommended for patients with two or more HAE attacks per month. However, as implementation of the guidance is still in progress, garadacimab is not considered established standard of care in UK clinical practice at the time of this appraisal.²⁷ As per the NICE process and methods, garadacimab is therefore not considered a relevant comparator in this appraisal and has been excluded from the	

			company's decision problem. ²⁸	
Outcomes	The outcome measures to be considered include: • angioedema attacks (including frequency, severity, location and duration) • attack-free period • time to first attack • need for acute treatment • mortality • adverse effects of treatment health-related quality of life (for patients and carers).	The outcome measures to be considered include: • angioedema attacks (including frequency, severity, location and duration) • need for acute treatment • mortality • adverse effects of treatment health-related quality of life (for patients and carers).	'Attack-free period' and 'time to first attack' were not included as the primary or secondary outcome measures in the pivotal phase III trial (OASIS-HAE) of donidalorsen and have therefore not been included in the company's decision problem.^{12,29} Furthermore, 'attack-free period' and 'time to first attack' are not considered principal outcome measures for the economic analysis, and these endpoints do not inform the analysis.	The outcomes included in the company decision problem broadly align with the NICE scope and capture key objectives of long-term prophylaxis in hereditary angioedema, including reduction in attack burden, use of acute treatment, adverse events, and health-related quality of life. The EAG notes that attack-free period and time to first attack are excluded in the OASIS-HAE trial as they were not prespecified endpoints. The EAG sought justification for the exclusion of these outcomes (Clarification Question A2). In response, the company stated that these endpoints were not treated as principal outcomes for the economic analysis and have not been key drivers in previous NICE appraisals for lanadelumab and berotralstat (TA606 and TA738, respectively). The EAG note, however, that attack-free period and time to first attack

				are clinically meaningful outcomes that may provide complementary information to mean attack rates, including the timing of treatment effect and sustained disease control. The EAG therefore considers these outcomes to be decision-relevant and recommends that any available exploratory data be presented, or that their absence be clearly justified as a limitation of data availability rather than a lack of relevance.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial	A cost-comparison analysis is presented in the base-case in patients with HAE aged 12 years and over who experience ≥ 2 clinically significant attacks per month, comparing donidalorsen against berotralstat, lanadelumab, and C1-INHs (IV Cinryze and IV Berinert). Please see Section 5.1 for further details. A cost-utility analysis in the same population is presented as a scenario analysis.	The efficacy of donidalorsen is assumed equal to the relevant comparators of this appraisal because there were no statistically significant differences observed between donidalorsen Q4W and comparator LTPs in the results of the indirect treatment comparison. Please see Sections 3.6.5.1, 3.6.6 and 5.2.3 for further details.	The economic analysis partially aligns with the stipulations in final scope as base case economic analysis is not presented in terms of incremental cost per QALY

	arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	Please see Appendix K for further details.		
Subgroups	NA	NA	NA	NA
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	As per draft scope.	N/A	The EAG note that access to long-term prophylaxis may be influenced by age, route of administration, treatment burden, and local implementation factors, which could differentially affect patient groups. However, with regards to equality considerations relating to patients who may decline plasma-derived products for religious or ethical reasons, the EAG could not identify any supporting evidence and therefore requested that the company provide data to substantiate this claim (clarification question A3). In response, the company provided a theoretical rationale based on definitions of religion or belief from UK statutory legislation, ⁴⁵ but did not provide real-world evidence, such as patient surveys, registry data, or utilisation analyses, to

				demonstrate the extent to which these factors affect treatment access, uptake, or persistence in clinical practice.
HAE, Hereditary angioedema; CS, company submission; EAG, evidence assessment group; HR-QoL, Health-related quality of life				

3 Clinical effectiveness

This section presents a summary and critique of the clinical-effectiveness evidence included in the company's submission. Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 provide a critique of the included studies. Section 3.3 critique of the results of OASIS-HAE. Section 3.4 critique of the results of OASISplus. Section 3.5 provides a critique of the adverse events. Section 3.6 provides a critique of the company's NMA and clinical-effectiveness analyses. Section 3.7 covers additional work done by the EAG

3.1 Critique of the methods of review

The company undertook a systematic literature review (SLR) to identify studies on clinical effectiveness and safety in patients aged 12 years and over with hereditary angioedema. The SLR is reported in full in a confidential document supplied in the reference pack accompanying the CS. Several reporting omissions, errors and discrepancies relating to the SLR were identified by the EAG, however these were all satisfactorily resolved at the clarification stage (see clarification responses A4, C2-6).

Table 6 summarises the EAG's assessment of the evidence base identified by the company's SLR and subsequently considered relevant to the appraisal. Overall, the SLR identified a substantial number of clinical studies evaluating prophylactic treatments for HAE, including randomised controlled trials (RCTs), extension studies, and observational studies across a range of established and emerging therapies. The included studies broadly cover the populations, outcomes, and interventions of interest for long-term prophylaxis in HAE.

The evidence base identified by the SLR includes pivotal trials for several comparators currently used in clinical practice, such as lanadelumab, berotralstat, and plasma-derived C1-inhibitor, as well as supporting long-term extension studies. These trials form the backbone of the comparative clinical evidence used in the submission and are generally appropriate for informing relative effectiveness from the NICE decision problem.

However, a key issue highlighted in the table is the disconnect between a study identified in the SLR and those ultimately used in comparative analyses. In particular, the SLR identified the VANGUARD trial evaluating garadacimab, a comparator that NICE explicitly requested to be considered. Despite this, the VANGUARD trial was not included in the company’s indirect treatment comparison or network meta-analysis. Garadacimab is a clinically relevant comparator within the scope of the appraisal, and VANGUARD represents a key source of randomised evidence informing its clinical effectiveness. Importantly, the VANGUARD trial has previously been used in a NICE health technology appraisal that resulted in a positive recommendation for use in the NHS (TA1101),⁴⁰ further underscoring its relevance and acceptability as part of the comparative evidence base. Excluding this trial from the ITC and NMA therefore results in an incomplete synthesis of available evidence, limits the ability to assess donidalorsen’s relative effectiveness against an established comparator, and is at risk of generating biased conclusions by omitting a potentially highly effective treatment. The EAG consider this omission to be a major limitation of the evidence synthesis, as it means that a relevant and recently recommended treatment is excluded from the comparative framework, despite being identified through the company’s own review process. This is explained further in sections 2.3 and 3.8.

In summary, the SLR identified an appropriate range of studies evaluating long-term prophylactic therapies for HAE. However, the selective use of this evidence, particularly the exclusion of the VANGUARD trial reduces confidence that the comparative clinical evidence fully reflects the available and relevant data.

Table 6: Summary of SLR methods and EAG assessment of robustness

Systematic review step	EAG assessment of robustness of methods
Searches Confidential Otsuka SLR 2025, Section 3.3 and Appendix A	Searches were conducted in June 2024, then updated in April 2025. Embase, MEDLINE and Cochrane CENTRAL were searched, which is an appropriate selection of databases when searching for clinical trials. MEDLINE and Embase were searched together in one search which is not best practice and limits the

Systematic review step	EAG assessment of robustness of methods
	effectiveness of the search filter used to identify RCTs, which is designed for Embase only. Some search terms that would have made the search more sensitive, for example ‘ruconest’, ‘conestat alfa’, ‘epidemiologic studies’ (MeSH heading), ‘controlled study’, ‘comparative study’ were not used. Google Scholar, ClinicalTrials.gov and the International Clinical Trials Registry Platform were also searched, however search strategies are not provided for these sources, so the EAG is unable to ascertain whether these searches were thorough or comprehensive. Websites of HTA agencies, proceedings of recent conferences and reference lists of other SLRs were also checked. Despite some concerns about the sensitivity and comprehensiveness of the company’s searches, the EAG deems it unlikely that any RCTs eligible for inclusion in the NMA were missed by the searches. The EAG also ran targeted searches for any studies relevant to the NICE scope that may have been added to databases since the company’s last search April 2025 (see Appendices for details); these identified no additional, relevant RCTs.
Inclusion criteria Confidential Otsuka SLR 2025, Section 3.2, Tables 1 and 2	The inclusion criteria were broadly appropriate and structured using the PICOS framework. The population of interest was people with HAE aged 12 years old and above as per the NICE scope and decision problem. Intervention and comparator inclusion criteria encompassed a wide range of therapies which extended beyond the NICE scope and decision problem. Eligible efficacy outcomes were appropriate (e.g., frequency, severity, location and number of angioedema attacks) as were safety outcomes (e.g., adverse events, discontinuation due to adverse events and incidence of emergency room visits). Only English language publications were considered, which may have excluded potentially relevant evidence from non-English publications. Additionally, both RCTs and non-RCTs were eligible of inclusion in the SLR.
Screening	The screening process was appropriate and in line with best practice for systematic reviews. Following deduplication, titles and

Systematic review step	EAG assessment of robustness of methods
Confidential Otsuka SLR 2025, 3.4	abstracts were screened independently by two reviewers against the pre-specified inclusion criteria. Studies passing this stage underwent full text screening, again by two independent reviewers. Any disagreements at either stage were resolved through discussion or via a third independent reviewer.
Selection of included studies Confidential Otsuka SLR 2025, 4.2	The EAG considers that the SLR was generally well conducted and that the range of included randomised and non-randomised studies was appropriate. However, the EAG identified a significant inconsistency between a study included in the SLR and those subsequently incorporated into the ITC and NMA. In particular, the SLR included the VANGUARD trial, an RCT evaluating garadacimab, a comparator explicitly requested by NICE. Despite this, the company did not include the VANGUARD trial in the ITC or NMA.
Data extraction Confidential Otsuka SLR 2025, 3.5	Data extraction methods were largely appropriate, using a pre-specified protocol to capture a variety of relevant data and information. Extraction was conducted by a single reviewer and checked by a second reviewer.
Tools for quality assessment Data on file, Donidalorsen SLR extractions quality assessment ⁴⁶	The risk of bias assessment for eligible RCTs were conducted using the Cochrane risk of bias 2 tool for RCT, and a separate assessment tool for non-RCTs. Many domains were rated as 'unclear (N/R)', often due to reporting gaps in primary publications, and it is unclear whether trial authors were contacted to resolve these uncertainties. It is also unclear whether the risk of bias assessment was conducted by a single reviewer or two reviewers.
Evidence synthesis Confidential Otsuka SLR 2025, 4.2	A summary of the 43 included clinical studies accounting for 61 references were provided in Table 7 of the confidential SLR report. However, no data from these 43 studies were tabulated, only a breakdown of intervention/comparator, study design, endpoints of interest and subgroups were presented. Nevertheless, there was narrative summaries for both clinical and safety findings. The

Systematic review step	EAG assessment of robustness of methods
	method in which to assess HRQoL from included studies was tabulated in in Table 11 with results presented in Table 13.

3.2 Critique of the methods of the pivotal trials

Donidalorsen

The pivotal study providing safety and efficacy data for HAE is the OASIS-HAE trial (NCT05139810).^{11, 47} The OASIS-HAE study characteristics are described in section 2.3.1 of the CS. The trial was a randomised, double-blind, placebo-controlled, multicentre phase 3 study that compared donidalorsen 80 mg administered subcutaneously every 4 weeks or every 8 weeks with placebo in people with HAE.

3.2.1 OASIS-HAE study design

The EAG summary of the key characteristics of the OASIS-HAE trial, based on the company submission, is reported in Table 7. OASIS-HAE was designed to evaluate the efficacy and safety of donidalorsen as long-term prophylaxis for HAE. The trial enrolled people with Type I or Type II HAE and represents the primary source of clinical evidence in the CS. The trial was conducted across multiple geographic regions, including the European Union (21 sites), North America (11 sites), the Middle East (5 sites) and the United Kingdom (2 sites) according to the CSR.¹¹ The EAG notes that the CS highlights a discrepancy in the number of sites reported, as the publication by Riedl et al. (2024) reports 42 sites whereas the CSR reports 39 sites. The CS reports both 39 and 40 sites.^{11, 47} The company subsequently confirmed that the number of sites that enrolled patients in OASIS-HAE was 39. The double-blind treatment period lasted 24 weeks, after which eligible patients could enter an open-label extension study, OASISplus, in which all participants received donidalorsen. OASISplus is described in section 3.4 of the EAG report.

Eligible participants were aged 12 years or older with a confirmed diagnosis of Type I or Type II HAE and documented history of recurrent investigator-confirmed angioedema attacks. Participants were required to have at least two investigator-confirmed HAE attacks during the run-in period (56 days to one day before

randomisation) to ensure enrolment of patients with active disease.^{11, 47} The CS excludes patients with Type III HAE. However, the EAG sought clarification as the exclusion of such patients may limit generalisability of the OASIS-HAE outcomes to a wider population (Clarification Question A12). In response the company stated that Type III HAE is rare, which therefore does not affect the broader generalisability of the OASIS-HAE results. The EAG clinical expert also agreed that the exclusion of Type III participants would not impact the generalisability of the trial.

The EAG notes that while the protocol states the exclusion of chronic prophylaxis such as lanadelumab, Cinryze or Ruconest, or berotralstat within five half-lives prior to screening, the CS section 2.3.1 states that “*chronic prophylaxis for angioedema attacks, except for a stable dose of androgens and tranexamic acid*” was not permitted during the trial. Therefore, this indicates that while most prophylactic therapies were disallowed, stable doses of androgens and tranexamic acid were explicitly permitted. However, the continued use of androgens and tranexamic acid during a prophylaxis trial is clinically unusual, as both agents are recognised to reduce HAE attack frequency and are typically excluded with a defined washout period in comparable trials.⁴⁸ Advice from the EAG clinical expert also highlighted that the inclusion of these therapies would be unexpected and may confound attribution of treatment effect. In addition, the clinical expert confirmed that clinical trials within this field typically exclude the use of androgens and tranexamic acid along with a significant washout period to ensure these treatments had no influence on the efficacy results. In response to clarification question A14, the company confirmed that [REDACTED] patients continued to receive androgens and [REDACTED] patient received tranexamic acid during the trial, with an imbalance in androgen use across treatment arms.¹¹ The EAG notes that no sensitivity analyses excluding these patients were provided. Given the small sample size, particularly within individual dosing arms, this introduces additional uncertainty regarding the magnitude of donidalorsen’s treatment effect.

Participants were randomised 2:1 into three treatment groups. While the study protocol planned for 54 participants to be randomised, actual enrolment was a total of 91 participants. The company presented the sample size calculation of OASIS-HAE in Table 8 of the CS, which was based on a Poisson regression model for HAE

attack counts and assumed a large treatment effect. Specifically, the sample size calculation assumed a 6-month HAE rate of 13.26 in the placebo group and 1.38 in the donidalorsen Q4W group, corresponding to a rate ratio of approximately 0.10, a 90% reduction in attacks on treatment. Under this assumption. A total sample size of 54 patients, randomised 2:1, was estimated to provide at least 90% power for the primary endpoint at a 5% significance level, with a planned enrolment of 84 patients to allow for dropouts and to support secondary and safety analyses. The EAG notes that this sample size calculation is primarily driven by an optimistic assumed treatment effect. Such an effect allows a small trial to achieve high power, but it also implies that the study is not well powered to detect more modest, but clinically relevant, differences between donidalorsen and placebo. Therefore, while OASIS-HAE was adequately powered to demonstrate superiority versus placebo under the company's assumptions, it provides limited precision for comparative effectiveness across active treatments in the NMA. This will be discussed later in section 3.8.

The trial involved comparing subcutaneous administration of either donidalorsen administered once every four weeks (Q4W) or donidalorsen once every eight weeks (Q8W) across a 24-week treatment period. The inclusion of two dosing regimens was intended to explore the balance between efficacy and dosing convenience. Matching placebo injections were administered at identical intervals in the control arms. Administration was either in a study centre or at home by a healthcare professional. Within each dosing cohort, participants were then randomised 3:1 to receive 80 mg of donidalorsen or a matching volume (0.8 ml) of placebo. Blinding was maintained for patients, investigators, and study personnel throughout the 24-week double-blind period, with placebo injections administered at matching frequencies to preserve blinding across dosing schedules. In the event of a serious adverse effect (SAE), the treatment assignment was revealed for that patient.^{11, 47}

The primary outcome of OASIS-HAE was the number of investigator-confirmed HAE attacks per four weeks from Week 1 to Week 25 for the donidalorsen Q4W group compared to placebo. This endpoint reflects a clinically meaningful measure of disease activity and is consistent with outcomes used in other HAE prophylaxis trials. Attacks were required to meet protocol-defined criteria and be confirmed by the investigator. However, the submission provided limited detail on how these attacks

were confirmed. Specifically, information was lacking on whether confirmation occurred in real time or retrospectively, the data sources used to identify attacks (e.g. patient diary, electronic diary, or telephone contact), and whether any procedures were implemented to ensure consistency and reliability of confirmation across study sites. This lack of detail introduces uncertainty regarding the potential for misclassification, particularly for milder attacks. In response to Clarification Question A8, the company stated that *“investigator-confirmed HAE attack was defined as an event with signs or symptoms consistent with an attack in at least one of the following locations: abdomen, periphery, or larynx. A discrete attack was counted if there was at least a 24-hour symptom-free period between attacks.”* Additionally, patients were instructed to report any details of HAE attacks using the Angioedema Activity Score (AAS) questionnaire within 72 hours of an attack.⁴⁹ The AAS questionnaire was administered daily to the patient electronically using a YPrime handheld device.¹¹

Secondary outcomes included multiple measures intended to capture both clinical and patient-reported aspects of disease control. Clinical secondary outcomes included, the investigator-confirmed HAE attacks from Week 1 to Week 25 for the other trial arms (measured the same way as the primary outcome), the severity of HAE attacks, use of on-demand medication, and the proportion of patients achieving attack-free status during the treatment period. While these outcomes are clinically relevant, the definition of certain endpoints, such as “attack-free” status, was not fully specified in the submission, and it is unclear whether attack freedom required continuous absence of attacks over a defined period or was based on one or more attack-free intervals. Differences in such definitions can materially influence interpretation and comparability with other HAE trials. Therefore, the EAG asked the company to define how “attack-free” status was defined in the study (Clarification Question A16). The company responded by stating that, *“attack-free status in OASIS-HAE was defined as patients who achieved a 100% reduction in HAE attacks from baseline from Week 5 to Week 25, i.e. no HAE attacks from Week 5 to Week 25.”*^{11, 47} Furthermore, this definition is consistent with other trials other trials (HELP²⁷ and APeX-2⁴⁴) and therefore, the EAG are satisfied with this “attack-free” definition.

Patient-reported outcomes (PROs) were assessed using validated disease-specific instruments, including the Angioedema Quality of Life Questionnaire (AE-QoL) and the Angioedema Control Test (AECT). These instruments aim to capture the impact of HAE and its treatment on HRQoL and disease control from the patient perspective. Although the use of these measures is appropriate, interpretation of the results depends on assumptions regarding the minimal clinically important difference (MCID), handling of missing data, and multiplicity control across multiple secondary endpoints. The EAG notes that the CS did not clearly state the MCIDs applied or how observed changes related to established thresholds of clinical relevance. The company were asked to provide detail on the MCID thresholds for both the AE-QoL and AECT (Clarification Question A13). The company responded by stating that the MCID threshold for AE-QoL was 6 points as defined by Weller *et al.* (2016)⁵⁰ and three points for AECT as reported by Fijen *et al.* (2023)⁵¹ The EAG were satisfied with this response following confirmation from the EAG clinical expert that these MCID thresholds were appropriate.

The safety of donidalorsen was assessed by means of clinical laboratory findings and the incidence of adverse events (AE) following use of donidalorsen. Safety endpoints included assessment, type and severity of AEs, clinical laboratory parameters, vital signs and electrocardiograms. Furthermore, exploratory PROs included, the generalised Anxiety Disorder-7 questionnaire score, Patient Global Impression of Severity, and the WPAI questionnaire activity impairment score. In addition, the CS presented safety reasons which would cause participation being halted. These included, death caused by the treatment drug, occurrence in any patient of a life-threatening serious AE, two occurrences of grade ≥ 3 toxicities and two occurrences of a clinically significant Grade ≥ 3 laboratory abnormality.

Table 7: Description of the pivotal study for the technology of interest

Trial number (acronym)	OASIS -HAE (NCT05139810)	Section(s) of CS of relevance or other source

Study details	The study was conducted at 42^a sites across 14 countries in four areas: Europe, North America, Middle East and the UK. OASIS-HAE is a phase III, multicentre, randomised, double-blind, placebo-controlled study of donidalorsen 80 mg or matching placebo administered Q4W or Q8W for 24 weeks in patients with HAE. The years of recruitment was not provided across any of the documents, however, the date the last patient was screened was 07 June 2023 and the last patient visit was 09 November 2023	Publication plus supplementary information of Riedl et al. (2024) ⁴⁷ and the CSR section 2 ¹¹
Intervention and administration	Participants were randomised 2:1 to receive either donidalorsen administered once every four weeks (Q4W) or donidalorsen once every eight weeks (Q8W) across a 24-week treatment period. Within each dosing cohort, participants were then randomised 3:1 to receive 80 mg of donidalorsen or a matching volume (0.8 mL) of placebo, administered subcutaneously.	Publication (Riedl et al., 2024) ⁴⁷ and the CSR section 2 ¹¹
Sample size	Donidalorsen 80 mg Q4W (n = 45) Donidalorsen 80 mg Q8W (n = 23) Placebo (n = 22)	Publication (Riedl et al., 2024) ⁴⁷ and the CSR section 2 ¹¹
Population and eligibility criteria	Key inclusion criteria included patients aged ≥ 12 years with Type I or Type II HAE, experienced a minimum of 2 HAE attacks (confirmed by investigator) during the screening period, female participants had to be nonpregnant and non-lactating, whilst male participants had to be surgically sterile.	Publication plus supplementary information of Riedl et al. (2024) ⁴⁷ and the CSR section 2 ¹¹

	A full list of the inclusion and exclusion criteria is presented in Table 5 of section 2.3.1 of the CS.	
Permitted and disallowed concomitant medication	Allowed concomitant medications included: the use of on-demand HAE medication (plasma-derived or recombinant C1-INH concentrate, bradykinin 2-receptor antagonist, or kallikrein inhibitor) to treat angioedema attacks was allowed as medically indicated. All other stable medications were allowed if dose and type was not expected to change during the study. Disallowed concomitant therapy included: chronic prophylaxis for HAE attacks, except for stable doses of androgens or tranexamic acid. Lanadelumab and berotralstat was also not permitted.	CSR section 9.4.7.2 ¹¹
Primary and key secondary outcomes	The primary outcome of the trial was the time-normalised number of investigator-confirmed HAE attacks (per 4 weeks) from Week 1 to Week 25 compared to placebo for the donidalorsen 80 mg Q4W. Key secondary outcomes of the trial included: attack severity, on demand medication use and attack free status. Safety outcomes included AE-QoL and AECT.	Publication plus supplementary information of Riedl et al. (2024) ⁴⁷ and the CSR section 2 ¹¹
Based on Table 5 of the CS and from the CSR^{11, 47} ^AThere were discrepancies in the number of sites reported across sources. The EAG has presented the number of sites reported in Riedl et al. (2024)⁴⁷ Abbreviations: Q4W = Once every four weeks; Q8W = Once every eight weeks; ACET = Angioedema Control Test; AE-QoL = Angioedema Quality of Life Questionnaire; CS = company submission; CSR = clinical study report.		

3.2.2 Critique of participants' baseline characteristics

Baseline demographic and disease characteristics in OASIS-HAE were generally similar across the donidalorsen and placebo arms. However, the EAG notes several imbalances and study features in interpreting the trial outcomes. The screened 116 participants, of which 91 met the inclusion criteria. One participant in the donidalorsen Q4W group withdraw consent and participation prior to receiving the study treatment.¹¹ Therefore, the study enrolled 90 treated patients (placebo n=22; donidalorsen Q4W n=45; donidalorsen Q8W n=23), resulting in small treatment groups in which baseline differences may have a disproportionate effect on estimates of treatment effect. Observed imbalances related primarily to baseline disease activity, sex distribution, and population representativeness. Additionally, the small number of patients in each arm limits the robustness of conclusions regarding comparative dosing strategies.

The CS and CSR only provide baseline characteristics from the full analysis set (FAS) and not per protocol set. The safety analysis set is the same as the FAS. A summary of baseline characteristics of the full analysis set is presented in Table 8. The study population consisted of 83 (92.22%) adults. The mean age distribution was generally similar across treatment arms (placebo = █ (█), donidalorsen Q4W = █ (█) and donidalorsen Q8W = █ (█) years, although the donidalorsen Q4W group was slightly older on average. Adolescent participants were limited (placebo = 0, donidalorsen Q4W = 4 (8.9%) and donidalorsen Q8W = 3 (13%)), restricting conclusions regarding efficacy and safety in younger patients. Sex distribution had a proportion of male participants in the placebo group (63.6%), with only 36.4% of females. The EAG clinical expert highlighted that more males were included in OASIS-HAE placebo compared to females which although not unusual, could be unexpected as more females may suffer HAE attacks due to hormonal differences.

Most participants were White (placebo = 18 (81.8%), donidalorsen Q4W = 42 (93.3%) and donidalorsen Q8W = 22 (95.7%)), reflecting the geographic distribution of recruiting centres. Ethnic diversity was limited, and only █ participants (█) were recruited across the two UK sites, which may limit the generalisability of the trial findings to the population in England and Wales.

As per the inclusion criteria, all enrolled patients had a confirmed diagnosis of Type I or Type II HAE and a documented history of recurrent angioedema attacks. Eligibility required at least two investigator-confirmed attacks during the run-in period, ensuring inclusion of patients with active disease. Despite this, baseline disease activity differed across treatment arms. Mean run-in attack rates were higher in the donidalorsen Q4W group (3.61 attacks per 4 weeks) and Q8W group (3.18) compared with the placebo group (2.90) (Table 8). In addition, the donidalorsen Q4W group reported a higher mean number of attacks in the 12 months prior to enrolment than the placebo group. Although baseline attack rate was included as a covariate in the primary analysis, these differences indicate that patients in the donidalorsen arms, particularly the Q4W arm, entered the study with a higher disease burden. The CS provides limited information on baseline attack severity by treatment arm, restricting assessment of whether disease severity was fully balanced at randomisation.

Patient disposition during the double-blind phase was broadly similar across treatment arms, with most randomised patients completing the 25-week treatment period. A high proportion (83%) of participants who completed the double-blind phase subsequently entered the open-label extension study (OASISplus), suggesting willingness to continue treatment and acceptable short-term tolerability. However, given the small sample size, even a small number of discontinuations may influence outcome estimates, particularly if discontinuation was related to lack of efficacy or adverse events. Although overall discontinuation numbers were reported, limited information was provided on the timing and reasons for discontinuation by treatment arm. In addition, the methods used to handle outcome data following discontinuation (for example, imputation assumptions) were not fully described. These limitations may affect the interpretation of both clinical outcomes and patient-reported outcomes. The high rate of rollover into the open-label extension also raises the possibility of unblinding at transition, which may affect subsequent PROs. However, this does not affect the internal validity of the double-blind phase and is discussed in section 3.4.

Table 8: Summary of patients' baseline characteristics of the included OASIS-HAE trial (full analysis set, 90)

Characteristic	Placebo (N =22)	Donidalorsen 80 mg every 4 weeks (N=45)	Donidalorsen 80 mg every 8 weeks (N=23)
Age (years)			
Mean (SD)	■ ■	■ ■	■ ■
Age Group (years)			
12 to 17	0	4 (8.9)	3 (13.0)
18 to 39	15 (68.2)	19 (42.2)	12 (52.2)
40 to 64	7 (31.8)	21 (46.7)	7 (30.4)
≥ 65	0	1 (2.2)	1 (4.3)
Sex, n (%)			
Male	14 (63.6)	17 (37.8)	11 (47.8)
Female	8 (36.4)	28 (62.2)	12 (52.2)
Ethnicity n (%)			
Hispanic or Latino	■	■	■
Not Hispanic or Latino	■	■	■
Race n (%)			
American Indian or Alaskan Native	2 (9.1)	0	1 (4.3)
Asian	0	1 (2.2)	0
Black or African American	1 (4.5)	1 (2.2)	0
White	18 (81.8)	42 (93.3)	22 (95.7)
Multiple	1 (4.5)	0	0
Other	0	1 (2.2)	0
Mean BMI, kg/m ² (SD) ^a	28.88 (9.22)	28.03 (6.74)	26.97 (5.40)
Family History of HAE, n (%)			
Yes	■	■	■
No	■	■	■
Mean number of attacks in past 12 months, (SD)	29.1 (21.13)	45.7 (43.04)	33.3 (21.95)
Historical C1-INH Activity (%)			
N	■	■	■

Characteristic	Placebo (N =22)	Donidalorsen 80 mg every 4 weeks (N=45)	Donidalorsen 80 mg every 8 weeks (N=23)
Mean (SD)	██████████ ██████████	██████████ ██████████	██████████ ██████████
Mean years from diagnosis to informed consent, (SD)	██████████ ██████████	██████████ ██████████	██████████ ██████████
Age at Onset (Years)			
N	██████████	██████████	██████████
Mean (SD)	12.9 (7.19, 1.57)	11.6 (9.85, 1.47)	10.9 (7.73, 1.61)
HAE Type, n (%)			
HAE-1	20 (90.9)	42 (93.3)	22 (95.7)
HAE-2	2 (9.1)	3 (6.7)	1 (4.3)
Types of Attacks Experienced, n (%)			
Peripheral	██████████	██████████	██████████
Abdominal	██████████	██████████	██████████
Laryngeal	██████████	██████████	██████████
Any Predefined Prophylactic Therapy Use, n (%) ^b			
Yes	██████████	██████████	██████████
No	██████████	██████████	██████████
Mean run-in period attack rate per 4 weeks, (SD) ^c	2.90 (1.66)	3.61 (2.24)	3.18 (2.15)
Run-in period HAE Attack Rate, n (%)			
≤ 2 attacks/4-weeks	██████████	██████████	██████████
2 to 5 attacks/4- weeks	██████████	██████████	██████████
> 5 attacks/4-weeks	██████████	██████████	██████████
Based on Table 6 of the CS Abbreviations: BMI – Body mass index; C1-INH – C1-inhibitor; CI – Confidence interval; HAE – Hereditary angioedema; kg – kilogram; m – metre; mg – milligrams; SD – Standard deviation Notes: ^a Total number of patients analysed for BMI in placebo group n = 21, which makes the total in the ‘All Patients’ group = 89. ^bFirst-line prophylactic agents and excluded attenuated androgens and tranexamic acid. ^cThe run-in period (Screening) HAE attack rate for each patient was calculated as the number of investigator-confirmed HAE attacks occurring during the run-in period divided by the number of days the patient contributed to the run-in period and then multiplied by 28. Source: OASIS-HAE CSR¹¹, Riedl et al. 2024⁴⁷			

Quality assessment of the OASIS-HAE trial

The company assessed the OASIS-HAE trial using the Cochrane Risk of Bias-2 tool for RCTs, and concluded there were “*no signs of significant bias*”, with randomisation being clearly described and baseline characteristics being balanced across cohorts. The EAG agrees with the company that randomisation and allocation concealment was clearly described, and blinding was appropriately maintained throughout the double-blind treatment period. Baseline characteristics were also broadly similar across treatments arms.

However, the EAG does not fully agree with the company’s conclusion that “*no signs of significant bias were identified*”. Therefore, the EAG assessed the OASIS-HAE trial using the Cochrane Risk of Bias-2 tool (Table 9). Although randomisation was adequate, clinically relevant baseline imbalances were observed, particularly in baseline attack frequency and prior long-term prophylaxis use. In a trial with a relatively small sample size, such imbalances may meaningfully influence estimates of treatment effect and introduce uncertainty regarding the magnitude of benefit, even if they do not indicate a failure of randomisation. The EAG considers OASIS-HAE to be at a low risk of bias, with some residual concerns that introduce uncertainty but do not constitute a high or moderate risk of bias.

Table 9: Company's and EAGs quality assessment of the OASIS-HAE trial

Domain	Question	CS	EAG assessment
Risk of bias arising from the randomisation process	1.1 Was the allocation sequence random?	Yes	Yes, participants were randomised 2:1 to receive either donidalorsen administered once every four weeks (Q4W) or donidalorsen once every eight weeks (Q8W) across a 24-week treatment period. Participants were then randomised 3:1 to receive 80 mg of donidalorsen or a matching volume (0.8 mL) of placebo.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NR	Yes, the study was double blind and allocation concealment was maintained through central randomisation and use of identical placebo injections administered at matching intervals. This indicates that allocation was concealed from investigators and participants at enrolment and beyond.
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No	No, despite some baseline imbalances being observed (e.g., baseline attack frequency and prior prophylaxis use), it is likely due to chance as a result of the small sample size as opposed to failure of randomisation. There is no evidence off allocation bias.
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1 Were participants aware of their assigned intervention during the trial?	No	No, the trial was double blind, with participants unaware of the treatment allocation during the 24-week period.

Domain	Question	CS	EAG assessment
	2.2 Were carers or people delivering the intervention aware of participants assigned intervention during the trial?	No	No
	2.3 If yes, probably yes or no information to 2.1 or 2.2, were there deviations from the intended intervention that arose because of the trial context?	NA	NA
	2.4 If yes or probably yes to 2.3, were these deviations likely to have affected the outcome?	NA	NA
	2.5 If yes or probably yes or no information to 2.4, were these deviations from intended intervention balanced between groups?	NA	NA

Domain	Question	CS	EAG assessment
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	Unclear, while intention to treat principles were reported, no sensitivity analysis excluding participants receiving androgens or tranexamic acid were presented, limiting confidence that deviations were adequately addressed analytically.
	2.7 If no, probably no or no information to 2.6, was there potential for a substantial impact (on the results of the failure to analyse participants in the group to which they were randomised)?	NA	NA
Risk of bias due to deviations from the intended interventions (effects of adhering to intervention)	2.1a Were participants aware of their assigned intervention during the trial?	No	No
	2.2a Were carers or people delivering the intervention aware of participants assigned intervention during the trial?	No	No

Domain	Question	CS	EAG assessment
	2.3a [if applicable] if yes, probably yes or no information 2.1a or 2.2a, were important non-protocol interventions balanced across intervention groups?	NA	NA
	2.4a [if applicable] Were there any failures in implementing the intervention that could have affected the outcome?	No	No
	2.5a [if applicable] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	NR	NR
	2.6a If no, probably no or no information to 2.3 or yes, probably yes or no information to 2.4 or 2.5, was an appropriate analysis used to estimate the effect of	NA	NA

Domain	Question	CS	EAG assessment
	adhering to the intervention?		
Risk of bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Yes - 91 underwent randomization and data is reported for 90 patients	Yes, completion rates after randomisation were high as 91 participants were screened but 90 participants entered the double-blind period were high across treatment arms with few discontinuations. There were discontinuations, with a total of eight patients discontinuing treatment early: two (4.3%) in the donidalorsen Q4W group, two (8.7%) in the donidalorsen Q8W group, and four (18.2%) in the placebo group.
	3.2 If no, probably no or no information to 3.1, is there evidence that the result was not biased by missing outcome data?	NA	NA
	3.3 If no or probably no to 3.2, could missingness in the outcome depend on its true value?	NA	NA

Domain	Question	CS	EAG assessment
	3.4 If yes, probably yes or no information to 3.3, is it likely that missingness in the outcome depended on its true value?	NA	NA
Risk of bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No	No, investigator confirmed HAE attacks are an appropriate and clinically relevant outcome for prophylaxis trials as confirmed by the EAG clinical expert.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No	Unclear, although the study was blinded, limited detail was provided on the operational process for investigator confirmation attacks, including timing and data sources.
	4.3 If no, probably no or no information to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Unclear	No, investigators confirming attacks were blinded to treatment allocation for the duration of the trial.
	4.4 If yes, probably yes or no information to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Yes	Yes

Domain	Question	CS	EAG assessment
	4.5 If yes, probably yes or no information to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No	No, blinding reduces the likelihood that outcome assessment was influenced by treatment knowledge.
Risk of bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes	Yes, a full statistical analysis plan was provided.
	5.2 Is the numerical result being assessed likely to have been selected, based on the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Yes	Yes
	5.3 Is the numerical result being assessed likely to have been selected, based on the results, from multiple eligible	Yes	Yes

Domain	Question	CS	EAG assessment
	analyses of the data?		
Company RoB ⁴⁶ Abbreviations: HAE = Hereditary angioedema			

3.3 Critique of the results of the trials of the technology of interest

3.3.1 Overview of efficacy results

Key results from the OASIS-HAE trial are summarised in Table 10. The primary analysis period was up to week 25. Efficacy analyses were conducted in the full analysis set (FAS). As mentioned in Section 3.2.2 one participant in the donidalorsen Q4W group withdraw consent and participation prior to receiving the study treatment,¹¹ therefore only the FAS results were provided and relevant. The CS states that *“the trial data are therefore presented as donidalorsen Q4W and donidalorsen Q8W;*

██████████” The EAG clinical expert confirmed the company’s position highlighting that there would be no difference in a 2-day variation.

Table 10: Summary of the primary and secondary outcome results from the OASIS-HAE trial

Outcome (Week 1 – 25 or Week 5 to 25)	Donidalorsen 80 mg Q4W (n = 45)	Donidalorsen 80 mg Q8W (n = 23)	Placebo (n =22)
Mean (SD) time-normalised HAE attack rate from week 1 to 25			
Investigator confirmed HAE attacks per 4 weeks (LSM 95% CI)	0.44 (0.27 to 0.73)	1.02 (0.65 to 1.59)	2.26 (1.66 to 3.09)
% reduction vs placebo (95% CI)	-81% (-89.3% to -64.9%)	-55% (-73.9% to -22.3%)	NA
P Value	< 0.001	0.004	NA
Mean (SD) time-normalised HAE attack rate from week 5 to 25			
Investigator confirmed HAE attacks per 4 weeks (LSM 95% CI)	0.30 (0.15 to 0.58)	0.90 (0.53 to 1.52)	2.25 (1.59 to 3.18)
% reduction vs placebo (95% CI)	-87% (-93.8% to -71.9%)	-60% (-78.8% to -25.2%)	NA
P Value	<0.001	0.004	NA
Mean (SD) time-normalised moderate or severe HAE attack rate from week 5 to 25			
Investigator confirmed moderate or severe HAE attacks per 4 weeks (LSM 95% CI)	0.12 (0.04 to 0.35)	0.68 (0.37 to 1.23)	1.15 (0.72 to 1.83)
P Value	<0.001	0.173	NA
% reduction vs placebo (95% CI)	-89% (-96.5% to -66.1%)	-41% (-72.4% to 26.0%)	NA
Participants with a ≥ 50% reduction in HAE attack n (%)	42 (93.3)	19 (82.6)	6 (27.3)
P Value			NA
Participants with a ≥ 70% reduction in HAE attack n (%)	37 (82.2)	15 (65.2)	4 (18.2)
P Value	< 0.001	0.004	NA
Participants with a ≥ 90% reduction in HAE attack n (%)	28 (62.2)	11 (47.8)	2 (9.1)
P Value			NA

AE-QoL Mean (SD) change from week 1 to 25			
AE-QoL LSM (95% CI) from week 1 to 25	-24.76	-19.85	
P value	<0.001	0.010	NA
Sources: CS, OASIS-HAE CSR ¹¹ and Riedl et al. 2024 ⁴⁷ Abbreviations: Q4W = Once every four weeks; Q8W = Once every eight weeks; CI = confidence interval; HAE = hereditary angioedema; LSM = least mean squares; SD = standard deviation			

Primary outcome

The primary outcome of the OASIS-HAE trial was investigator confirmed HAE attack rate (per 4 weeks) from week 1 to week 25. The mean (SD) time normalised investigator confirmed HAE attack rate (per 4 weeks) was [REDACTED] for the donidalorsen 80 mg Q4W arm compared to [REDACTED] for the placebo arm.¹¹ Therefore, donidalorsen 80 mg Q4W demonstrated a statistically significant and clinically meaningful reduction in investigator-confirmed HAE attacks compared with placebo over Weeks 1 to 25. The least squares mean (LSM) time-normalised attack rate was 0.44 attacks per 4 weeks in the Q4W group compared with 2.26 in the placebo group, corresponding to an 81% reduction relative to placebo (95% CI: -89.3% to -64.9%; $p < 0.001$).^{11, 47}

Secondary outcomes

Secondary outcomes presented in the CS, CSR and Riedl et al. (2024), including investigator-confirmed HAE attack rate (per 4 weeks), donidalorsen Q8W vs placebo, Week 1 to Week 25, investigator-confirmed HAE attack rate (per 4 weeks), Week 5 to Week 25, moderate or severe investigator-confirmed HAE attacks (Week 5 to Week 25) and quality of life which will be outlined below.^{11, 47}

Investigator-confirmed HAE attack rate (per 4 weeks), donidalorsen Q8W vs placebo, Week 1 to Week 25

Similar to the primary outcome, participants receiving donidalorsen 80 mg Q8W also experienced a statistically significant reduction in HAE attack rate compared with placebo. The LSM time-normalised attack rate was 1.02 attacks per 4 weeks in the Q8W group versus 2.26 with placebo, representing a 55% reduction (95% CI:

–73.9% to –22.3%; $p=0.004$). The mean (SD) time-normalised HAE attack rate (per 4 weeks) from Week 1 to Week 25 was [REDACTED] for the donidalorsen Q8W arm compared to [REDACTED] for the placebo group.¹¹ The magnitude of effect was smaller than that observed with Q4W dosing.

Investigator-confirmed HAE attack rate (per 4 weeks), Week 5 to Week 25

When excluding the early treatment period, donidalorsen Q4W was associated with a larger treatment effect. From Week 5 to Week 25, the mean (SD) time-normalised HAE attack rate from Week 5 to Week 25 was [REDACTED] in the placebo arm, [REDACTED] in the donidalorsen Q4W arm and [REDACTED] in the donidalorsen Q8W arm. The LSM attack rate was 0.30 (0.15 to 0.58) for Q4W compared with 2.25 (1.59 to 3.18) for placebo, corresponding to an 87% reduction (95% CI: –93.8% to –71.9%; $p < 0.001$). For Q8W dosing, the LSM attack rate was 0.90 (0.53 to 1.52), equating to a 60% reduction relative to placebo (95% CI: –78.8% to –25.2%; $p = 0.004$).^{11, 47} These results indicate a dose-frequency response favouring Q4W administration.

Investigator-confirmed moderate or severe HAE attack rate (per 4 weeks) from Week 5 to Week 25

Donidalorsen Q4W substantially reduced the rate of moderate or severe HAE attacks compared with placebo. The mean (SD) time-normalised HAE attack rate from Week 5 to Week 25 for moderate or severe attacks was [REDACTED] for the placebo arm, [REDACTED] for the donidalorsen Q4W arm and [REDACTED] for the donidalorsen Q8W arm. The LSM rate was 0.12 (0.04 to 0.35) attacks per 4 weeks for Q4W versus 1.15 (0.72 to 1.83) for placebo, representing an 89% reduction (95% CI: –96.5% to –66.1%; $p<0.001$).^{11, 47} A comparison of donidalorsen Q4W to donidalorsen Q8W (0.68 (0.37 to 1.23) was not provided. Nevertheless, the reduction observed with donidalorsen Q8W dosing (41%) did not reach statistical significance ($p = 0.173$) when compared to placebo, indicating uncertainty around the effect of less frequent dosing on more severe attacks.

Number of patients with a $\geq 50\%$, $\geq 70\%$, or $\geq 90\%$ reduction from Baseline in investigator-confirmed HAE attacks (per 4 weeks) from Week 5 and Week 25

A higher proportion of patients receiving donidalorsen achieved clinically meaningful reductions in attack frequency compared with placebo. For the $\geq 70\%$ reduction threshold, response rates were 82.2% (Q4W) and 65.2% (Q8W) compared with 18.2% for placebo ($p < 0.001$ and $p = 0.004$, respectively).^{11, 47} Similar patterns were observed for the $\geq 50\%$ (placebo = 27.3%, Q4W = 93.3% and Q8W = 82.6%, [REDACTED] and [REDACTED]) and $\geq 90\%$ (placebo = 9.1%, Q4W = 62.2% and Q8W = 47.8%, [REDACTED] and [REDACTED]) reduction thresholds, with consistently higher response rates in the Q4W group than the Q8W group.^{11, 47}

Health related quality of life

As mentioned in section 3.2.1 the OASIS-HAE trial used the AE-QoL and AECT assessments to estimate the impact of donidalorsen on QoL. The results of these are described below.

Change in AE-QoL Questionnaire Total Score at Week 25

Donidalorsen treatment resulted in clinically meaningful improvements in angioedema-specific QoL. At Week 25, the LSM improvement in AE-QoL total score was -24.8 [REDACTED] points for Q4W and -19.85 [REDACTED] points for Q8W compared with [REDACTED] points for placebo. The between-group differences versus placebo were -18.56 (-27.67 to -9.45) points for the Q4W arm which was statistically significant ($P < 0.001$) and -13.65 (-24.02 to -3.29) points for the Q8W arm which was also statistically significant ($P = 0.010$), both exceeding the accepted minimal clinically important difference, which was confirmed by the EAG clinical expert.¹¹

Percentage of well-controlled patients on the AECT at Week 25

At Week 25, a higher proportion of patients receiving donidalorsen achieved well-controlled disease (AECT ≥ 10) when compared with placebo. A total of 91.1% in the Q4W arm and [REDACTED] in the Q8W group versus 40.9% with placebo arm. The odds ratios (OR) of achieving disease control were significantly higher for both dosing regimens. This being for donidalorsen Q4W an OR of 14.81 (95% CI: 3.90 to 56.14; $P < 0.001$) and for donidalorsen Q8W an OR of [REDACTED].¹¹

3.4 OASISplus trial methodology and results

The following section will outline the methods and results from the open label extension study OASISplus.

3.4.1 OASISplus study design and methods

OASISplus is an ongoing, open-label, multicentre extension study designed primarily to assess the long-term safety of donidalorsen in patients with HAE, with efficacy outcomes included as secondary or exploratory objectives. The study includes two distinct populations:

- An open-label extension (OLE) cohort comprising patients who completed the randomised OASIS-HAE trial, and
- A switch cohort enrolling patients who transitioned to donidalorsen from established long-term prophylactic (LTP) therapies, including lanadelumab, berotralstat, and C1-INH.

Patients completing OASIS-HAE were eligible to enrol in OASISplus, with 83 participants entering the OLE cohort.^{7, 52} Patients who withdrew from the OASIS-HAE trial due to a lack of efficacy after week 5 were also eligible to enrol in the OLE cohort.^{7, 52} Patients received donidalorsen 80 mg administered either every 4 weeks (Q4W) or every 8 weeks (Q8W). Importantly, treatment allocation in OASISplus was not randomised. All patients previously randomised to placebo or Q4W dosing in OASIS-HAE received Q4W dosing in the extension, while patients initially assigned to Q8W dosing were either maintained on Q8W or escalated to Q4W based on attack control during OASIS-HAE.⁷ This adaptive dosing approach, while clinically pragmatic, complicates interpretation of dose-specific long-term efficacy and safety. The second cohort in the OASISplus study was the switch cohort. The switch cohort enrolled 64 patients who transitioned from stable treatment with lanadelumab, berotralstat, or C1-INH to donidalorsen 80 mg Q4W. Patients were required to have received prior LTP therapy for at least 12 weeks before enrolment.⁵² The cohort is heterogeneous with respect to prior therapy, baseline attack rates, and disease control, which complicates interpretation of pooled efficacy results. In addition, the absence of a comparator arm and the lack of a formal washout period introduce

uncertainty regarding whether observed changes in attack rates reflect true treatment effects, residual effects of prior therapy, or natural fluctuation in disease activity.

The primary objective of OASISplus is long-term safety of donidalorsen in patients with HAE. Efficacy endpoints included investigator-confirmed HAE attack rates and patient-reported outcomes (AE-QoL and AECT).⁷ However, PROs were only reported up to Week 25, despite longer treatment exposure in a subset of patients. At the data cut-off (28 February 2024), only 7 patients (8.4%) had completed 52 weeks of treatment, indicating that long-term data remain immature.^{7, 52} Follow-up for efficacy outcomes in the switch cohort was limited to week 17, which is insufficient to characterise long-term outcomes or to fully assess safety, particularly for outcomes such as hepatic laboratory abnormalities that may emerge with prolonged exposure. The EAG notes that as an uncontrolled, unblinded study, OASISplus may be subject to multiple sources of bias, including selection bias, expectancy effects, and regression to the mean. Consequently, the study is not designed to provide robust comparative efficacy evidence, and its results should be interpreted as supportive and descriptive rather than confirmatory. Furthermore, the EAG clinical expert noted that as with the OLE nature of OASISplus, patients would be aware they are receiving a treatment. This may reduce anxiety and stress which the clinical expert noted were triggers for HAE attacks.

3.4.2 OASISplus results

In the OLE cohort, all enrolled patients received at least one dose of donidalorsen, with a mean exposure of approximately 228 days. While discontinuation rates (2) were low at the time of data cut-off, cumulative discontinuation data and reasons for discontinuation over longer follow-up were not fully characterised, limiting assessment of long-term treatment persistence.⁷ In the switch cohort, 89.2% of patients completed Week 16, with few early discontinuations. Four participants discontinued the study, of which 3 participants were from the lanadelumab cohort for reasons of adverse events, lost to follow up and not taking a dose, whilst one patient was from the C1-INH cohort who discontinued themselves.⁵² The EAG asked the company to provide cumulative discontinuation data from OASISplus (to the latest

data cut), whilst also providing the reasons for discontinuation (Clarification Question A10). The company responded with a new data cut of January 27, 2025. It was reported that a total of █ (████) participants discontinued early all participants were from the donidalorsen Q4W arm (n=█; █████). Reasons for early termination included █ participants withdrawal by subject (████), █ participants from adverse events (████) and █ participant for pregnancy (████). Discontinuation was higher in the switch cohort, with a total of █ participants (████) terminating early. This included █ participants who switched from lanadelumab (████) and █ participants who switched from C1-INH (████). The most common reason for early termination from those who switched from lanadelumab was lack of efficacy (n=█; █████).⁵³

Patients in the OLE cohort experienced sustained low HAE attack rates during open-label treatment. Relative to baseline attack rates observed in OASIS-HAE, reductions of 93% for Q4W dosing and 92% for Q8W dosing were reported.⁷ While these findings suggest maintenance of effect, interpretation may be limited by the lack of a comparator, and the non-randomised dosing strategy. In addition, it remains unclear whether attack rates were adjusted for baseline characteristics or prior prophylaxis exposure, which may influence long-term outcomes. In the switch cohort, donidalorsen treatment was associated with a mean 62% reduction in attack rate from baseline at Week 17. Reductions varied by prior LTP, with 73% for berotralstat, 65% for lanadelumab, and 41% for C1-INH, respectively.⁵² These subgroup differences may reflect heterogeneity in baseline disease control or prior treatment effectiveness rather than true differences in response to donidalorsen. The absence of a control group and the short duration of follow-up preclude conclusions regarding comparative effectiveness or long-term benefit following switching.⁵²

Improvements in AE-QoL exceeding the accepted minimal clinically important difference were reported in a high proportion of patients at Week 25, and more than 91% and 100% of patients were classified as having well-controlled disease based on AECT scores. However, the open-label design, absence of blinding, and incomplete long-term PRO data raise concerns regarding expectancy effects and reporting bias. Furthermore, PROs were not reported beyond Week 25 despite longer treatment exposure in some patients, limiting assessment of durability of patient-perceived benefit. OASISplus provides additional information on longer-term

exposure to donidalorsen. However, detailed longitudinal safety data, including hepatic laboratory abnormalities (ALT/AST), severity, and resolution over time, were limited at the current data cut-off. Therefore, the EAG requested hepatic safety results from the OASISplus trial (Clarification Question A9). The company responded stating that

OASISplus provides supportive evidence suggesting that donidalorsen's effects on HAE attack reduction and quality of life may be maintained over time and following switching from other prophylactic therapies. However, the open-label, uncontrolled design, short follow-up in the switch cohort, limited maturity of long-term data, and the safety and patient-reported outcomes limited to the latest cut-off substantially limit the strength of conclusions that can be drawn. The EAG considers OASISplus to be hypothesis-generating and supportive, but not sufficient to reduce uncertainty regarding long-term comparative effectiveness or safety.

The CS report that safety and tolerability of donidalorsen were assessed using data from OASIS-HAE, and the ongoing OLE, OASISplus. OASIS-HAE provides short-term, comparative safety data over a 24-week treatment period, while OASISplus contributes additional longer-term safety information in the absence of a comparator.

A summary of adverse events is reported in Table 11, whilst a breakdown of specific adverse events is reported in Table 12. Safety data from OASIS-HAE were collected over a mean exposure duration of approximately 24 weeks, with mean treatment

exposure of [REDACTED] days in the donidalorsen Q4W group and [REDACTED] days in the Q8W group. Overall, treatment-emergent adverse events (TEAEs) were common across all treatment arms, although the proportion of patients experiencing at least one TEAE was higher in the placebo group ([REDACTED]) compared with donidalorsen Q4W ([REDACTED]) and donidalorsen Q8W ([REDACTED]). Most TEAEs were reported as mild or moderate in severity, with severe TEAEs occurring infrequently across all arms.

A higher proportion of patients experienced TEAEs considered related to study drug in the donidalorsen Q4W group ([REDACTED]) compared with the Q8W group ([REDACTED]) and placebo ([REDACTED]). This difference appears to be driven primarily by injection-site reactions, which were more frequent with Q4W dosing ([REDACTED]) than with Q8W dosing ([REDACTED]) or placebo ([REDACTED]). All injection-site reactions were reported as non-serious, mild in severity, and self-limiting, with no associated treatment discontinuations. Headaches ([REDACTED]) and nasopharyngitis ([REDACTED]) were the most common TEAE in the placebo arm. Whilst influenza ([REDACTED]) followed by nasopharyngitis ([REDACTED]) were most common in the Q8W arm. In the Q4W arm, headache and injection site erythema were the most common TEAEs reported in [REDACTED] of participants.

Serious adverse events were uncommon. [REDACTED] serious adverse event occurred in the placebo group and was considered unrelated to study treatment. No serious adverse events related to donidalorsen were reported in either active treatment arm. [REDACTED] patient in the donidalorsen Q8W group discontinued treatment permanently due to a TEAE of elevated alanine aminotransferase (ALT), representing the only discontinuation attributed to an adverse event in the trial. While this event was isolated, the short duration of follow-up limits the ability to characterise the frequency and clinical significance of hepatic laboratory abnormalities.

No adverse events of special interest, including severe reductions in platelet count or bleeding events, were reported in any treatment arm during OASIS-HAE.

Table 11: Summary of adverse events in OASIS-HAE (safety population)

Safety outcome	Donidalorsen 80 mg Q4W (N=45) n (%)	Donidalorsen 80 mg Q8W (N=23) n (%)	Placebo (N=22) n (%)
Mean (SD) treatment exposure (days)			NA
Patients with any adverse event, n (%)			
Patients with any TEAE, n (%)			
Patients with any mild TEAE n (%)			
Patients with any moderate TEAE n (%)			
Patients with any severe TEAE n (%)			
Discontinuations due to TEAEs, n (%)			
Sources: CS, CSR and Riedl et al. (2024). ^{11, 47}			
Abbreviations: TEAE = treatment-emergent adverse events; SD = standard deviation			

Table 12: Most common TEAEs (>5% of patients in any treatment group), Safety set, OASIS-HAE

Preferred term ^a	Donidalorsen 80 mg Q4W (N=45) n (%)	Donidalorsen 80 mg Q8W (N=23) n (%)	Placebo (N=22) n (%)
Patients with any TEAE ^b , n (%)			
Headache			
Nasopharyngitis			
Urinary tract infection			1
Upper respiratory tract infection			

Preferred term ^a	Donidalorsen 80 mg Q4W (N=45) n (%)	Donidalorsen 80 mg Q8W (N=23) n (%)	Placebo (N=22) n (%)
Patients with at least 1 treatment emergent injection-site reaction	██████	██████	██████
Injection site erythema	██████	██████	█
Injection site discolouration	██████	██████	█
Injection site pruritus	██████	█	█
Injection site pain	██████	█	█
Abdominal discomfort	██████	█	█
Influenza	██████	██████	██████
Abdominal pain	██████	█	██████
Covid-19	██████	█	██████
Gastroenteritis	██████	██████	██████
Dyspepsia	█	█	██████
Limb injury	█	██████	██████
Oral herpes	█	██████	█
Sinusitis	█	█	██████
Vomiting	█	██████	██████
Based on Table 26 of the CS Abbreviations: AE – Adverse event; mg – milligrams; TEAE – Treatment-emergent adverse event ^a At each level of summation (overall, preferred term), patients reporting at least 1 relevant event were counted only once for the total incidence and for each treatment. ^b A TEAE was defined as any AE starting or getting worse on or after the first dose of the study drug Source: OASIS-HAE CSR¹¹			

3.5.2 OASISplus

OASISplus provides longer-term safety data for donidalorsen. However, interpretation may be limited by its open-label, uncontrolled design and selective enrolment of patients who completed OASIS-HAE. Patients could receive treatment for up to 157 weeks, although mean exposure at the February 2024 data cut was approximately 227 days overall, indicating that long-term safety data remain relatively immature for a treatment intended for lifelong use.

In the open-label extension cohort, 79.5% of patients experienced at least one TEAE, with a slightly higher incidence in the Q4W group (81.2%) compared with the Q8W group (71.4%). TEAEs related to study drug were reported in 23.2% of Q4W

patients and 14.3% of Q8W patients (Table 13). As in OASIS-HAE, the majority of events were mild or moderate in severity. No patients discontinued treatment due to TEAEs, and no serious adverse events were considered related to donidalorsen.

In the switch cohort, which included participants transitioning from placebo to active treatment, 70.3% experienced at least one TEAE, with 26.6% reporting TEAEs considered related to study drug. One serious adverse event leading to discontinuation was reported; however, this was attributed to complications of pre-existing congestive heart failure and was not considered related to donidalorsen.

While the OASISplus data do not identify new safety signals, the absence of a comparator, lack of blinding, and relatively limited cumulative exposure constrain the conclusions that can be drawn. In particular, the EAG notes that long-term hepatic safety and the evolution of laboratory abnormalities over extended treatment durations are not yet fully characterised. Consequently, although the safety profile observed to date appears acceptable, uncertainty remains regarding long-term safety, especially given the chronic nature of HAE prophylactic treatment.

The EAG notes that, safety data from OASIS-HAE and OASISplus suggest that donidalorsen is generally well tolerated in the short to medium term, with injection-site reactions representing the most common treatment-related adverse events and occurring more frequently with Q4W dosing. However, the short duration of randomised safety data, reliance on open-label extension data, and immaturity of long-term exposure limit confidence in the long-term safety profile. These limitations should be considered when interpreting the clinical evidence, particularly in the context of lifelong prophylactic treatment.

Table 13: Summary of adverse events in OASISplus (interim data safety population)

Safety outcome	OLE cohort Q4W (n=69)	OLE cohort Q8W (n=14)	Swich cohort (n=64)
Any TEAE n (%)	56 (81.2)	10 (17.4)	45 (70.3)
Any treatment-related TEAE, n (%)	16 (23.2)	2 (14.3)	17 (26.6)

Safety outcome	OLE cohort Q4W (n=69)	OLE cohort Q8W (n=14)	Swich cohort (n=64)
Patients with any mild TEAE n (%)	28 (40.6)	5 (35.7)	17 (26.6)
Patients with any moderate TEAE n (%)	26 (37.7)	4 (28.6)	5 (39.1)
Patients with any severe TEAE n (%)	2 (2.9)	1 (7.1)	3 (4.7)
Discontinuations due to TEAEs, n (%)	0 (0)	0 (0)	1 (1.6)
Sources: CS, Tachdjian et al. (2024) and Riedl et al. (2025) ^{7, 52} Abbreviations: TEAE = treatment-emergent adverse events; SD = standard deviation			

3.6 Critique of the indirect comparison or multiple treatment comparison

3.6.1 Company's feasibility assessment

A meta-analysis was not conducted as the key efficacy and safety data for donidalorsen comes from one pivotal study, OASIS-HAE, only, and since there are no head-to-head studies comparing donidalorsen to other LTPs, the company performed a network meta-analysis comparing outcomes for donidalorsen against berotralstat, lanadelumab, and plasma-derived IV C1-INHs.

The EAG requested the company's feasibility assessment for the NMA which was provided by the company in response to CQ A20. The critique of the company's feasibility assessment is as follows.

3.6.2 Studies included in the network meta-analysis

The company conducted an SLR in April 2025 to identify published trial data on the safety and efficacy of LTPs in patients 12 years or older with HAE. Of the 6,110 records that were initially identified, plus an extra 20 records identified through grey

literature, 74 articles were extracted and four were ultimately included in the NMA. These were:

- OASIS HAE: donidalorsen vs placebo
- APeX-2: berotralstat vs placebo
- HELP: lanadelumab vs placebo
- CHANGE: plasma-derived IV C1-INH vs placebo

The PICO criteria are presented in Table 2 of the company's feasibility assessment report v8.0, the PRISMA diagram in Figure 1, and the reasons for excluding studies in Table 3. A full critique of the company's search strategy is presented in section 3.1.

3.6.3 Critique of the network meta-analysis

In this section, the EAG presents the company's feasibility assessment of this NMA, detailing the baseline characteristics, methodology, outcomes, placebo-responses, and results of the company's NMA analyses.

3.6.3.1 Comparison of the study design of the included studies

The company provided a comparison of the study design of the four included studies in Table 6 of the feasibility report and is presented below (Table 14). OASIS-HAE, HELP, and APeX-2 were parallel in design, while the CHANGE study is a cross-over study with no washout period. In the context of long-term prophylactic treatments for HAE, the absence of a washout period raises concerns about potential residual treatment effects, particularly given the prolonged effects of C1-INH therapies. Such lingering effects may bias treatment effect estimates and challenge the assumption that outcomes observed in each period are independent.

The CHANGE study is limited by its relatively low sample size compared with the other trials included in the network, limiting statistical power and increasing the uncertainty around the treatment effect estimates which will contribute to wide credible intervals in the NMA.

It is unclear whether the CHANGE study was conducted as a multicentre trial, as this is not explicitly reported, despite being conducted in two countries. Differences in

trial timing may reflect changes in background standard of care, availability of on-demand treatments, diagnostic practices, or trial conduct over time. Such differences are not adjusted for in the NMA and may contribute to unobserved heterogeneity between studies.

There is no overlap in the study start and end dates between all four of the included studies. CHANGE was the earliest study, ending in 2009, while the next study to be conducted was HELP from 2016 to 2017, then APeX-2 in 2018 to 2019, and finally OASIS-HAE which was conducted in 2021 to 2023. The lack of overlap in study periods indicates that the trials were conducted over more than a decade, during which time there may have been changes in clinical practice, background standard of care, availability and use of on-demand treatments, and trial conduct, among others.

The treatment period was similar between the studies at 24 weeks, except for the HELP study which had a treatment period of 26 weeks. The only point of concern here is related to the cross-over nature of CHANGE since the 24 weeks consists of two 12-week periods which complicates the direct comparison of treatment periods and outcome timings relative to the parallel-group trials.

Overall, the four included studies exhibit differences in design that may impact the comparability of their results. These differences, coupled with incomplete reporting of baseline characteristics, may introduce heterogeneity and challenge the assumption of exchangeability across studies. While the company's random-effects NMA attempts to synthesis the available evidence, these design differences and the resulting between-study heterogeneity should be acknowledged when interpreting comparative efficacy results. The company's use of a random-effects Bayesian model helps to account for this heterogeneity and produce more realistic credible intervals.

Table 14. Comparison of study design between trials included in the NMA

	OASIS-HAE	HELP	APeX-2	CHANGE (Prophylaxis Trial)
Study design	Multicentre Placebo-controlled Parallel arm	Multicentre Placebo-controlled Parallel arm	Multicentre Placebo-controlled Parallel arm	Placebo-controlled Crossover
Phase	Phase 3	Phase 3	Phase 3	Phase 3
Randomisation	Yes	Yes	Yes	Yes
Blinding	Double-blind	Double-blind	Double-blind	Double-blind
Total sample size	90	125	121	22*
Start and end date	December 2021 to November 2023	March 2016 to April 2017 (first randomisation to last follow-up)	February 2018 April 2019 (study start to primary completion)	June 2006 to March 2009
Data cut-off				
Treatment period	24 weeks	26 weeks	24 weeks (placebo- controlled)	24 weeks (two 12-week crossover periods)
Total number of arms	3	4	3	4
Number of arms included in NMA	3	3	2	2
Intervention (bold denotes inclusion in company's NMA)	Donidalorsen 80mg Q4W Donidalorsen 80 mg Q4W	Lanadelumab 300 mg Q2W Lanadelumab 150 mg Q4W Lanadelumab 300 mg Q4W	Berotrastat 110 mg QD Berotrastat 150 mg QD	C1INH-nf 1000 IU BIW
Comparator	Placebo	Placebo	Placebo	Placebo
Method of administration	Subcutaneous	Subcutaneous	Oral	Intravenous
Site of treatment administration	Trial-site visits	Trial-site visits	Self-administered at home, with dosing instructed to occur at the same time each	Trial-site visits

	OASIS-HAE	HELP	APeX-2	CHANGE (Prophylaxis Trial)
			day with the largest meal, no parenteral administration was required	
Key inclusion/exclusion criteria	Inclusion: Were ≥12 years of age at screening, had a confirmed diagnosis of HAE Type I or Type II, had ≥2 investigator-confirmed HAE attacks during the run-in period, defined as 56 days to 1 day before randomisation, and provided written informed consent Exclusion: Patients with other forms of angioedema, including HAE with normal C1-INH, patients with comorbidities, prohibited medications were excluded	Inclusion: Were ≥12 years of age, had a confirmed diagnosis of HAE Type I or Type II, experienced ≥1 investigator-confirmed HAE attack per 4 weeks during the run-in period (4-week run-in; could be extended to 8 weeks if needed), were able to comply with study procedures Exclusion: Other forms of angioedema (including non-C1-INH-mediated angioedema), use of prohibited long-term prophylactic therapies during the study period (e.g. androgens, ACE inhibitors); short-term prophylaxis for procedures was permitted if medically indicated, significant comorbidities	Inclusion: Were ≥12 years of age (≥18 years in Europe), had Type I or Type II HAE due to C1-INH deficiency, confirmed by laboratory criteria (C1-INH function and C4 levels, with alternative genetic/family history criteria permitted), experienced ≥2 investigator-confirmed HAE attacks during the first 56 days of a prospective run-in period, had access to approved on-demand HAE therapy and were medically suitable for on-demand treatment alone during the study, demonstrated adequate diary compliance during screening Exclusion: use of androgen or tranexamic acid prophylaxis within 28 days of screening, use of C1-INH prophylaxis within 14 days of screening, comorbidities	Inclusion: Be ≥6 years of age, have a confirmed diagnosis of HAE due to C1-INH deficiency, supported by- low C4, normal C1q, low antigenic or functional C1-INH or a known pathogenic SERPING1 mutation. Acute-attack trial: present with an eligible acute attack meeting protocol criteria. Prophylaxis trial: Have a history of ≥2 attacks per month. Exclusion: Low C1q levels (to exclude acquired angioedema), history of B-cell malignancy, presence of anti-C1-INH antibodies, prior allergic reaction to C1-INH or plasma products pregnancy or narcotic addiction. For the acute-attack study, attacks were excluded if: Narcotics had been used in the preceding 7 days, androgen dose had recently increased, the attack was laryngeal (these were treated open-label).

	OASIS-HAE	HELP	APeX-2	CHANGE (Prophylaxis Trial)
How HAE reports were recorded	Reported by patients and required investigator confirmation to be included in efficacy analyses. Exact process of confirmation e.g., diaries, electronic reporting not detailed)	Reported by patients prospectively using a daily diary (onset date and time, symptoms, attack location, severity and use of on-demand treatment) and required investigator confirmation to be included in efficacy analyses	Reported by patients daily using an electronic diary (frequency, duration, location, functional impact, use of on-demand treatment). Investigators contacted patients within 2 business days of each reported attack to evaluate the event. Only investigator-confirmed attacks, defined by symptoms of swelling and meeting protocol criteria, were included in efficacy analyses	Acute-attack trial: Patients presented to the site during an attack, symptoms were assessed every 15 minutes after dosing, attacks were confirmed by investigators; questionable cases were reviewed by an independent blinded expert if laboratory findings (C4) were atypical. Prophylaxis trial: Patients kept a daily symptom diary documenting attacks throughout each 12-week period, all acute attacks were eligible for open-label rescue therapy and recorded
How severity was graded	Severity is categorised as moderate or severe but grading criteria not provided	Using a prespecified, ordinal clinical scale classified into four defined severity categories: mild, moderate, severe, very severe	Attack severity was assessed based on functional impairment, treatment requirement, and clinical features. For inclusion and baseline calculations, attacks had to: Require treatment, or require medical attention, or cause documented functional impairment. Severity was not reported using a multi-level ordinal scale in the main analysis; instead, functional impact	Acute-attack trial: At each affected site, severity was graded as none, mild, moderate, or severe. Only moderate or severe attacks involving eligible sites qualified for randomised treatment. Prophylaxis trial: Attack severity was scored on a 3-point scale: 1 = mild, 2 = moderate, 3 = severe. Mean severity per treatment period was a prespecified secondary endpoint

	OASIS-HAE	HELP	APeX-2	CHANGE (Prophylaxis Trial)
			and treatment requirement were central to severity classification	
Location	21 sites in countries in the European Union, 11 in North America, 5 in the Middle East, 2 in the United Kingdom	41 sites in Canada, Europe, Jodan, and the United States of America	40 sites in Canada, Europe, and the United States of America	Israel and United States of America
Funding	Ionis Pharmaceuticals	Dyax Corp (now Shire Human Genetic Therapies)	BioCryst Pharma Inc	Lev Pharma
*The Zuraw et al. 2010 publication featured two trials making up CHANGE: the Acute-Attack treatment Trial and the Prophylaxis Trial. The NMA included the Prophylaxis trial only. Abbreviations: BIW = twice a week; HAE = Hereditary angioedema; IU = international units; mg = Milligrams; Q2W = every two weeks; Q4W = every four weeks; QD = daily				

3.6.3.2 Treatments and administration

There are notable differences in the method and frequency of treatment administration across the four included studies (Table 15). Donidalorsen and lanadelumab were both administered subcutaneously, while berotralstat was given orally and C1INH-nf intravenously. Within the HELP study, although the lanadelumab Q4W group was dosed every four weeks, patients in this group received placebo injections during the intervening weeks, effectively maintaining a two-weekly injection regimen like the Q2W group. These differences in administration may influence adherence, tolerability, and patient experience, and should be considered when comparing treatments across studies.

Table 15: Comparison of treatment administration

Trial	Intervention	Timing	Dose	Comparator	Method of administration
OASIS-HAE	Donidalorsen	Q4W	80 mg	Placebo	Subcutaneous
		Q8W	80 mg		
HELP	Lanadelumab	Q2W	300 mg	Placebo	Subcutaneous
		Q4W	300 mg		
APeX-2	Berotralstat	QD	110 mg	Placebo	Oral
			150 mg		
CHANGE	C1INH-nf	BIW	1000 IU	Placebo	Intravenous
Abbreviations: BIW = twice a week; IU = international units; mg = Milligrams; Q2W = every two weeks; Q4W = every four weeks; QD = daily					

3.6.3.3 Comparison of Baseline Characteristics and TEMs

The company provided information on the availability and a comparison of the baseline characteristics of the four included studies in Table 9 and Table 10 of the feasibility report, respectively, which were collected in Table 16 along with the berotralstat 110 mg arm from APeX-2 and the lanadelumab 150 mg Q4W arm from HELP despite these two arms not being included in the NMA.

Comparisons within studies

In the OASIS-HAE trial, there were a few imbalances in baseline characteristics despite randomisation. In particular, the proportion of male patients in the placebo arm (63.6%) was notably higher than the two donidalorsen arms (37.8% and 47.8%), and the prior exposure to C1-esterase inhibitor treatment appeared lower in the placebo arm (31.8%) compared to the active treatment arms (48.9% and 56.5%). Smaller imbalances were observed between arms for prior prophylactic treatment, attacks in 12 months prior to screening, and run-in attack rates.

In APeX-2, moderate differences between arms were observed for age, previous androgen, and previous C1-INH treatment. In CHANGE, major differences in previous androgen treatment, proportion of males, and minor differences in mean age. In HELP, with major differences in the proportion of males and previous C1-INH treatment, and minor differences laryngeal attack history.

Comparisons between studies

The EAG identified several differences that may challenge the transitivity assumption underpinning the NMA. The proportion of male patients varied between studies, ranging from 17.5% in the placebo arm of HELP to 63.6% in the placebo arm of OASIS-HAE, however the EAG notes that all the other arms had majority (over 50%) women recruited. Ethnic composition also differed between studies. While all the studies recruited predominantly white patients, some trials recruited a high proportion of Black/African American patients, while others recruited Asians or Native Americans. In addition, the geographic region of enrolment was only reported in HELP and APeX-2 and varied slightly. While most patients were recruited from North America (Canada or the United States), the proportion of patients enrolled from Europe varied considerably, ranging from 13.8% to 32.5%, potentially introducing differences in clinical practice and management of HAE.

Prior treatment exposure differed notably between studies, particularly with respect to previous prophylactic treatment and prior C1-INH use, which ranged from around 32% to 62%. The use of concomitant and on-demand medications at baselines also varied between studies, with some trials reporting no on-demand treatment use at baseline, while others reported use in most patients. Furthermore, measures of disease severity differed across trials, including the number of HAE attacks in the 12

months prior to screening, which were reported using different summary measures (mean vs median) and spanned a wide range of values, suggesting differences in baseline disease burden between study populations.

The interpretation of these between-study differences is further limited by incomplete and inconsistent reporting of baseline characteristics, with several variables not reported mainly in APeX-2 and CHANGE. This lack of comprehensive reporting restricts the ability to fully assess population comparability and increases uncertainty around the validity of the NMA.

The company highlighted these differences in the NMA Feasibility Assessment v8.0 report and stated that a “network meta regression will be considered to adjust for moderate heterogeneity of TEMs if sufficient data are available”. However, the 2019 appraisal of lanadelumab (TA606) had an NMA which included the CHANGE study, and a published NMA by Watt et al. 2023⁵⁵ included HELP, APeX-2, and CHANGE. In TA606, the EAG accepted the NMA and used it for the base-case. In the published NMA, the authors discussed limitations related to residual heterogeneity and differences in study design, therefore advising caution in its interpretation. The company’s advisors concluded that the studies were similar enough to allow comparison.

In this submission, despite similar limitations being present, the company did not explore alternative analytical approaches, such as network meta-regression to adjust for important TEMs or a population-restricted network, at the time of original submission and instead concluded that the studies were sufficiently similar to support comparison. This judgement relies on qualitative assessment alone and is not supported by additional quantitative analyses, contributing further uncertainty to the NMA results.

Table 16: Baseline characteristics of studies included in the NMA

Study	OASIS-HAE			HELP				APeX-2			CHANGE	
Arm	Doni Q4w	Doni Q8w	Placebo	Lana Q2W	Lana 300mg Q4W	Lana 150mg Q4W	Placebo	Bero 110mg	Bero 150mg	Placebo	Placebo -> C1INH-nf	C1INH-nf -> placebo
N	45	23	22	27	29	28	41	41	40	40	11	11
Age												
Mean (SD)	39.6 (15.23)	34.1 (13.22)	35.4 (11.03)	40.3 (13.3)	39.5 (12.8)	42.4 (14.9)	40.1 (16.8)	40.4 (17.5)	40.0 (14.0)	44.5 (14.1)	41.7 (19.3)	34.5 (14.8)
12 to 17	4 (8.9%)	3 (13.0%)	0 (0.0%)	2 (7.4%)	3 (10.3%)	1 (3.6%)	4 (9.8%)	NR	NR	NR	NR	NR
18 to 39	19 (42.2%)	12 (52.2%)	15 (68.2%)	25 (92.6%)	26 (86.7%)	24 (85.7%)	35 (85.4%)	NR	NR	NR	NR	NR
40 to 64	21 (46.7%)	7 (30.3%)	7 (31.8%)					NR	NR	NR	NR	NR
≥ 65	1 (2.2%)	1 (4.3%)	0	0	0	3 (10.7%)	2 (4.9%)	NR	NR	NR	NR	NR
Male	17 (37.8%)	11 (47.8%)	14 (63.6%)	12 (44.4%)	10 (34.5%)	8 (28.6%)	7 (17.1%)	11 (27%)	17 (42%)	13 (32%)	2 (18.2%)	0 (0%)
BMI (SD)	28.03 (6.738)	26.97 (5.396)	28.88 (9.216)	31.0 (7.8)	28.1 (5.1)	26.9 (4.7)	27.5 (7.7)	27.5 (7.3)	30.4 (6.7)	29.3 (6.8)	NR	NR
Ethnicity												
White	42 (93.3%)	22 (95.7%)	18 (81.8%)	26 (96.3%)	23 (79.3%)	25 (89.3%)	39 (95.1%)	38 (93%)	38 (95%)	37 (93%)	10 (90.9%)	11 (100%)
Asian	1 (2.2%)	0	0	0	0	2 (7.1%)	0	NR	NR	NR	0	0
Black/African American	1 (2.2%)	0	1 (4.5%)	1 (3.7%)	6 (20.7%)	1 (3.6%)	2 (4.9%)	NR	NR	NR	1 (9.1%)	0

Study	OASIS-HAE			HELP				APeX-2			CHANGE	
Arm	Doni Q4w	Doni Q8w	Placebo	Lana Q2W	Lana 300mg Q4W	Lana 150mg Q4W	Placebo	Bero 110mg	Bero 150mg	Placebo	Placebo -> C1INH-nf	C1INH-nf -> placebo
American Indian/ Alaskan Native	0	1 (4.3%)	2 (9.1%)	0	0	0	0	NR	NR	NR	0	0
Multiple	0	0	1 (4.5%)	0	0	0	0	NR	NR	NR	0	0
Other	1 (2.2%)	0	0	0	0	0	0	NR	NR	NR	0	0
Region of enrolment												
Europe	NR	NR	NR	7 (25.9%)	4 (13.8%)	NR	12 (29.3%)	9 (22.0%)	13 (32.5%)	12 (30.0%)	NR	NR
Jordan	NR	NR	NR	0	1 (3.4%)	NR	1 (2.4%)	0	0	0	NR	NR
North America	NR	NR	NR	20 (74.1%)	24 (82.8%)	NR	28 (68.3%)	32 (78.0%)	27 (67.5%)	28 (70.0%)	NR	NR
HAE Type												
Type I	42 (93.3%)	22 (95.7%)	20 (90.9%)	23 (85.2%)	27 (93.1%)	25 (89.3%)	38 (92.7%)	NR	NR	NR	9 (82.2%)	9 (82.2%)
Type II	3 (6.7%)	1 (4.3%)	2 (9.1%)	4 (14.8%)	2 (6.9%)	3 (10.7%)	3 (7.3%)	NR	NR	NR	2 (18.2%)	2 (18.2%)
Previous family history of HAE: Yes	41 (91.1%)	20 (87.0%)	17 (77.3%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Age of symptom onset	11.6 (9.85)	10.9 (7.73)	12.9 (7.19)	15.0 (8.7)	14.6 (11.2)	12.0 (8.8)	11.2 (8.2)	NR	NR	NR	NR	NR

Study	OASIS-HAE			HELP				APeX-2			CHANGE	
Arm	Doni Q4w	Doni Q8w	Placebo	Lana Q2W	Lana 300mg Q4W	Lana 150mg Q4W	Placebo	Bero 110mg	Bero 150mg	Placebo	Placebo -> C1INH-nf	C1INH-nf -> placebo
HAE attack history												
Peripheral	43 (95.6%)	22 (95.7%)	20 (90.9%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Abdominal	43 (95.6%)	22 (95.7%)	20 (90.9%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Laryngeal	22 (48.9%)	13 (56.5%)	2 (54.5%)	20 (74.1%)	17 (58.6%)	17 (60.7%)	27 (65.9%)	NR	NR	NR	NR	NR
Previous prophylactic treatment = Yes	6 (13.3%)	5 (21.7%)	5 (22.7%)	Oral: 0 (0%) Combi: 3 (11.1%)	Oral: 1 (3.4%) Combi: 1 (3.4%)	Oral: 2 (7.1%) Combi: 1 (3.6%)	Oral: 1 (2.4%) Combi: 1 (2.4%)	32 (78.0%)	30 (75.0%)	29 (72.5%)	NR	NR
Previous androgen treatment = Yes	NR	NR	NR	NS	NS	NR	NR	19 (46.0%)	21 (53%)	25 (63%)	2 (18.2%)	1 (9.1%)
Previous C1-INH treatment = Yes	48.9%	56.5%	31.8%	11 (40.7%)	18 (62.1%)	9 (32.1%)	22 (53.7%)	16 (39.0%)	21 (53%)	16 (40%)	NR	NR
Other prior treatments												
Icatibant acetate	46.7%	39.1%	50.0%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Icatibant	13.3%	21.7%	22.7%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Paracetamol	20.0%	13.0%	4.5%	NR	NR	NR	NR	NR	NR	NR	NR	NR

Study	OASIS-HAE			HELP				APeX-2			CHANGE	
Arm	Doni Q4w	Doni Q8w	Placebo	Lana Q2W	Lana 300mg Q4W	Lana 150mg Q4W	Placebo	Bero 110mg	Bero 150mg	Placebo	Placebo -> C1INH-nf	C1INH-nf -> placebo
Concomitant medication								NR	NR	NR	NR	NR
Any on demand	0.0%	0.0%	0.0%	85.2%	93.1%	NR	90.2%	NR	NR	NR	NR	NR
Any supportive treatment	0.0%	0.0%	0.0%	14.8%	6.9%	NR	12.2%	NR	NR	NR	NR	NR
C1 esterase inhibitors	37.8%	52.2%	50.0%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ecallantide	0.0%	0.0%	0.0%	3.7%	20.7%	NR	4.9%	NR	NR	NR	NR	NR
Ibuprofen	22.2%	34.8%	22.7%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Icatibant	22.2%	13.0%	27.3%	48.1%	44.8%	NR	53.7%	NR	NR	NR	NR	NR
Icatibant acetate	35.6%	39.1%	50.0%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nano filtered/plasma-derived C1 inhibitor	0.0%	0.0%	0.0%	44.4%	48.3%	NR	53.7%	NR	NR	NR	NR	NR
Paracetamol	24.4%	34.8%	31.8%	NR	NR	NR	NR	NR	NR	NR	NR	NR
HAE attacks prior to screening												
Attacks 12m before screening	45.7 (43.0)	33.3 (22)	29.1 (21.1)	median (IQR): 20 (8-36)	median (IQR): 24 (12-50)	Median (IQR): 34 (12-55)	median (IQR): 30 (17-59)	NR	NR	NR	NR	NR

Study	OASIS-HAE			HELP				APeX-2			CHANGE	
Arm	Doni Q4w	Doni Q8w	Placebo	Lana Q2W	Lana 300mg Q4W	Lana 150mg Q4W	Placebo	Bero 110mg	Bero 150mg	Placebo	Placebo -> C1INH-nf	C1INH-nf -> placebo
Attacks during run-in period	3.6 (2.2)	3.2 (2.1)	2.9 (1.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baseline monthly attack rate	NR	NR	NR	3.5 (2.3)	3.7 (2.5)	3.2 (1.8)	4.0 (3.3)	2.97 (1.36)	3.06 (1.56)	2.91 (1.12)	NR	NR
Abbreviations: BMI = body mass index; C1 esterase inhibitors = C1 esterase inhibitor therapies; C1-INH = C1 esterase inhibitor; C1INH-nf = nano filtered plasma-derived C1 esterase inhibitor; Combi = combination therapy; Doni = donidalorsen; HAE = hereditary angioedema; IQR = interquartile range; Lana = lanadelumab; Mean = mean; mg = milligrams; NR = not reported; NS = not stated; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SD = standard deviation												

Treatment effect modifiers

The EAG requested the company for information regarding any differences in distribution of treatment effect modifiers (TEMs) across studies. If differences did not exist, then the NMA approach would be appropriate. The company provided this information in section 3.2.2 of the Feasibility Assessment report v8.0.

The company provided the following list of TEMs based on the previously mentioned NMA by Watt et al. 2023 with some additional TEMs: age, sex, ethnicity, HAE type, family history of HAE, BMI, age of symptom onset, number of HAE attacks, and type of HAE attack experienced. Additionally, the EAG's clinical experts identified mean baseline attack rate as one of the most important TEMs, which most aligns with mean run-in period attack rate per 4 weeks from the reported baseline characteristics.

A review of the available baseline data shows that several of the identified TEMs were not evenly distributed across the four included studies. Differences were observed in sex distribution, baseline disease severity, and prior treatment exposure, including previous prophylaxis and C1-esterase inhibitor use. Mean baseline attack rate also varied across studies and was inconsistently reported. For other TEMs, reporting was incomplete or unavailable for some studies, limiting assessment of their distribution across the four included studies.

The EAG asked the company in CQ A26 if a multi-level network meta-regression (ML-NMR) was considered due to the availability of IPD for OASIS-HAE and the potential imbalance in TEMs across studies. (The EAG was not provided with the distribution of TEMs prior to clarifications.) The company stated in their response that an ML-NMR was considered but deemed inappropriate, primarily on the grounds that it would introduce, rather than solve, the additional uncertainty around between-study differences. However, this conclusion is largely qualitative and is not supported by exploratory analyses demonstrating the magnitude of such uncertainty or the feasibility of alternative analyses. While the company highlighted several methodological constraints, including baseline adjustment in least-squares means, network sparsity, and issues in outcome distribution, no formal sensitivity analyses or partial adjustments were presented to assess the impact of the identified treatment effect modifiers on the NMA results.

As a result, although the company concluded that a conventional NMA represents the most robust approach given the available data, uncertainty arising from imbalances in key treatment effect modifiers remains unaddressed. This residual uncertainty is particularly relevant given the subsequent assumption of equal efficacy across treatments in the economic model, which relies heavily on the validity of the NMA results.

3.6.3.4 Comparison of outcomes used in the network meta-analysis

The company presented the outcomes of interest that were under consideration for synthesis in the NMA Feasibly Assessment report section 3.4. After assessing which outcomes were reported in all four studies (Table 12 of NMA Feasibility report), the following outcomes, which includes the widest range of LTP comparators, were included in the NMA:

- The mean number of HAE attacks per month
- Percentage reduction in HAE attacks from baseline (50%, 70%, 90%)
- Severity of HAE attacks
- Use of on-demand medication
- Change in the total AE-QoL score

The results for each study are presented in Table 13 of the company's NMA report. Across the included trials, efficacy outcomes were reported using broadly similar constructs (such as attack frequency and severity) but with differences in estimands and summary measures. These differences in outcome definition, normalisation, and follow-up duration limit comparability of absolute effects and may potentially contribute to between-study heterogeneity. While these variations should not greatly affect the NMA, being placebo-anchored, it increases uncertainty in the estimated treatment effects and complicates interpretation of non-significant differences as evidence of equivalence between interventions.

3.6.3.5 Placebo responses

The company did not present a comparison of placebo response across studies, stating that variation in baseline risk does not determine NMA feasibility and is addressed using a random-effects model. While this is methodologically correct in

principle, the absence of a descriptive comparison of placebo outcomes limits assessment of transitivity and interpretability of the results.

In this network, all treatments are connected exclusively through placebo, with one study per comparison and no multi-study closed loops, meaning that differences in placebo response directly influence all indirect comparisons. Although a random-effects model can reflect unexplained heterogeneity through wider credible intervals, it does not explain the sources of, or adjust for, systematic differences in baseline risk. A descriptive assessment of placebo attack rates and follow-up duration would therefore have been informative for contextualising the NMA results and the subsequent assumption of equal efficacy in the economic model, even if it did not alter the feasibility of conducting the NMA.

The EAG extracted the exact placebo responses as presented in the CS for OASIS-HAE and the respective publications for placebo in the comparator studies in Table 17. While the placebo arms generally reflect the same direction of effect, the absolute rates differ across trials, reflecting underlying heterogeneity in baseline disease activity and study design. These differences are relevant for interpreting the NMA, as all active treatments are connected through placebo, meaning that variation in placebo response contributes directly to heterogeneity in the relative treatment effect estimates.

Table 17: Efficacy results of placebo arms included in the NMA with adjustment

Placebo responses	OASIS-HAE (N=22)	HELP (N=41)	APeX-2 (N=40)	CHANGE (N=22)
Mean number of HAE attacks per month	2.26 (1.66 to 3.09)	1.97 (1.64 to 2.36)	2.35	3.1825*
Mean number of moderate or severe HAE attacks per month	1.15 (0.72 to 1.83)	1.99 (1.65 to 2.39)	NA	NA
Proportion of patients achieving ≥50% reduction in HAE attacks from baseline	6 (27.3%)	13 (31.7%)	10 (25.1%)	NA
Proportion of patients achieving ≥70% reduction in HAE attacks from baseline	4 (18.2%)	4 (9.8%)	6 (15.1%)	NA

Proportion of patients achieving $\geq 90\%$ reduction in HAE attacks from baseline	2 (9.1%)	2 (4.9%)	3 (7.49%)	NA
Mean number of HAE attacks requiring on-demand medication	1.80 (1.23 to 2.62)	1.64 (1.34 to 2.00)	NA	NA
Mean change from baseline in AE-QoL score		-4.62 (-10.46 to 1.02)	-9.69 (2.64)	NA
Data presented as mean rate (95% CI) or mean rate (SD)				
*Estimated by digitising Figure 2 of Zuraw et al. 2010 over 12 weeks and converting to monthly				

3.6.4 Network meta-analysis methods and assumptions

The company's NMAs were conducted using the 'multinma' package in R. This package uses a Bayesian framework to fit fixed and random-effects NMA models and can incorporate individualised patient data (IPD) and aggregate data (AgD) to generate absolute and relative treatment effects. The EAG requested the company's statistical analysis plan (SAP) which included the methods for the NMA which was provided by the company in response to CQ A19. Section 5 of the SAP details the statistical methods used for the NMA.

Outcomes were of three types: count data, binary, and continuous. Each of these require different model forms, described in section 5.2.1 of the company's NMA SAP. The EAG agrees with the company regarding the model specification for the different outcomes analysed.

Priors used

The company used vague normal priors to assess the trial-specific baseline log attack rate (intercept) and the relative treatment effect (log rate ratios). A weakly informative, empirically derived prior was specified for the between-study variance. This log-normal prior on the heterogeneity variance was taken from Turner et al. 2015⁵⁶ study of 14,886 binary-outcome meta-analyses, and corresponds to the heterogeneity estimates observed in pharmacological versus placebo/control comparisons, informed from a total of 5,599 meta-analyses. For the QoL outcome, the prior for quality of life/functioning was used from Turner et al. 2015.

While the use of an informative heterogeneity prior is consistent with NICE recommendations, the company did not report whether alternative priors for treatment effects or heterogeneity were explored in sensitivity analyses. Exploration of alternative plausible prior specifications would be important to assess the robustness of the NMA results, particularly given the sparse network and the subsequent assumption of equal efficacy.

The EAG reran the company's NMA with different priors, shown in Table 18, to explore the robustness of the results. Narrowing the treatment-effect priors (Scenarios 1 and 2) produced slightly narrower credible intervals for the active treatments, but point estimates remained largely unchanged, indicating that the results are relatively insensitive to plausible variation in treatment-effect priors. Adjusting the heterogeneity prior had a more noticeable impact. A conservative half-normal prior on tau (Scenario 3) increased the estimated between-study heterogeneity, which in turn pulled the placebo response closer to the active treatments and widened the credible intervals. Conversely, assuming a higher expected heterogeneity through a less informative log-normal prior (Scenario 4) had minimal effect on the point estimates. Modifying the baseline rate prior (Scenario 5) produced negligible changes, suggesting the network is not sensitive to the intercept prior. Overall, these analyses demonstrate that the assumption of broadly similar efficacy between active treatments is robust across a range of plausible prior specifications, but highlights that estimates in this sparse, placebo-anchored network are particularly influenced by assumptions about heterogeneity.

Table 18: EAG's exploration of using different priors on the company's NMA

Scenario	Baseline rate	Treatment effects	Heterogeneity
Company submission	Normal (0, 100 ²)	Normal (0, 100 ²)	LogNormal (-2.06, 1.512)
1: More informative treatment-effect prior	Normal (0, 100 ²)	Normal (0, 2.5²)	LogNormal (-2.06, 1.512)
2: Stronger prior of treatment effects	Normal (0, 100 ²)	Normal (0, 1.5²)	LogNormal (-2.06, 1.512)
3: Conservative heterogeneity prior	Normal (0, 100 ²)	Normal (0, 100 ²)	Half-Normal (1)
4: Higher expected heterogeneity	Normal (0, 100 ²)	Normal (0, 100 ²)	LogNormal (-1.5, 1.0)
5: More informative baseline rate prior	Normal (0, 5²)	Normal (0, 100 ²)	LogNormal (-2.06, 1.512)

NMA assumptions

The assumption of similarity requires that the included studies are sufficiently comparable with respect to patient populations, interventions, and outcomes, so that

any differences in treatment effects are attributable to the treatments themselves rather than study characteristics. The EAG noted some potential concerns, including differences in study populations, timing of intervention, and prior treatment exposure, which could affect similarity.

Homogeneity assumes that within each direct comparison, the true treatment effect is the same across studies, with an observed variation due only to random error.

Given that two studies are 2-arm, and two studies are 3-arm, all compared to placebo, formal tests of heterogeneity are limited, but the random-effects Bayesian NMA partly accounts for between-study variability.

The formal testing of the consistency assumption was not undertaken. The only loops in the network arise from the two 3-arm trials, OASIS-HAE and HELP. The other two studies are single-arm comparisons to placebo. Since these loops are entirely contained within individual trials, there are no independent indirect comparisons to evaluate against direct evidence.

While internal consistency within the 3-arm trials is ensured by randomisation, residual uncertainty remains regarding the comparability of populations and study designs across trials, which should be considered when interpreting the NMA results.

NMA inputs

Examination of the NMA inputs suggests that different estimands were used across trials. For OASIS-HAE, attack rates for donidalorsen were derived from least-squares mean (LSM) time-normalised estimates. HELP calculated the mean attacks per month using a Poisson regression model, APeX-2 used a negative binomial model, and CHANGE calculated attack rate as total number of attacks divided by the number of days the patient participated in that trial period. This mixing of model-based and crude estimands within a placebo-anchored sparse network likely contributes to the wide credible intervals observed and limits the ability of the NMA to support assumptions of equal efficacy.

Model diagnostics

The EAG requested model diagnostics for the NMAs in CQ A21 in order to assess the adequacy of model fit, the plausibility of the assumptions, and the robustness of the estimated relative treatment effects.

The company presented goodness-of-fit, between-study heterogeneity (tau), surface under the cumulative ranking (SUCRA) values, posterior treatment ranks, and R-hat values for each NMA. The EAG examined the model diagnostics for each NMA outcome to assess goodness-of-fit, convergence, and heterogeneity. Overall, residual deviance indicated an adequate fit for most outcomes, with all models showing convergence ($R_{\text{hat}} \approx 1$). Between-study heterogeneity, as measured by tau, was generally low to moderate. For most outcomes, SUCRA values overlapped across treatments, suggesting no clear ranking, except for the $\geq 50\%$ reduction in HAE attacks, where lanadelumab appeared meaningfully superior. The AE-QoL outcome showed $\tau = 0.15$ between-study heterogeneity ($\tau = 0.15$), indicating $\tau = 0.15$ results across studies.

3.6.5 Results of the company's network meta-analysis

The company presented the base case random-effects NMA results in section 2.10.4 of the CS and section 3.5 of the NMA Feasibility Assessment v8.0 report. The results are summarised below.

Figure 1 presents the general shape of the network; however, C1INH-nf was only included for the analysis of the mean number of HAE attacks per month outcome, and berotralstat was not included in the analysis of the mean number of moderate or severe HAE attacks per months and mean number of HAE attacks requiring on-demand medication outcomes.

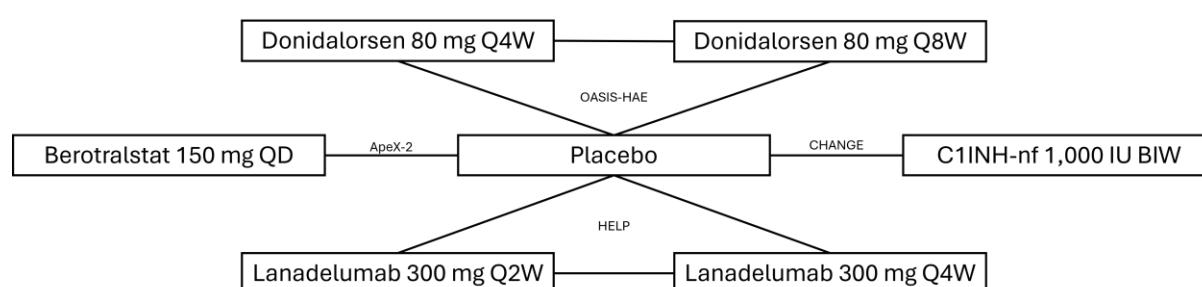


Figure 1. Shape of company's NMA when all studies are included

3.6.5.1 Base case NMA

$\tau = 0.15$ were observed between the reference treatment, donidalorsen 80mg Q4W and the other active treatments across most of the outcomes (Table 19). Meaningful differences (where the 95% credible intervals (CrI)

included 1 for odds/rate ratios and 0 for mean difference) were observed for the following outcomes and treatments.

Both lanadelumab arms had [REDACTED] for the proportion of patients achieving at least a 50% reduction in HAE attacks compared to donidalorsen Q4W, and these 95% Crls [REDACTED] despite being [REDACTED]. This result is expected since all the patients in the lanadelumab arms achieved this endpoint.

According to the company's results in Table 23 of the CS, a

[REDACTED]

[REDACTED], as indicated by the Crls of the mean difference which do not include 0.

.

Table 19: Full results of the company's NMA compared to the reference treatment (donidalorsen Q4W)

	Placebo	Donidalorsen Q8W	Lanadelumab Q2W	Lanadelumab Q4W	Berotralstat	C1INH-nf
HAE attacks						
Moderate or severe HAE attacks						
Proportion achieving ≥50% reduction in HAE attacks						
Proportion achieving ≥70% reduction in HAE attacks						
Proportion achieving ≥90% reduction in HAE attacks						
HAE attacks requiring on-demand medication						
Mean change from baseline in AE-QoL score						
Bold denotes statistically meaningful result						

3.6.5.2 Sensitivity analyses

The company presented sensitivity analyses for the base case NMA results in response to CQ A23 where the EAG wanted to check if the robustness of the NMA was tested (Table 20). The company presented NMA results for the following:

- Excluding CHANGE since it was not captured in the SLR and was used as a proxy for IV Berinert. This only affected the mean attacks per month outcome.
- Analysing the efficacy of donidalorsen, lanadelumab, and berotralstat in each trial's steady state period. Results for the mean attacks per month were available from all three studies, while results for the mean number of moderate or severe attacks, and the mean number of attacks requiring on-demand medication were available from OASIS-HAE and HELP only.

The results of the first sensitivity analysis, removing the CHANGE study, resulted in [REDACTED] median HAE attack rate ratios as the base case NMA with [REDACTED] CrIs. The second sensitivity analysis for this outcome produced [REDACTED], with results [REDACTED] donidalorsen Q4W [REDACTED] except the comparison to [REDACTED] [REDACTED].

The other comparisons from the second sensitivity analysis resulted in [REDACTED] conclusions to the base case NMA; due to [REDACTED] 95% CrIs, there were [REDACTED] between the active treatments, though the median rate ratios [REDACTED] for the moderate or severe HAE attacks outcome for all treatments. Furthermore, placebo was [REDACTED] to donidalorsen in this analysis.

Table 20: Results of the company's NMA sensitivity analyses

	Placebo	Donidalorsen Q8W	Lanadelumab Q2W	Lanadelumab Q4W	Berotralstat
SA1: HAE attacks	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
SA2: HAE attacks	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
SA2: Moderate or severe HAE attacks	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	

	Placebo	Donidalorsen Q8W	Lanadelumab Q2W	Lanadelumab Q4W	Berotrastat
SA2: HAE attacks requiring on-demand medication					

3.6.6 Implications of assuming equal efficacy in the economic model

The company concluded from the NMA that the assumption of equal efficacy of the active comparators is clinically appropriate, and expanded on this in section 3.3.1.3 of the CS. The company's NMA did not identify statistically meaningful differences in efficacy between donidalorsen Q4W and the compactor long-term prophylactic treatments across most outcomes, as evidenced by wide and overlapping 95% credible intervals. While this indicates substantial uncertainty in the relative treatment effects, it does not necessarily constitute evidence of equivalence between treatments.

The interpretation of the NMA is further complicated by heterogeneity in study design, patient populations, and baseline characteristics across trials, as well as the sparse network which is anchored only by the placebo arm of each trial. These limitations contribute to the wide Crls and reduce the ability of the NMA to distinguish between treatments. While the company conducted feasibility assessments and two sensitivity analyses, residual heterogeneity remains a concern.

The company's assumption of equal efficacy appears to be based primarily on the lack of meaningful differences in the NMA and further backed by clinical expert opinion, seemingly beyond what the evidence can support. The wide and overlapping Crls reflects limited precision rather than evidence of equivalence. Formal equivalence or non-inferiority was not assessed, and no margins were prespecified to justify collapsing treatment effects. This approach therefore risks overstating confidence in relative efficacy estimates and obscures plausible differences suggested by point estimates and sensitivity analyses. As a result, the cost-comparison framework is conditional on an assumption that is stronger than what the statistical evidence alone can substantiate, and the implications of residual uncertainty in relative treatment effects are not propagated through the economic results.

3.6.7 EAG's replication of company's base case NMA

The EAG requested a sample of the R code and data used by the company to replicate and validate the company's NMA. The company provided the code and the data for the mean HAE attacks outcome in response to CQ A22. The EAG used the results provided the CS, the NMA Feasibility Assessment report, and the publications of the comparator treatments to extract the results for the other outcomes used in the NMA.

The EAG then reran the company's base case NMA and produced similar results, differing only due to minor differences in computational implementation and the default prior distributions used in the Bayesian model. The only exception is the moderate or severe HAE attacks outcome where the EAG's replication resulted in rate ratios higher than the company's, strengthening the effect of donidalorsen Q4W over the other treatments. The EAG used the LSM-derived estimates from OASIS-HAE, HELP, and APeX-2 when running this NMA. Though the results were not meaningfully different to the company's, the differences likely reflect the sparse structure of the network, reliance on single studies per comparison, and sensitivity of this outcome to small changes in model specification and estimation approach, rather than substantive differences in the underlying data.

3.6.8 Conclusion of the company's NMA

Overall, the EAG considers the company's NMA to be methodologically sound and conducted in line with NICE DSU guidelines. The EAG's replication of the NMAs and exploration of alternative priors produced consistent results to those reported by the company, with no material differences in conclusions across outcomes.

However, the network is sparse and only anchored by the placebo arm from each trial, and further limited by heterogeneity in study design, patient populations, outcome definitions, and estimands, which together result in wide CrIs and uncertainty in relative treatment effects.

The absence of statistically meaningful differences between active treatments in this context reflects limited precision rather than evidence of equal efficacy. Therefore, while the NMA provides a useful synthesis of the available evidence, it does not robustly support a strong assumption of equal efficacy across long-term prophylactic

treatments. The EAG therefore considers that conclusions drawn from the NMA, and any economic modelling assumptions that rely on equal efficacy, should be interpreted with caution.

3.7 Additional work on clinical effectiveness done by the EAG

Considering NICE's stance on the inclusion of garadacimab in the company's network, the EAG included garadacimab in the company's NMA. The EAG undertook additional work to assess the quality of the VANGUARD trial using the Cochrane Risk of Bias 2 tool (RoB 2) (Table 21). This was undertaken because, although a quality appraisal using a checklist adapted from CRD guidance was conducted in TA1101, the previous EAG report noted that this assessment lacked supporting rationale for individual judgements and did not provide an overall risk-of-bias conclusion, limiting its transparency and interpretability. The EAG therefore applied the Cochrane RoB 2 framework to critically appraise VANGUARD, providing a structured, domain-based assessment aligned with current best practice for randomised controlled trials, enabling clearer evaluation of potential sources of bias and strengthening confidence in the interpretation of the clinical evidence. Overall, the VANGUARD trial was judged to be at low risk of bias across all key domains.

Table 21: Company's and EAGs quality assessment criteria of the VANGUARD trial

Domain	Question	EAG assessment
Risk of bias arising from the randomisation process	1.1 Was the allocation sequence random?	Yes, Participants were randomised using an interactive response technology (IRT) system in a 3:2 ratio to garadacimab or placebo. Randomisation was stratified by age group (≤ 17 vs > 17 years) and baseline attack rate, indicating a robust random sequence generation process.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes. The randomisation list and codes were held by the IRT provider with no access by site staff or sponsor representatives. Identical volume-matched injections were used, ensuring allocation concealment.
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No. Baseline demographic and disease characteristics were similar across groups, including age, sex, HAE type (Type I ~88%, Type II ~13%), BMI, race, baseline attack rates during run-in, and prior prophylaxis use. Minor differences were consistent with chance in a small sample.

Domain	Question	EAG assessment
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1 Were participants aware of their assigned intervention during the trial?	No. The trial was double-blind, with participants unaware of the treatment allocation during the study period
	2.2 Were carers or people delivering the intervention aware of participants assigned intervention during the trial?	No
	2.3 If yes, probably yes or no information to 2.1 or 2.2, were there deviations from the intended intervention that arose because of the trial context?	NA
	2.4 If yes or probably yes to 2.3, were these deviations likely to have affected the outcome?	NA

Domain	Question	EAG assessment
	2.5 If yes or probably yes or no information to 2.4, were these deviations from intended intervention balanced between groups?	NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes, primary analyses used the intention-to-treat population with appropriate statistical models adjusting for baseline attack rate
	2.7 If no, probably no or no information to 2.6, was there potential for a substantial impact (on the results of the failure to analyse participants in the group to which they were randomised?	NA
Risk of bias due to deviations from the intended interventions (effects of adhering to intervention)	2.1a Were participants aware of their assigned intervention during the trial?	No

Domain	Question	EAG assessment
	2.2a Were carers or people delivering the intervention aware of participants assigned intervention during the trial?	No
	2.3a [if applicable] if yes, probably yes or no information 2.1a or 2.2a, were important non-protocol interventions balanced across intervention groups?	Yes. On-demand therapies were permitted as needed and were substantially reduced in the garadacimab group compared with placebo.
	2.4a [if applicable] Were there any failures in implementing the intervention that could have affected the outcome?	No. Most participants received all scheduled doses (95%).
	2.5a [if applicable] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	NR

Domain	Question	EAG assessment
	2.6a If no, probably no or no information to 2.3 or yes, probably yes or no information to 2.4 or 2.5, was an appropriate analysis used to estimate the effect of adhering to the intervention?	Yes
Risk of bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Yes. Completion rates were high. Only three patients in the placebo group discontinued early; no discontinuations occurred in the garadacimab group.
	3.2 If no, probably no or no information to 3.1, is there evidence that the result was not biased by missing outcome data?	No
	3.3 If no or probably no to 3.2, could missingness in the outcome depend on its true value?	Unlikely, due to small number of withdrawals and transparent reporting

Domain	Question	EAG assessment
	3.4 If yes, probably yes or no information to 3.3, is it likely that missingness in the outcome depended on its true value?	No
Risk of bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No. Investigator-confirmed HAE attack rates are standard and clinically relevant for prophylaxis trials.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Unlikely. All participants used electronic diaries (eDiaries) to record symptoms, followed by investigator confirmation.
	4.3 If no, probably no or no information to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No. Investigators were blinded.
	4.4 If yes, probably yes or no information to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Unlikely due to masking.
	4.5 If yes, probably yes or no information to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No, blinding reduces the likelihood that outcome assessment was influenced by treatment knowledge.

Domain	Question	EAG assessment
Risk of bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes. A prespecified statistical analysis plan and hierarchical testing strategy were reported.
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No. The primary endpoint (monthly investigator-confirmed HAE attack rate) was clearly defined and consistently reported.
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	No evidence of selective reporting. Sensitivity analyses were also conducted

3.7.1 Justification for the inclusion of garadacimab

As stated in section 2.2 and 2.3 of the EAG report, garadacimab was excluded from the company's NMA despite it receiving recent NICE approval. Therefore, the EAG reran the company's NMA but included the VANGUARD study which compared the safety and efficacy of garadacimab 200 mg QM to placebo to reflect the full set of currently available licensed prophylactic treatments and to assess whether the inclusion of garadacimab alternated the relative treatment effects and conclusion of the company's NMA.

3.7.2 Study design

The study design of the garadacimab study included in the EAG's NMA is presented in Table 22. Like the other four studies, VANGUARD was multicentre, phase 3, randomised, and placebo-controlled, maintaining network connectivity, as well as being parallel-group similar to OASIS-HAE, HELP, and APeX-2.

Eligibility criteria were broadly similar across studies. VANGUARD required a minimum recent attack frequency, comparable to the thresholds used in HELP and APeX-2, although CSL312_2001 imposed a higher short-term attack requirement which may have resulted in a sample with higher disease activity at baseline. VANGUARD included adolescents aged ≥ 12 years, aligning closely with OASIS-HAE and HELP.

Overall, the VANGUARD is sufficiently aligned with the existing trials to support inclusion in the NMA, but a few differences reiterate the importance of cautious interpretation of the NMA results.

Table 22: Study design of the VANGUARD trial

	VANGUARD
Study design	Multicentre Placebo-controlled Parallel arm
Phase	Phase 3
Randomisation	Yes
Blinding	Yes
Total sample size	64
Start and end date	January 2021 to June 2022
Data cut-off	01 June 2022
Treatment period	6 months (182 days)
Total number of arms	2
Number of arms included in NMA	2
Intervention (bold denotes inclusion in NMA)	Garadacimab 200 mg QM

Comparator	Placebo
Method of administration	Subcutaneous
Site of treatment administration	Initial doses at study sites; subsequent doses self-administered (or caregiver-administered) at home
Key inclusion/exclusion criteria	Inclusion: Age ≥ 12 years; type I or II HAE; ≥ 3 attacks in the prior 3 months (or ≥ 1 /month); washout from prior LTP. Exclusion: Other forms of angioedema; recent monoclonal antibody use; planned major surgery; oestrogen-containing medications
How HAE reports were recorded	Patient electronic diaries (eDiary) with investigator confirmation
How severity was graded	Investigator-assessed severity using prespecified criteria (mild, moderate, severe)
Location	Canada, Germany, Hungary, Israel, Japan, the Netherlands, USA (no UK sites)
Funding	CSL Behring

3.7.3 Treatment and administration

In VANGUARD, garadacimab was administered once a month, similar to a four-weekly regimen but not identical (Table 23). This small difference in timing could influence exposure and attack-rate over the long-term and cannot be quantified easily. The relevant dose in this appraisal is the 200 mg dose, and it was given subcutaneously, like donidalorsen and lanadelumab. While this alignment in administration supports comparability, the difference in timing should be noted as a minor potential source of heterogeneity.

Table 23: Treatment administration and dosage of VANGUARD

Trial	Intervention	Timing	Dose	Comparator	Method of administration
VANGUARD	Garadacimab	QM	200 mg	Placebo	Subcutaneous

3.7.4 Baseline characteristics and TEMs

The reported baseline characteristics of the VANGUARD are presented in Table 24. The baseline characteristics of patients enrolled in the garadacimab arm of

VANGUARD show broad similarities with the patients of the studies included in the company's NMA, but differences and inconsistent reporting limits this comparison.

Demographic characteristics in VANGUARD were generally comparable to the other LTP trials included in the NMA. Baseline disease burden appeared similar to that reported in OASIS-HAE, HELP, and APeX-2, although attack history was summarised using different time windows and measures. However, a full assessment of comparability is constrained by incomplete reporting in VANGUARD.

Overall, while the available data suggest broad similarity in key demographic and disease characteristics, residual uncertainty regarding baseline comparability remains, and should be considered when interpreting any expanded NMA including garadacimab.

Table 24: Baseline characteristics of VANGUARD

Arm	Garadacimab 200mg	Placebo
N	39	25
Age		
Age at screening, Mean (SD) [range]	43.3 (17.5) [12 - 69]	37.8 (12.8) [14 - 62]
Patient age group at diagnosis, years (%)		
≤17	18 (46)	12 (48)
>17 to ≤40	18 (46)	11 (44)
>17	NA	NA
>40	3 (8)	2 (8)
≤65 years	NA	NA
>65 year	NA	NA
Male, %	15 (38)	11 (44)
BMI: Mean (SD)	27.9 (6.0)	28.4 (7.6)
Race (%)		
White	33 (85)	22 (88)
Asian (Japanese)	4 (10)	2 (8)
Asian	NA	NA
Black/African American	0	1 (4)
Native Hawaiian or other	1 (3)	0
American Indian/Alaskan Native	NA	NA
Multiple	NA	NA
Other	1 (3)	0
HAE Type (%)		

Type I	34 (87)	22 (88)
Type II	5 (13)	3 (12)
HAE-Nc1inh	NA	
Previous family history of HAE: n (%)	34 (87)	23 (92)
Age of symptom onset	NR	NR
HAE attack history (%)		
Peripheral	1 (3)	0
Abdominal	30 (77)	18 (72)
Laryngeal	21(54)	17 (68)
Cutaneous (extremities)	30 (77)	20 (80)
Facial	13 (33)	8 (32)
Throat, larynx, or tongue	3 (8)	2 (8)
Trunk	NR	NR
Previous prophylactic treatment = Yes	14 (36)	7 (28)
Previous androgen treatment = Yes	NR	NR
Previous C1-INH treatment = Yes	NR	NR
Other prior treatments		
Icatibant acetate	NR	NR
Icatibant	NR	NR
Paracetamol	NR	NR
Concomitant medication		
Any on-demand	NR	NR
Any supportive treatment	NR	NR
C1 esterase inhibitors	NR	NR
Ecallantide	NR	NR
Ibuprofen	NR	NR
Icatibant	NR	NR
Icatibant acetate	NR	NR
Nano filtered/plasma-derived C1 inhibitor	NR	NR
Paracetamol	NR	NR
HAE attacks prior to screening		
Attacks 12m before screening (3 months before screening or at the start of prophylaxis)	8·6 (6·3–10·9)	9·3 (6·4–12·2)
Attacks during run-in period	3·1 (2·4–3·7)	2·5 (2·1–2·9)
Baseline monthly attack rate	NR	NR

3.7.5 Outcomes

The publication for VANGUARD reported results all seven outcomes used in company's NMA. The primary endpoints, mean number of HAE attacks per month was reported as the mean, median, and the least squares mean, the latter was used in the EAG's NMA to keep the inputs consistent to the company's NMA. The mean

number of moderate or severe HAE attacks and those requiring on-demand medication do not report LSMs.

Only the mean change from baseline of the AE-QOL outcome was presented in the supplementary material of the VANGUARD publication. No confidence interval, SE, SD, or any other precision metrics were presented. Therefore, to allow its inclusion in the EAG's NMA, the mean change from baseline in AE-QOL score was calculated for the trial period 1 (TP1) of the CSL312_2001 study for both the garadacimab and placebo arms, assuming a baseline–follow-up correlation of 0.5 and used as the SDs for the same arms in VANGUARD. This approach assumes comparable variability in AE-QoL change between the two studies and introduces additional uncertainty that is not captured in the reported VANGUARD data, which should be considered when interpreting the NMA results. Sensitivity analyses were conducted assuming correlations of 0.3 and 0.7 and resulted in no meaningful differences.

3.7.6 Placebo response

The EAG extracted the placebo responses from VANGUARD (Table 25). Placebo responses in VANGUARD were consistent with those in the comparator trials (Table 17), especially compared to OASIS-HAE, and here are minor differences between other studies. These differences are relevant for interpreting indirect comparisons, given that all active treatments are linked exclusively via placebo.

Table 25: Placebo response for VANGUARD

Placebo responses	VANGUARD (N=25)
Mean number of HAE attacks per month	2.01 (1.44 to 2.57)
Mean number of moderate or severe HAE attacks per month	1.35 (0.86 to 1.84)
Proportion of patients achieving ≥50% reduction in HAE attacks from baseline	8 (32%)
Proportion of patients achieving ≥70% reduction in HAE attacks from baseline	4 (17%)
Proportion of patients achieving ≥90% reduction in HAE attacks from baseline	2 (8%)
Mean number of HAE attacks requiring on-demand medication	1.86 (1.26 to 2.46)
Mean change from baseline in AE-QoL score	-3.4

3.7.7 NMA methods and assumptions

The EAG reviewed the company's NMA methodology, including model structure, choice of effect measures, prior distributions, and handling of heterogeneity, and did not identify any substantive methodological issues. The priors used by the company were considered appropriate and sensitivity analyses indicated that the results were robust to alternative prior specifications.

The EAG therefore implemented an NMA using the same analytical approach as the company, with the sole difference being the inclusion of evidence from the VANGUARD trial to extend the treatment network to garadacimab. As such, any differences between the company's results and the EAG's results are driven by the additional data rather than by methodological differences in the NMA approach.

Garadacimab is informed by a single study and contributed no closed loops to the network, limiting the ability to assess consistency and increasing uncertainty around its relative effects.

3.7.8 Results of the EAG's NMA including garadacimab

Figure 2 presents the general shape of the EAG's network when VANGUARD is included. VANGUARD has results for all outcomes and therefore is included in every NMA model analysed.

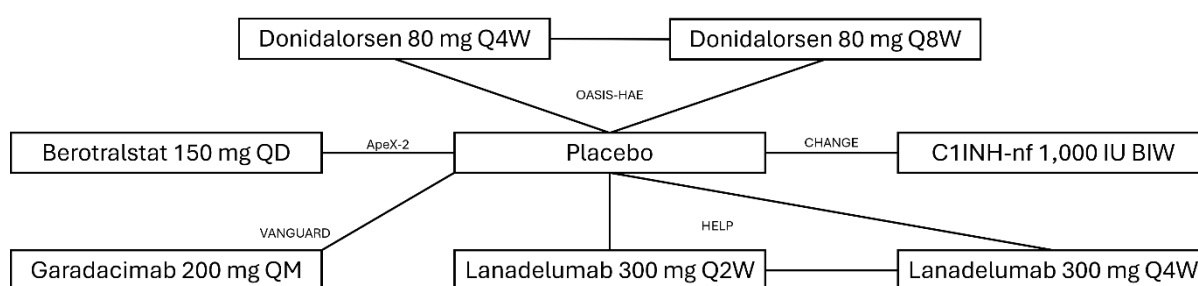


Figure 2. Shape of EAG's NMA when all studies are included

Results

The results of the EAG's NMA is presented in Table 26. Compared with donidalorsen Q4W (reference treatment), garadacimab 200 mg QM was associated with [REDACTED] RRs for overall HAE attacks, moderate or severe HAE attacks, and HAE attacks requiring on-demand medication, alongside [REDACTED] proportions of patients achieving at $\geq 50\%$, $\geq 70\%$, and $\geq 90\%$ reduction in HAE attacks, and a

██████████ in AE-QOL from baseline. However, for all outcomes, the corresponding 95% credible intervals ██████████ (1 for rate and odds ratios, 0 for mean differences), indicating that these differences were ██████████.

Results for the remaining pairwise comparisons were consistent with those reported in the company's base-case NMA. This is expected as the only structural difference between the company's and EAG's NMAs was the inclusion of garadacimab, which is linked to the network solely through placebo and has no direct or indirect connections to the long-term prophylactic treatments. Consequently, the inclusion of garadacimab had minimal impact on the relative treatment effects among existing comparators.

The EAG explored both fixed-effects and random-effects models. Due to the underlying heterogeneity between the studies and the similarity of the deviance information criterion (DIC) between the fixed and random-effects models, the random-effects model was chosen.

Overall, the EAG considers that the results of the updated NMA do not provide robust evidence of ██████████ in efficacy between donidalorsen and the relevant comparators. Although numerical differences were observed ██████████ garadacimab across ██████████ and donidalorsen Q4W over berotralstat for ██████████, these differences were generally characterised by wide Crls and underlying uncertainty.

Model diagnostics

The EAG examined the model diagnostics for the EAG's NMAs and found them to be consistent with those presented by the company for their base-case NMAs. Across all outcomes, residual deviance was very close to the number of data points indicating good model fit, and all models demonstrated good convergence, with R-hat values equal to ██████████ when rounded. Between-study heterogeneity was low to moderate and comparable to that reported by the company, with no indication of excessive unexplained variability. Treatment ranking metrics, including SUCRA values and posterior ranks, broadly overlapped across treatments, indicating

substantial uncertainty and no clear hierarchy between most comparators. For the AE-QoL outcome, between-study heterogeneity remained [REDACTED], reflecting consistent effects across the contributing studies. Overall, the inclusion of the VANGUARD study did not materially affect model fit, convergence, or heterogeneity, and the EAG did not identify any concerns regarding the adequacy or stability of the NMA models.

Table 26: Full results of the EAG's NMA including garadacimab compared to the reference treatment (donidalorsen Q4W)

	Placebo	Donidalorsen Q8W	Lanadelumab Q2W	Lanadelumab Q4W	Berotrastat	C1INH-nf
HAE attacks						
Moderate or severe HAE attacks						
Proportion achieving ≥50% reduction in HAE attacks						
Proportion achieving ≥70% reduction in HAE attacks						
Proportion achieving ≥90% reduction in HAE attacks						
HAE attacks requiring on-demand medication						
Mean change from baseline in AE-QoL score						

Bold denotes statistically meaningful result

3.7.9 Conclusion of the EAG's NMA

The inclusion of the VANGUARD trial was methodologically appropriate and does not raise concerns regarding network connectivity, model fit, or convergence. While [REDACTED] garadacimab compared with donidalorsen Q4W, these differences were consistently characterised by wide 95% CIs and were [REDACTED] results.

Results for the remaining treatments were largely unchanged from the company's base-case NMA, as expected given that garadacimab is linked to the network solely through placebo. The updated NMA therefore does not provide robust evidence of clinically meaningful differences in efficacy between donidalorsen and the other comparators. Therefore, assumptions regarding comparative efficacy in the economic model remain subject to substantial uncertainty and should be interpreted with caution.

3.8 Conclusions of the clinical-effectiveness section

The CS presents evidence from the OASIS-HAE trial, a double-blind phase 3 randomised controlled trial evaluating donidalorsen as a long-term prophylactic treatment administered subcutaneously every 4 weeks (Q4W) or every 8 weeks (Q8W) compared with placebo. The inclusion of two dosing regimens aimed to explore the balance between efficacy and dosing convenience. Participants aged 12 years or older were recruited across Europe, North America, the Middle East and the United Kingdom and were required to have a confirmed diagnosis of Type I or Type II hereditary angioedema. While baseline demographic and disease characteristics were broadly similar across treatment arms, some imbalances were observed, including in baseline attack frequency, sex distribution and population representativeness. However, it is unclear to the EAG if these differences reflect the key prognostic factors of HAE rather than chance effects associated with the modest sample size. The EAG clinical expert also highlighted that, although fewer females were enrolled than males, female patients may experience greater disease activity due to hormonal influences. The trial was adequately powered for the primary endpoint, and the EAG assessment using the Cochrane Risk of Bias 2 tool identified some concerns, but overall internal validity was considered acceptable.

Donidalorsen 80 mg administered Q4W demonstrated statistically significant reductions in investigator-confirmed HAE attack rates compared with placebo, including significantly lower time-normalised attack rates. Statistically significant improvements were also observed for the Q8W regimen compared with placebo across several secondary endpoints, including reductions in attack frequency. Both dosing regimens were associated with clinically meaningful improvements in health-related quality of life. A direct comparison between the Q4W and Q8W regimens was not reported. Adverse event rates were generally similar across groups, although treatment-related adverse events were more frequent in the Q4W group. The most commonly reported events were mild injection-site reactions, and no deaths were observed.

The EAG clinical experts considered the OASIS-HAE population to be broadly representative of patients with HAE in UK clinical practice, although limited UK recruitment and low ethnic diversity may restrict generalisability.

As no head-to-head comparative trials were identified in the company's SLR, the company conducted an NMA to estimate the relative effectiveness of donidalorsen compared with alternative long-term prophylactic treatments, lanadelumab, berotralstat, and C1INH-nf. However, the NMA excluded garadacimab, a relevant LTP therapy that, based on clinical expert opinion and recent NICE approval, is expected to play a key role in UK clinical practice. The EAG considers the exclusion of garadacimab to be a major limitation, introducing uncertainty regarding the relative effectiveness of donidalorsen within the evolving treatment landscape. Therefore, the EAG extended this evidence base by including garadacimab in this network.

The company's NMA results concluded that there were no differences between LTPs, with 95% credible intervals overlapping across the treatments for most outcomes, and the EAG was able to replicate the company's NMA using the same modelling approach and obtained similar results, indicating that the company's analytical implementation was appropriate. However, no alternative NMA approaches were explored to validate results of the base case NMA. Across outcomes, the NMAs were characterised by wide credible intervals and substantial uncertainty, reflecting the small number of trials, placebo-anchored network structure and between-study differences in populations and trial design.

4 Cost effectiveness

This section presents a summary and critique of the cost-effectiveness evidence included in the company's submission. Section 4.1 focuses on the company's review of the cost-effectiveness evidence and section 4.2 covers the company's economic evaluation.

4.1 Critique of the review of cost-effectiveness evidence

The company undertook an SLR to identify studies on cost-effectiveness, health-related quality of life (HRQoL), cost and resource use, and burden of disease relating to patients aged 12 years and over with hereditary angioedema. This was combined with the clinical effectiveness SLR critiqued in 3.1 above. The SLR is reported in full in a confidential document supplied in the reference pack accompanying the company submission. Several reporting omissions, errors and discrepancies relating to the SLR were identified by the EAG, however these were all satisfactorily resolved via the clarification process (see clarification responses A4, C2-6).

4.1.1 Literature searches

Searches were conducted in June 2024, then updated in April 2025. In Embase and MEDLINE, search filters are used to identify cost-effectiveness, HRQoL, resource use and burden studies. However, MEDLINE and Embase are searched together in one search which is not best practice and limits the effectiveness of search filters designed for only one of those databases. Other sources searched were SCHARRHUD (which is no longer available), the EuroQoL database and the HTA and NHS EED databases from Centre for Reviews and Dissemination (which have not been updated since 2015). A more appropriate and up-to-date source would have been the International HTA Database provided by INAHTA. A search filter for economic studies was used in the HTA and NHS EED databases, which is unnecessarily restrictive given that the databases only include health technology assessments and economic evaluations. Websites of HTA agencies, proceedings of recent conferences and reference lists of other SLRs were also checked. The company's search therefore had several limitations. However, the main sources of evidence used to inform the economic model are previous NICE appraisals, which the EAG considers appropriate. The EAG ran targeted searches for any studies

relevant to the NICE scope that may have been added to MEDLINE/Embase since the company's last search in April 2025 (see Appendices for details); NICE TA1101⁴⁰ was the only additional, relevant economic study identified by these searches.

4.2 Critique of the submitted economic evaluation

The company submission presented economic results for populations experiencing ≥ 2 and ≥ 8 HAE attacks per month. The EAG's detailed critique of the economic evaluation is provided in Sections 4.2.1 to 4.2.7; however, an important omission in the submitted evidence is highlighted here.

Of particular relevance to decision making is the exclusion of garadacimab as a comparator in the population with ≥ 2 attacks per month. The company states that the anticipated marketing authorisation for donidalorsen applies to patients

[REDACTED]. The EAG considers that excluding garadacimab results in an incomplete comparator set and incomplete economic evidence for this population. The EAG therefore considers that garadacimab should have been included in both the company base-case cost-comparison analysis and the cost-utility scenario analysis.

Other areas of critique and the EAG's corresponding analyses are discussed in the relevant sections of Section 5.2.

4.2.1 NICE reference case checklist

The EAG assessment against the NICE reference checklist is presented in Table 27

Table 27: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	NA
Perspective on costs	NHS and Personal Social Services	Yes
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	A cost-comparison analysis was performed as base case and

Element of health technology assessment	Reference case	EAG comment on company's submission
		cost-utility analysis presented as scenario analysis. EAG choice of base case is a cost-utility analysis
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, a life-time horizon (62.8 years) was modelled with a starting age of 37.2 years.
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes, but only applies to cost-utility scenario analysis
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	Based on external data source – a Swedish registry of patients with HAE.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes, utility scores derived using the UK EQ-5D-5L crosswalk value set
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
NA, not applicable; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D-3L, EuroQol-5 dimension-3levels.		

4.2.2 Model structure

Model Structure

A de novo Markov-based model was developed in excel with a 28-days cycle length over a lifetime horizon to evaluate the costs and clinical outcomes of donidalorsen

against its comparators. The model includes two distinct, all-inclusive health states: alive or dead (Figure 3).

Patients enter the model in the alive health state and can either be treated with Donidalorsen Q1M, Berotralstat, Lanadelumab Q2W or C1- INH. In each cycle, in the alive state, patients can either experience HAE attack or be attack-free. The frequency and duration of the HAE attacks is used to assess the costs and health care resource use (HCRU) per cycle in the model. The death state is an absorbing health state.

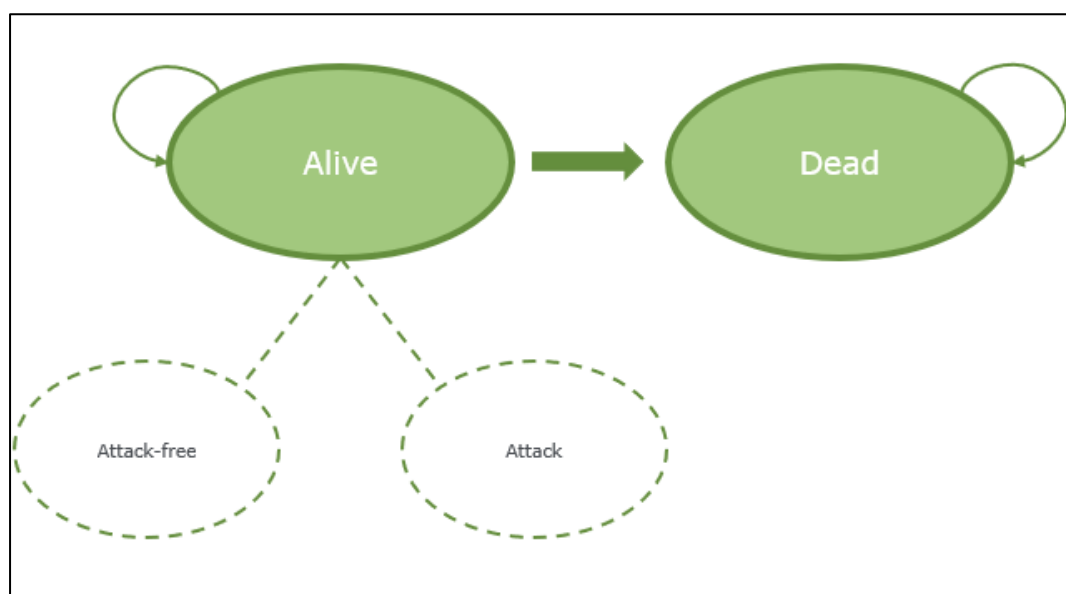


Figure 3: Model structure

(Source: Figure 31 CS, pg 136)

The company noted the selection of this model type was deemed appropriate because it has been previously used in NICE appraisals of HAE (TA 606 and TA 738)^{38, 39} and it had the capacity to account for all the differences in costs and clinical outcomes such as HAE attacks when comparing donidalorsen with the other LTPs.

EAG comment

- The EAG considers the model type to be appropriate but expressed structural concerns regarding the exclusion of berotralstat stopping rule and parameterisation, as discussed in detail in the sections below.

Discount rate/ Perspective

The analysis was performed from perspective of the NHS and PSS with a 3.5% discount rate per year applied to both costs and outcomes as per the NICE reference case.

4.2.3 Population

The patient population evaluated in the economic model aligns with the anticipated marketing authorisation: patients

[REDACTED]

The baseline characteristics of patients used in the cost-effectiveness model (CEM) are consistent with OASIS-HAE clinical trial for donidalorsen. As previously described (section 3.2), OASIS -HAE trial was a phase III, multicentre, double-blind, randomised controlled study of patients with type I and type II HAE who are experiencing ≥ 2 attacks per month. Clinical expert to the EAG indicated that these baseline characteristics broadly align with HAE patients in UK but noted that more males were included in OASIS-HAE placebo compared to females which although not unusual, could be unexpected as more females may suffer HAE attacks due to hormonal differences.

Two subgroups of patients were considered in the model as seen in NHS England (NHSE).

- Patients with ≥ 2 attacks per month who received berotralstat as LTPs
- Patients with ≥ 8 attacks per month who received lanadelumab and C1-INH as LTPs.

A mean age of 37.2years, with an average weight of [REDACTED] kg and 46.70% males were applied in the economic model.

4.2.4 Interventions and comparators

Intervention

The technology under evaluation is donidalorsen which is intended for routine use in the

[REDACTED]
[REDACTED].

The dosing regimen of donidalorsen used in the CEM corresponds with the marketing authorisation (MA) which states that patients initiate treatment with

[REDACTED]
[REDACTED]
[REDACTED].

The EAG notes that there are differences with the dosing frequency stated in the marketing authorisation and those used in the OASIS-HAE trial. In the OASIS-HAE trial, donidalorsen was administered as 80mg Q4W and 80mg Q8W while the MA states it should be given as 80mg Q1M and then 80mg Q2M. The company indicated in its submission that there are no differences in terms of efficacy and safety between the dosing frequencies used in the trial and that of the MA. During clarification (clarification question C1), the EAG asked the company to provide specific clinical and pharmacokinetic data that provides a demonstration of equivalence in efficacy, safety and pharmacological response between the two dosing frequencies (Q4W/Q8W and Q1M/Q2M) for donidalorsen. In response, the company acknowledged that the two dosing schedules are clinically not identical but no meaningful differences in outcome is expected. The company noted the treatment period in OASIS-HAE trial was 28 days $\pm$ 3 days and so the efficacy of donidalorsen observed in the trial can reflect a dosing of up to 31 days which aligns the Q4W with the Q1M dosing. Results from the trial showed a long-term stability in

pharmacodynamic effect of donidalorsen between dosing regimens (Q4W and Q8W) despite of a 4-week difference in frequency, which shows there might not be any difference in outcomes between Q4W and Q1M dosing and Q8W and Q2M dosing. The company again notes the simulations of 10,000 patients treated with donidalorsen showed similarities in HAE attack rates between the two dosing frequencies with a reduction in HAE attack rates of 84.1% and 82.9% for Q4W and Q1M respectively and 72.6% and 70.2% for Q8W and Q4W respectively.

Clinical expert to EAG agrees with the company and notes there might not be any significant difference with the two dosing schedules as drugs are not designed to cease working the minute you stop taking them. Nevertheless, the EAG has explored the use of Q4W and Q8W dosing frequencies in the model to align with the data obtained from the QASIS-HAE trial and to assess the level of uncertainty of the dosing frequency of donidalorsen used in the model. The scenario analysis shows that the cost savings associated with donidalorsen [REDACTED] by [REDACTED] and [REDACTED] when compared with lanadelumab and C1-INH respectively. Donidalorsen was found [REDACTED] to produce any [REDACTED] when compared with berotralstat under this scenario (see section 5.2.2 for full results).

Comparators

The comparators used in the CEM are divided into two subgroups depending on number of attacks that patients experience per month. For patients who experience ≥ 2 attacks per month, the comparator is berotralstat while lanadelumab and C1-INH are for patients who experience ≥ 8 attacks per month. The company indicated these comparators are in line with NICE scope and established standard of care in the NHSE for patients with HAE, but EAG notes the exclusion of some comparators like Garadacimab, Ruconest and attenuated androgens and antifibrinolytics from their analysis. Further details on the appropriateness of excluding these comparators are presented in section 2.3 whilst the impact of excluding garadacimab is explored further in the EAG exploratory analyses in section 5.2.3

A dose of 150mg once daily of berotralstat was applied in the model based on its SmPC. The implementation of lanadelumab dosage is a starting dose of 300mg

Q2W with a reduction to 300mg Q4W in patients who are stably attack free. In practice, a consideration is given to patients whose body weight is less than 40kg with a starting dose of 150mg lanadelumab but the company maintained a 300mg dose throughout the model due to indifference in the cost of 150mg and 300mg lanadelumab.

C1-INHs was presented as a singular comparator in the model but its inputs reflect two C1-INHs: IV Cinryze and off label IV berinert. A dose of Cinryze of 1000 international units (IU) every three or four days (twice per week) in accordance with the SmPC was used in the CEM. Since IV Berinert is an off-label medication, the clinical experts to the company consulted as part of this appraisal advised that a constant 1500 IU dose of Berinert with alterations for individuals whose weight is significantly high or low is usually administered.⁵⁷ This resulted in implementation of a distribution of patients receiving 1000IU or 1500 IU of berinert with an assumption that [REDACTED] of patients take 1000IU ([REDACTED]) and [REDACTED] of patients take 1500 IU ([REDACTED]).

A distribution of 27% IV Cinryze and 73% IV Berinert sourced from NICE appraisal TA 606 of lanadelumab³⁹ was applied in the model to calculate the cost of C1-INH treatment. The EAG clinical expert sees this distribution as reasonable as more patients use more of Berinert than Cinryze in practice.

EAG comment

The company stated that the comparator set was consistent with the NICE scope and established standard of care in NHS England for HAE. However, the EAG notes the exclusion of some comparators, including garadacimab, Ruconest, attenuated androgens, antifibrinolytics, and subcutaneous Berinert, listed in the final NICE scope, as discussed in Section 2.3.

Garadacimab was excluded from the economic evaluation despite final NICE guidance (TA1101) being published on 8 October 2025,⁴⁰ prior to the company submission, and despite its inclusion in the final NICE scope. During clarification (Questions A1 and B1), the company was asked to justify this exclusion, assess the associated uncertainty, and provide a scenario analysis including garadacimab. In

response, the company argued that implementation of the NICE recommendation was ongoing with limited NHS uptake, and that garadacimab was not listed on the NHS England high-cost commissioning list, and therefore not considered established standard care.

Notwithstanding this position, the company presented clinical efficacy data for garadacimab from the VANGUARD phase III RCT and conducted a naïve comparison with donidalorsen. The company further cited a MAIC conducted by CSL Behring, which reported no statistically significant difference between garadacimab Q1M and donidalorsen Q4W in time-normalised HAE attack rates, and used this to support an equal efficacy assumption within a cost-comparison framework.

However, the company did not update its economic model to formally include garadacimab, relying instead on a naïve comparison while maintaining that garadacimab was not a base-case comparator. The EAG therefore considers that garadacimab has been excluded from the company's economic evaluation. The EAG's rationale for including garadacimab as a base-case comparator is presented in Sections 2.3 and 3.7.

4.2.5 Treatment effectiveness and extrapolation

Clinical parameters and variables

The clinical parameters used in the company's cost-comparison analysis (company's preferred base case) and cost-utility (scenario analysis) were sourced from the OASIS-HAE trial and from the NMA. In the section below we present how the data were applied (including underlying assumptions) in the cost-comparison (CCA) and cost-utility analysis (CUA)

Attack Rates in the cost-effectiveness model

Baseline attack rate (CCA)

An equal baseline attack rate was assumed for all patients irrespective of treatment received. The baseline attack rate of 0.725 per week which is the mean run-in period HAE attack rate in the placebo arm of the OASIS-HAE trial of 2.90 per 4 weeks was used for the ≥ 2 attacks per month population in the model.¹¹ For the patient population experiencing ≥ 8 attacks per month, a baseline attack rate of 2 attacks per week was used, which is equivalent to 8 attacks per month in line with reimbursement criteria for lanadelumab.³⁹ The company noted these values were validated by their clinical experts.

Baseline attack rate (CUA)

The baseline attack rates for the population experiencing ≥ 2 attacks and ≥ 8 attacks per month were modelled as per the base-case cost-comparison analysis as explained above.

EAG comment

The EAG suggested pooling baseline attack rates for all LTPs from their respective trials, considering that the EAG clinical expert advised that the choice of prophylactic treatment is influenced by the baseline attack rate.

This scenario was requested from the company at clarification stage (clarification question B7) and the company adjusted the model structure to allow the use of the pooled attack rate (0.818) for the ≥ 2 attacks per month patient population.

The results show an [REDACTED] in costs for both donidalorsen and berotralstat due to the [REDACTED] in the rate of HAE attack, but the incremental cost was still the same as the base case result because of the equal number of attacks based on equal efficacy assumption within the cost-comparison analysis.

Using the pooled baseline attack rate for the cost-utility analysis resulted in incremental costs of [REDACTED] and incremental QALYs of [REDACTED] for donidalorsen vs berotralstat.

Attack rate per week (CCA)

In line with the duration of the OASIS-HAE trial (24 weeks), attack rate per week for the first 24 weeks was estimated by multiplying the median rate ratio ([REDACTED]) derived

from the NMA for donidalorsen Q4W with the weekly attack rate observed in the placebo arm of the OASIS-HAE trial.

Attack rate from week 25 onwards was estimated as the average attack rate from the time point at which donidalorsen Q4W had reached maximum effect (Week 5) based on the steady state definition, until the end of the trial period (week 25).

The company assumed equal efficacies for all LTPs because of the results obtained from the NMA (See section 3.6.5 for details of the NMA). Therefore, in the CEM, the HAE attack rate per cycle for all LTPs was set equal to that of donidalorsen Q4W (Q1M as per MA) in the cost comparison analysis.

Attack rate per week (CUA)

A NMA of the mean monthly number of attacks was undertaken for donidalorsen and comparator long-term prophylaxis (LTP) treatments versus placebo. Treatment effects were expressed as rate ratios relative to placebo. The median rate ratios from the NMA (Table 28) were applied in the economic model to derive treatment-specific attack rates.

Weekly attack rates observed in the placebo arm of the OASIS-HAE trial (Weeks 1–25) were used to represent ‘no LTP’ for the first 24 weeks of the model. Weekly attack rates for donidalorsen Q1M, donidalorsen Q2M, berotralstat, lanadelumab Q2W, lanadelumab Q4W and C1-INH were estimated by multiplying the placebo weekly attack rates by the relevant median NMA rate ratios (Table 28). These treatment-specific weekly rates were applied for the first 24 weeks, consistent with the duration of the OASIS-HAE trial. Assumptions regarding extrapolation beyond Week 25 are described below.

Table 28: Median rate ratios and 95% CrIs from the NMA for mean number of HAE attacks per month (RE) with placebo as reference treatment

Treatment	Median RR (95% CrI)
Donidalorsen Q4W	██████████
Donidalorsen Q8W	██████████
Berotralstat	██████████
Lanadelumab Q2W	██████████

Treatment	Median RR (95% CrI)
Lanadelumab Q4W	
C1-INH*	

Abbreviations: C1-INH – C1-esterase inhibitor; CrI – Credible interval; NMA – Network meta-analysis; Q2W – Once every two weeks; Q4W – Once every four weeks; RE – Random effects; RR – Rate ratio

*C1-INH results reflect the relative efficacy of Cinryze IV from the CHANGE study.

Source: Table 5 (CS;Appendix K)

Summary

- An NMA estimated treatment effects as rate ratios versus placebo; median estimates were used to derive attack rates in the economic model.
- Placebo weekly attack rates from the OASIS-HAE trial informed ‘no LTP’; treatment rates were calculated by applying NMA rate ratios for the first 24 weeks.

Extrapolation of attack rates beyond 24 weeks

From week 25 onwards, the company assumed constant HAE attack rates for donidalorsen, calculated as the average rate observed during weeks 5–24, corresponding to the post–steady-state period (Table 29). The same approach was applied to all comparators, except C1-INH, for which time to full treatment effect was assumed to be zero weeks due to a lack of data (Table 30).

The EAG acknowledges that long-term effectiveness is uncertain for all treatments because of limited long-term data and considers the application of consistent assumptions across treatments to be reasonable. However, the company did not explore alternative approaches to address uncertainty in long-term extrapolation, such as zero-inflated or Poisson regression models that account for the high proportion of attack-free periods observed in HAE.

Previous NICE appraisals (TA738 and TA1101)^{38, 40} have shown that long-term extrapolation assumptions can materially affect the ICER. In the absence of individual patient data, the EAG was unable to assess the impact of alternative extrapolation approaches on cost- effectiveness. The EAG therefore concludes that long-term extrapolation of attack rates remains an area of unresolved uncertainty

Table 29: Steady state period for each treatment comparator and economic model assumptions

Treatment	Steady state period as defined in the clinical trial	Timepoint of full treatment effect used to extrapolate attack rate in the economic model
Donidalorsen	Weeks 5-25	5 weeks
Berotralstat	Days 8-168	1 week
Lanadelumab	Days 70-182	10 weeks
C1-INH	NR	0 weeks

Source: Table 7 (CS, Appendix K)

Table 30: Extrapolated attack rate for each treatment intervention/ comparator and 'no LTP'

Treatment	Extrapolated average attack rate per cycle
Donidalorsen - Q1M	■
Donidalorsen - Q2M	■
Berotralstat	■
Lanadelumab - Q2W	■
Lanadelumab - Q4W	■
C1-INH	■
'No LTP'*	■

Source: Table 8 (CS; Appendix K)

* No LTP' is included in this table to show the attack rate patients experience when they discontinue their LTP treatment. 'No LTP' is not a comparator within the economic model.

Attack duration and severity

A mean duration of 2.9 days per HAE attack was used in the model. This is based on a weighted average of missed work and leisure days due to HAE attack using data from Lumry et al (2010)⁵⁸ which reported reduced productivity and missed opportunities for patients each time they experience an HAE attack. The company notes that no data were available from OASIS-HAE on attack duration.

Attack severity was classified based on the definitions used for attacks in OASIS-HAE trial.

- Moderate attacks are mild to moderate limitation in activity requiring assistance.

- Severe attacks are defined as severe limitation in activity requiring assistance

In the OASIS-HAE trial, the LSM HAE attack rate was reported for all attacks (moderate/severe and laryngeal) for weeks 1 – 25. The proportion of attacks classified as moderate/severe was estimated by dividing the number of moderate/severe attacks per month by the total number of attacks per month. Laryngeal attacks were estimated from moderate/severe attacks as all attacks that occur in the larynx can lead to suffocation. Mild attack proportion was estimated as one minus moderate/severe proportion. The proportions of attacks used in the CEM are presented in Table 31.

Table 31: Proportion of attacks by severity

Attack classification	Proportion of all attacks	Source
All	-	OASIS-HAE, donidalorsen Q4W all attacks Weeks 1-25 LSM ⁷⁶
Laryngeal	█%	OASIS-HAE, donidalorsen Q4W laryngeal attacks Weeks 1-25 LSM ⁷⁶
Moderate/severe (excluding laryngeal attacks)	█%	OASIS-HAE, donidalorsen Q4W moderate/severe Weeks 1-25 LSM ⁷⁶
Mild	█%	Assumed to be 1 minus moderate/severe proportion

HAE, Hereditary angioedema; Q4W, Once every four weeks
Source: CS Table 32

The company's approach to estimating attack duration is consistent with that accepted in TA1101,⁴⁰ where the HRQoL impact of an HAE attack was assumed to last 3.13 days based on Lumry et al. (2010),⁵⁸ capturing both acute physical and psychological effects. Although this exceeded the mean attack duration observed in VANGUARD trial, the TA1101 committee accepted the assumption based on patient and clinical expert testimony that recovery can take up to a week. On this basis, the EAG considers the company's attack duration assumptions to be reasonable.

However, the EAG notes that the TA1101 committee ultimately preferred a simpler modelling approach driven primarily by attack frequency rather than varying

disutilities by attack severity, reflecting the view that HAE-related quality-of-life impacts may persist beyond the average duration of individual attacks.

In the current appraisal, no trial data were available to inform attack duration for donidalorsen. Consequently, the EAG cannot assess whether the assumed duration of 2.9 days is over- or underestimated.

Mortality

No disease specific mortality was implemented in the model. General population mortality was informed by life tables sourced from the UK Office for National statistics matched for age and sex of the model cohort.⁵⁹ In each model cycle, a risk of death was applied which transitions a proportion of patients from the 'alive' to 'dead' health state.

The company acknowledged that exclusion of disease specific mortality from the model is conservative assumption which was initiated by the paucity of available evidence needed to estimate the percentage of laryngeal attacks resulting in death due to asphyxiation as a proportion of all laryngeal attacks for HAE patients on LTPs. The EAG acknowledges that there is lack of data to inform the modelling of the mortality in HAE patients on LTPs. Also, clinical expert to the EAG stated that there is low mortality risk associated with HAE in patients.

Treatment Discontinuation

The company modelled time-to-treatment discontinuation in section 3.3.4 of the CS. Of the 69 patients who were randomised to one of the two donidalorsen arms in OASIS-HAE, only four (5.8%) patients discontinued treatment. In HELP, five (6%) of the 84 patients randomised to one of the three lanadelumab arms discontinued treatment. In CHANGE, two (8.3%) of the 24 patients discontinued treatment. The company argues that, because discontinuation rates were low and similar across studies, treatment discontinuation was assumed to be the same for donidalorsen, lanadelumab, and C1-INH. While the number of discontinuation events was low across OASIS-HAE, HELP and CHANGE, follow-up durations in these trials were relatively short and varied between studies. As a result, the time-to-discontinuation data informing the Kaplan–Meier curve for donidalorsen are immature, with the KM

plot ending at over ■ people on treatment at six months, increasing uncertainty around long-term extrapolation beyond the observed trial period.

The assumption of equal discontinuation implicitly assumes that discontinuation is independent of treatment efficacy. However, in HAE prophylaxis, lack of efficacy is a key driver of treatment discontinuation in clinical practice, suggesting that differences in treatment response may translate into differences in long-term persistence. Furthermore, the company further assumed identical discontinuation rates for donidalorsen Q4W and Q8W. While plausible, given similar safety profiles, this assumption was not formally explored and adds further uncertainty to the modelling of treatment persistence.

These limitations are particularly relevant when considering berotralstat, for which treatment discontinuation in UK clinical practice is governed by a formal stopping rule. Berotralstat is subject to a NICE-mandated stopping rule requiring discontinuation in patients who do not achieve at least a 50% reduction in monthly HAE attack rate after three months of treatment. In APeX-2, around 42% of patients receiving berotralstat failed to meet this response threshold, indicating that a substantial proportion of patients would be expected to discontinue treatment in UK clinical practice.

Despite this, the economic model assumes equal discontinuation across treatments and does not explicitly reflect response-based discontinuation for berotralstat. This creates an inconsistency whereby long-term outcomes for berotralstat may be overstated relative to the trial-based efficacy estimates used in the NMA, while discontinuation for donidalorsen is modelled using an extrapolated time-to-event curve without an equivalent stopping rule. Similarly, long-term costs for berotralstat are likely to be overestimated because, in the absence of a stopping rule, patients who would otherwise discontinue treatment in line with clinical recommendations are assumed to continue treatment in the model.

The company fit parametric survival models to the observed all-cause discontinuation data from OASIS-HAE to extrapolate TTD over a lifetime horizon. Due to the short follow-up, all the parametric survival models fit the observed data well (Table 33 of CS) with the company's chosen exponential model having the

lowest AIC and BIC, suggesting the best statistical fit. The other models had similar fit. The company's clinical experts agreed with the company's choice of the exponential model which estimated ■ of patients still on treatment at 5 years, and ■ at 10 years.

The EAG fit parametric survival models to the TTD KM data from the company's economic model and also selected the exponential model based on goodness-of-fit. As with the company's analysis, alternative parametric models produced comparable fits to the observed data but diverged substantially in their long-term extrapolations. This reflects the immaturity of the discontinuation data rather than a clear preference for one functional form and introduces uncertainty around long-term treatment persistence that cannot be resolved with the currently available evidence.

4.2.6 Health-related quality of life

As aforementioned, an equal efficacy was assumed in the company base case (cost-comparison analysis), therefore no HRQoL (patient utility, administration disutility and carer disutility) is included for the cost-comparison analysis. However, the company conducted a cost-utility analysis as a scenario analysis. The sub-section below provides the company's approach to estimating HRQoL across the intervention and comparator technologies.

4.2.6.1 Measurement and validation of health effects: cost-utility analysis scenario

The OASIS-HAE trial collected EQ-5D-5L data at weeks 1, 13, and 25. However, these data were not used to inform the cost-utility analysis. The company stated that the 3-month data collection interval was unlikely to coincide with a hereditary angioedema (HAE) attack, and that this misalignment meant the EQ-5D-5L scores would not adequately capture the acute impact of HAE attacks on patients' (HRQoL).

Similar concerns were raised in TA606 (lanadelumab) and TA1101 (garadacimab). In both appraisals, the committees accepted the use of externally sourced utility values from Nordenfelt et al. (2014)⁶⁰ to estimate HRQoL in patients with HAE.

Other disease-specific PRO measures were collected in the OASIS-HAE trial, including the Angioedema Quality of Life Questionnaire (AE-QoL). However, these measures could not be used to inform the cost-utility analysis because no validated mapping algorithm is available to convert scores from the AE-QoL to EQ-5D utility values. A similar limitation was noted in TA1101 (garadacimab).

Health-related quality of life studies

The company conducted a SLR to support the cost-effectiveness analysis. The review identified 3 out of 34 studies that were potentially relevant and included EQ-5D values. However, the EQ-5D values reported for one of the studies were in different health states to those defined in the company's economic model. The following two studies were thus chosen by the company as most relevant for inclusion in the economic model.

- **Nordenfelt et al. (2014)**⁶⁰ reported a retrospective survey of Swedish patients that investigated the burden of HAE using data from the Sweha-Reg census. The study collected EQ-5D-5L responses for both the attack-free health state and during the most recent HAE attack. In the absence of Swedish EQ-5D-5L reference values, utility scores were derived using the UK EQ-5D-5L crosswalk value set.
- **Aygören-Pürsün et al. (2016)**⁶¹ conducted a cross-sectional survey in Spain, Germany, and Denmark to assess the real-world experience of patients with HAE. The study used data from the HAE-BOIS-Europe survey and identified items that most closely aligned with EQ-5D domains to derive utility values for health states both during HAE attacks and in attack-free periods.

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

Baseline utility values

The Nordenfelt et al. (2014)⁶⁰ study informed the baseline utility values in the company's cost utility scenario analysis. These values were used in previous related HTA appraisals of HAE attacks (TA1101, TA606 and TA738)³⁸⁻⁴⁰ and have been accepted by appraising committees. The equation for the calculation of baseline

utilities assumes that baseline utility is a function of age of patient and number of HAE attacks in previous cycles (see equation 1; sourced from company appendix K).

Equation 1: Attack-free utility formula used in the economic model

The baseline utility value also informs the attack disutilities and is derived by subtracting the 'attack' state utility value of 0.512 from the baseline (attack-free) utility value of 0.825 to give an attack disutility value of -0.313. As attack duration is assumed to be 2.9 days across all treatments, the resulting quality adjusted life year (QALY) decrement per attack was estimated to be -0.0025.

Although Aygören-Pürsün et al. (2016)⁶¹ reported EQ-5D utility values, the company did not include these estimates in its base-case analysis, citing the use of an unvalidated approach to mapping EQ-5D. The EAG considers this concern to be justified. Specifically, the study relied on strong structural assumptions, including that the EQ-5D self-care domain is unaffected both during and between HAE attacks, and that the mobility domain is unaffected in the attack-free state. The EAG notes that these assumptions are not supported by qualitative or clinical evidence and are likely to underestimate the impact of HAE attacks on HRQoL. Consequently, the validity of the resulting utility estimates is uncertain, and their use in the base-case analysis would introduce additional methodological uncertainty. The company explored the impact of the utility estimates via a scenario analysis; the cost-effectiveness results for the scenario were consistent with the base case results for all pairwise comparisons with donidalorsen.

Disutilities associated with route of administration

The company applied a disutility associated with route of administration based on Johnston et al. (2021) , citing evidence that patients generally prefer oral treatments over subcutaneous administration, and subcutaneous over intravenous administration⁶² In Johnston et al. 2021 study utility decrements per annual injection

were assumed to be -0.0003 for intravenous administration and -0.0002 for subcutaneous administration. The EAG agrees that applying a disutility associated with method of administration in the base case is reasonable and is consistent with previous NICE appraisals, including TA606.³⁹

However, the EAG considers that the company's approach does not adequately capture the potential impact of frequency of administration on HRQoL, as the applied disutility varies only by route of administration and not by the number of administrations. Clinical expert advice to the EAG suggested that treatment burden is likely to be influenced by both route and frequency, and that ignoring frequency may underestimate the disutility associated with more frequently administered therapies.

In TA1101,⁴⁰ the company explored this issue in a scenario analysis using disutility estimates from Matza et al. (2013),⁶³ which report disutility per administration and therefore allow scaling according to the number of administrations for each long-term prophylaxis (LTP) option. However, while the EAG in TA1101 agreed with the general principle that more frequent administration is likely to be associated with greater disutility, it raised concerns regarding the face validity of the magnitude of the disutility applied to C1-INH therapies. In addition, the EAG did not agree that total administration disutility could be calculated by simply multiplying the disutility associated with a single administration by the total number of administrations.

The EAG further noted that evidence from Hu et al. (2023),⁶⁴ which informed administration disutilities in TA606 and TA738, suggests that the incremental disutility associated with each additional infusion diminishes compared with previous infusions, rather than increasing linearly.

In the current appraisal, the company presented a scenario excluding administration disutilities. Although the overall cost-effectiveness conclusions were consistent with the base case, QALY differences were more pronounced in the comparison between donidalorsen and C1-INH, suggesting that, in combination with other assumptions,

administration disutilities may materially affect the ICER. Results are shown in company CS, appendix K.

Carer disutility

The company included a carer disutility in the base-case cost–utility (scenario) analysis, stating that this was necessary to capture the impact of HAE on carers. In previous NICE appraisals for HAE, including TA606 (lanadelumab)³⁹ and TA738 (berotralstat),³⁸ carer disutilities were either not included or not accepted in the base case because of limited evidence to inform appropriate carer utility values.

However, in TA1101 (garadacimab),⁴⁰ the committee accepted the inclusion of carer disutilities in the base-case cost-effectiveness analysis and preferred the EAG's approach, which assumed a carer disutility of 0.0123 for every 0.1 decrement in patient utility.

In the current appraisal, the company has applied the same approach as that accepted in TA1101⁴⁰ to estimate carer disutilities. The EAG considers the inclusion of carer disutilities to be acceptable and consistent with the committee's most recent recommendations for garadacimab.

Adverse reactions

The company omitted adverse events from the economic model justified by the absence of severe TEAEs from OASIS-HAE trial for donidalorsen and the comparator trials. Clinical advice to the EAG agrees that the LTPs are usually well tolerated with high discontinuation rates observed with berotralstat.

4.2.7 Resources and costs

A SLR performed identified 81 records that met the pre-selection criteria of costs and resource use. Of these studies, 51 were abstracts, 19 full text journal articles and 11 were HTA appraisals. No full-text studies reported costing for England, and two of

the HTA appraisals which are NICE appraisals were used to inform the cost and healthcare resource used in the economic model.

Detailed critique of the SLR of cost and HCRU can be found in section 4.1

Intervention and comparator cost and resource use.

The main costs categories included in the base-case cost-comparison analysis are drug acquisition and administration costs for the intervention (donidalorsen) and the comparators, and resource use costs associated with HAE attacks. Costs were based on the 2023/2024 financial year.

Drug acquisition costs

The dosing regimen of donidalorsen used in the model is consistent with the marketing authorisation which states; patients should initiate treatment at a dose of [REDACTED].⁶⁵

[REDACTED]

Donidalorsen 80mg is available as a pre-filled pen at list price of £[REDACTED] per pre-filled pen. A PAS price of [REDACTED] was applied in the model to the list price resulting to a cost of [REDACTED] per pre-filled pen.

The dosing regimen for the LTP comparators (berotralstat, lanadelumab, and C1-INH) used in the model aligns with their SmPC (Table 32; Table 33). For C1-INH, the cost per cycle was based on the cost of IV Cinryze at a dose of 1000 IU twice per week and IV berinert at a distributed dose of 1000 IU received by [REDACTED] and 1,500 IU received by [REDACTED] of patients. All list prices for the comparators were sourced from the British National Formulary (BNF) as recommended in the NICE reference case guidelines.^{66, 67}

In the economic model,

[REDACTED]

[REDACTED].⁶⁵ The time point (6 months) of this reduction and percentage of patients ([REDACTED]%) who were assumed to switch were obtained from the full population data of the OASIS-HAE trial which indicated that this proportion of

patients remained attack free for [REDACTED].⁶⁸ A scenario analysis assuming [REDACTED]% of patients remained attack-free for [REDACTED] was performed based on a subgroup analysis of European patients in the OASIS-HAE trial.⁶⁸

For lanadelumab, the company modelled a dose reduction after 12 months in line with the SmPC, which allows a switch from 300 mg Q2W to 300 mg Q4W in patients who are stably attack-free, particularly those of lower body weight. The proportion of patients switching (45%) was sourced from a UK observational study by Dorr et al. (2023), based on data from 60 patients.⁶⁹ The 12-month switching time point was aligned with NICE TA606 and was stated by the company to have been validated by clinical experts. A scenario assuming switching at 6 months was also explored. This approach is consistent with the committee-preferred assumption in TA1101.⁴⁰ However, the EAG's clinical expert advised that, in practice, switching occurs at variable time points and dosing frequencies. This is supported by Dorr et al. (2023), which reported a mean time of 15.2 ± 12.1 weeks to achieve Q4W dosing among patients who switched.⁶⁹ Based on this evidence, the EAG explored a scenario in which 45% of patients switch at 3 months. This resulted in a [REDACTED] in the cost savings of donidalorsen compared with lanadelumab.

In estimating the cost of C1-INH, the dosage of IV Berinert used in the model was informed by the company's clinical experts – [REDACTED] of patients on 1500IU and [REDACTED] on 1000IU. There seems to be a great uncertainty around the dosing of Berinert in practice as mentioned in the CS and the EAG notes the company's assumption is rather conservative. In NICE TA 606 and TA1101, different approaches were applied. In TA 1101 the company applied a dose 1000 IU equivalent to that of IV Cinryze as both belong to the same protein group. EAG clinical expert indicated that the dose of Berinert is based on weight, with a dose of 20 IU/Kg prescribed, consistent with the advice of the EAG clinical expert in TA606. Applying this in the model based on the average weight of the cohort would result in a [REDACTED] treatment cost for C1-INH, therefore generating [REDACTED] costs savings for donidalorsen.

For berotralstat, the company did not apply the continuation (stopping) rule in either the base-case cost-comparison analysis or the cost-utility scenario analysis. In NHS clinical practice, berotralstat is commissioned with a continuation rule whereby treatment is discontinued if the attack rate is not reduced by at least 50% from baseline after 3 months.

In response to EAG clarification question B1, the company argued that it was implausible to assume equal efficacy across all LTPs while applying a stopping rule for berotralstat in the cost-comparison base case. The company further stated that implementing the discontinuation rule would remove acquisition costs for non-responders without capturing the increased attack burden associated with no LTP. The EAG agrees with the company's rationale for a cost-comparison analysis. The company explored the stopping rule in a cost-utility scenario analysis, which changed the ICER result from donidalorsen [REDACTED] berotralstat to an ICER of [REDACTED] (see Section 5.2.2).

The EAG notes that applying the berotralstat continuation rule was the committee-preferred assumption in both TA738 and TA1101. Clinical expert advice also indicated that excluding the stopping rule does not reflect real-world use of berotralstat. On this basis, and consistent with previous appraisals, the EAG applied the berotralstat stopping rule in its base-case analysis.

Table 32 : Dosing regimens of intervention and comparators

Treatment	Dosing regimen
Donidalorsen	The anticipated recommended starting dose in adult and adolescent patients [REDACTED] [REDACTED] ⁶⁵
Berotralstat	150 mg once daily ⁷⁰

Treatment	Dosing regimen
Lanadelumab	The recommended starting dose is 300 mg lanadelumab Q2W. In patients who are stably attack-free on treatment, a dose reduction to 300 mg lanadelumab Q4W may be considered, especially in patients with low weight.⁷¹ In patients with a body weight of less than 40 kg, a dose of 150 mg instead of 300 mg may be considered. However, as the unit price is the same for 300 mg and 150 mg this dose reduction for patients with a low weight is not modelled.
C1-INH	IV Cinryze: 1,000 IU every 3 or 4 days ⁷²
	IV Berinert is not licensed for routine prevention of HAE attacks, but an average dose of ■■■ IU is assumed based on insights from clinical experts obtained in June 2025. ⁷³
Source: Table 34, CS Q1M, every one month; Q2M, every 2 months; Q2W, every two weeks; Q4W, every 4 weeks; IV, intravenous; IU, international units.	

. Note: 100% treatment compliance is assumed for all treatments in the economic model in base case analysis

Table 33: Drug dosage, frequency and costs for intervention and comparators

Treatment	units	Administration frequency	Costs per pack	Acquisition cost per model cycle (28 days)
Donidalorsen	80 mg x 1	80 mg Q1M with █% of patients transferring to Q2M at month 6.	█ (with PAS discount)	Assuming a █%/█% Q1M/Q2M split: £█ (with PAS discount)
Berotrastat	150 mg x 28	150 mg once daily	£10,205.00	£10,205.00
Lanadelumab	300 mg x 1	300 mg Q2W with 45% of patients transferring to 300 mg Q4W after year 1.	£12,420.00	Assuming a 55%/45% Q2W/Q4W split: £19,251.00
C1-INH	Cinryze: 500 IU x 2	1,000 IU twice per week	£1,336.00	Assuming a 27%/73% Cinryze/ Berinert split: £█
	Berinert: 500 IU x 1	█ of patients receiving 1,000 IU and █ of patients receiving 1,500 IU of IV Berinert twice per week.	£670.00	

Source: Table 35, CS

Hereditary angioedema; IU, International unit; IV, Intravenous; mg, milligram; PAS, Patient access scheme; Q1M, Once every month; Q2M, Once every two months; Q2W, Once every two weeks; Q4W, Once every four weeks; SmPC, Summary of Product Characteristics

Administration costs

Administration costs were estimated in the model dependent

+

on whether patients self-administer or need support with administration and the route of administration. ■ and ■ of patients were assumed to self-administer their treatment through subcutaneous (SC) and intravenous (IV) routes respectively. For these patients, it was assumed that they received a one-off training session with a band 6 hospital nurse, lasting 45min or 30min for IV and SC treatments respectively. Based on the cost per hour for a band 6 hospital nurse of £62.00, the cost per 45-minute training session was estimated as £46.50 and that of a 30min training session as £31.00.^{57, 74} Using the proportions of patients that self-administer IV and SC treatments, the weighted one-off training cost ■ per patient for intravenous therapy (£46.50*■) and ■ per patient for subcutaneous therapy (£31.00*■).

No cost was associated with oral treatments (berotralstat) as applicable in standard practice.

Clinical experts to the EAG indicate that the assumptions seem reasonable, as they will expect more training time for patients who self-administer their IV LTPs because of the delicate nature of this type of administration.

HAE on-demand attack management and drug acquisition costs

A total cost of £1382.20 of on-demand medications used to treat acute HAE attack were applied in the model to all LTPs. The on-demand drugs used in the model are C1-INH (IV Cinryze and IV Berinert), Icatibant (Firazyr) and Ruconest. These therapies are consistent with currently used therapies in the UK, with no treatment included to reflect the fact that some attacks that are mild may not require on-demand treatment. The costs of on-demand treatments were estimated based on their cost per pack and dosing regimen (Table 34), with dose per attack of therapies (Berinert and Ruconest) that are weight-dependent calculated using the mean weight of the ITT population of the OASIS-HAE trial (■). Patients receiving Ruconest

were divided into two separate dosing groups depending on the weight of the patient. 50U/kg was used for patients weighing less than 84kg and a fixed dose of 4200 U was used for patients with weight at least 84kg. The mean weight and standard deviation from the ITT population in the OASIS-HAE trial () was used to estimate the proportion of patients in each category using a normal distribution.¹¹

No administration costs were applied to on-demand medications by the company justified with the fact that patients self-administer their medications at home. The EAG notes a lack of consistency in this approach because patients that self-administer their LTPs at home incurred a training cost. This was queried during the clarification stage (clarification question B6). In response, the company stated the assumption has been previously accepted in NICE TA738 of berotralstat. A scenario analysis which excluded administration costs for LTPs was presented by the company in response to the clarification question. However, this scenario differed from what the EAG had requested which was to apply administration costs for on-demand medications.

Clinical expert to the EAG advised that patients usually go the hospital to receive their on-demand medications, therefore administration costs should be applied to the management of acute attacks. Therefore, the EAG has explored a scenario analysis in section 5.2 where administration costs are applied to on-demand treatment of acute attacks.

Table 34: Dosage of on-demand medications

On-demand treatment	Labelled dose regimen per attack	Total dose per attack	Source
All cycles – Cinryze	1,000 IU	1,000.00 IU	SmPC ⁷²
All cycles – Berinert	20 IU/kg	IU	SmPC ⁷³
All cycles – Ruconest (weight <84 kg)	50 U/kg	U	SmPC ⁷⁵
All cycles – Ruconest (weight ≥84 kg)	4,200 U	4,200.00 U	SmPC ⁷⁵
All cycles – Firazyr	30 mg	30.00 mg	SmPC ³⁶

On-demand treatment	Labelled dose regimen per attack	Total dose per attack	Source
Source: Table 36, CS IU, International unit; kg, kilogram; mg, milligram; SmPC, Summary of Product Characteristics; U, Unit			

The acquisition costs and distribution of on-demand medications used in the model are presented in Table 35. The company assumed the distribution and costs of on-demand treatments used to treat mild, moderate/severe are equal for all LTPs as a simplified approach. These distributions were multiplied by the drugs cost per administration, and the proportion of patients experiencing mild and moderate/severe attacks and summed up to obtain the total pharmacological cost per attack (£1,382.20).

Table 35: Acquisition costs of on-demand treatment

Treatment	Unit size	Cost per unit	Treatment distribution per attack: mild	Treatment distribution per attack: moderate/severe
Berinert	500.00 IU	£670.00	20%	20%
Cinryze	500.00 IU	£668.00	20%	20%
Ruconest	2,100.00 IU	£750.00	20%	20%
Firazyr	30.00 mg/3ml	£1,395.00	20%	20%
No treatment	N/A	£0.00	20%	20%
Source: Table 37, CS IU, International unit; mg, milligram; ml, millilitre; N/A, not applicable				

EAG comment

The EAG considers that the simplified assumption of an equal distribution of on-demand therapies across treatments may not reflect differences in the frequency and severity of acute attacks experienced by patients receiving different LTPs and therefore may not capture the true costs of on-demand treatment. In sensitivity

analyses provided in response to Clarification Question A23, median rate ratios for attacks requiring on-demand medication differed substantially across donidalorsen Q8W, lanadelumab Q4W, and lanadelumab Q8W (see Section 3.6.5.2). This suggests that, despite overlapping credible intervals, applying identical on-demand treatment costs across all LTPs may obscure meaningful differences in costs driven by varying need for acute therapy. Clinical experts advising the EAG also indicated that assuming an equal distribution of attack severity across all LTPs does not reflect real-world patient experience.

The EAG also noted discrepancies between the on-demand medications used in the OASIS-HAE trial and those modelled in the economic analysis (Clarification Question B5). While the treatments differ in some respects, the EAG's clinical expert confirmed that the on-demand therapies modelled are consistent with UK clinical practice.

Health State unit costs and resource use

No health care resource use (HCRU) was applied in the model base-case due to the equal efficacy assumption implemented within the cost-comparison analysis. The company notes, HCRU has rather been applied in the cost utility analysis scenario analysis. The EAG asked the company to apply HCRU in the cost-comparison base case to reflect the 'true' total HCRU costs associated with donidalorsen and its comparator LTPs. The company provided an additional setting within the model that allows the implementation of HCRU within the cost-comparison framework but still excluded it from their base case.

Adverse reaction costs and resource use

As aforementioned, no adverse reactions were included in the model, therefore no costs associated with adverse reactions are included in the cost-comparison analysis.

Subsequent treatment costs

In the model, patients did not receive subsequent treatment after treatment discontinuation on initial LTPs but received on-demand medications for acute HAE attacks. The EAG inquired from the company if the absence of subsequent treatment records in OASIS-HAE indicates that no subsequent treatments were received by patients in the OASIS-HAE trial during follow-up or that no data was collected on subsequent treatment in the trial (Clarification question C8). The company confirmed that the absence of subsequent treatment in QASIS-HAE trial means that subsequent treatment data were not collected as part of QASIS-HAE.

Severity

The company did not apply severity weighting modifier to donidalorsen and the EAG confirms that severity weighting does not apply for this appraisal (see section 5.3).

Uncertainty

The company acknowledged several limitations in its analysis.

- Limited comparative effectiveness evidence:

The pivotal OASIS-HAE trial for donidalorsen was of limited duration and did not include head-to-head comparisons with relevant comparators. As a result, a NMA was used to estimate relative treatment effects. The company attributed uncertainty in the NMA primarily to heterogeneity in data availability across comparators, rather than to methodological limitations of the NMA itself.

- Data limitations related to disease rarity:

The company highlighted the rarity of HAE and the resulting scarcity of published data to inform model inputs, leading to reliance on clinical expert opinion. While necessary, this introduces additional uncertainty, particularly where expert views differ. The company also noted challenges in estimating lifetime healthcare costs and health-related quality of life due to heterogeneity in patient experiences over time. The EAG clinical expert agreed with the latter and indicated that without real-world evidence data, it is difficult to model HCRU that would closely reflect that of HAE patients.

5 Cost-effectiveness results

Section 5.1 summarises the company's cost-effectiveness results, section 5.2 presents the EAG's additional work and preferred assumptions, and section 5.3 explores decision modifiers including the company's and EAG's preferred QALY weighting for severity.

5.1 Company's cost-comparison results

5.1.1 Company's base case

The company reported deterministic and sensitivity analysis results for the cost-comparison between donidalorsen and comparators in two subgroups.

- i. Berotralstat for ≥ 2 attacks per month.
- ii. Lanadelumab and C1-INH for ≥ 8 attacks per month.

Main outcomes are reported in terms of mean costs and mean life years and incremental costs. All results reflect the application of a PAS discount of [REDACTED]% for donidalorsen with a net price of £[REDACTED] per 80mg pre-filled pen and list prices for berotralstat, lanadelumab and C1-INH.

Company's deterministic results

In Table 36, we present the results of the company's deterministic base case which shows that treatment with donidalorsen is associated with a cost saving of £[REDACTED] versus berotralstat in HAE patients experiencing ≥ 2 attacks per month over a lifetime horizon.

In patients experiencing ≥ 8 attacks per month, treatment with donidalorsen was associated with a cost savings of £[REDACTED] versus lanadelumab and £[REDACTED] versus C1-INH (Table 37).

Table 36: Company's deterministic base -case results, using PAS price for donidalorsen (≥ 2 attacks per month)

Treatment	Total costs (£)	Incremental costs versus donidalorsen (£)
Donidalorsen	██████	██████
Berotrastat	██████	██████

Table 37: Company's deterministic base -case results, using PAS price for donidalorsen (≥ 8 attacks per month)

Treatment	Total costs (£)	Incremental costs versus donidalorsen (£)
Donidalorsen	██████	-
Lanadelumab	██████	██████
C1-INH	██████	██████

Company's probabilistic sensitivity analysis results

Using 1000 iterations, the joint parameter uncertainty was assessed by assigning probability distributions to key model parameters based on their characteristics. The mean costs and QALYs were obtained by randomly selecting variables from each distribution. The PSA results are presented in Table 38 and Table 39. It shows that while considering joint uncertainty, treatment with donidalorsen is expected to save £██████ versus berotrastat, £██████ versus lanadelumab and £██████ versus C1-INH.

Table 38: Company probabilistic sensitivity results, using PAS (≥ 2 attacks per month)

Treatment	Total costs (£)	Incremental costs (£)
Donidalorsen	██████	-
Berotrastat	██████	██████

Table 39: Company probabilistic sensitivity results, using PAS (≥ 8 attacks per month)

Treatment	Total Costs (£)	Incremental costs (£)

Donidalorsen	██████	-
Lanadelumab	██████	██████
C1-INH	██████	██████

5.1.2 Company's sensitivity and scenario analyses

Deterministic sensitivity analysis

Numerous parameters were individually varied in a one-way sensitivity analysis (OWSA) to explore the uncertainty associated with each parameter on the model results. Seven to ten most impactful parameters were presented in a tornado diagrams (see Figure 5; Figure 6). Each parameter was varied systematically by increasing and decreasing based on 95% CIs or using standard error of $\pm 20\%$ of mean of each parameter (in the absence of data) and applying appropriate distributions. The results show that donidalorsen dose reduction one-off percentage was the most impactful parameter for donidalorsen versus berotralstat and lanadelumab. For donidalorsen versus C1-INH, the proportion of patients taking Cinryze was the most influential parameter, followed by donidalorsen dose reduction one-off percentage (see Table 40; Table 41 and Table 42).

Table 40: OWSA incremental costs of most impactful parameters (donidalorsen vs berotralstat)

Parameter name	Lower bound incremental costs (£)	Upper bound incremental costs (£)
Donidalorsen dose reduction one-off percentage	██████	██████
Donidalorsen dose reduction timepoint (cycles)	██████	██████
Age	██████	██████
Percentage male	██████	██████
Subcutaneous administration cost	██████	██████
Proportion of patients requiring SC injection support	██████	██████

Parameter name	Lower bound incremental costs (£)	Upper bound incremental costs (£)
Weighted one-off SC administration training cost per patient in cycle 1 (£)	■■■■■	■■■■■
Source: CS, Table 45		

OWSA, one -way sensitivity analysis; SC, subcutaneous

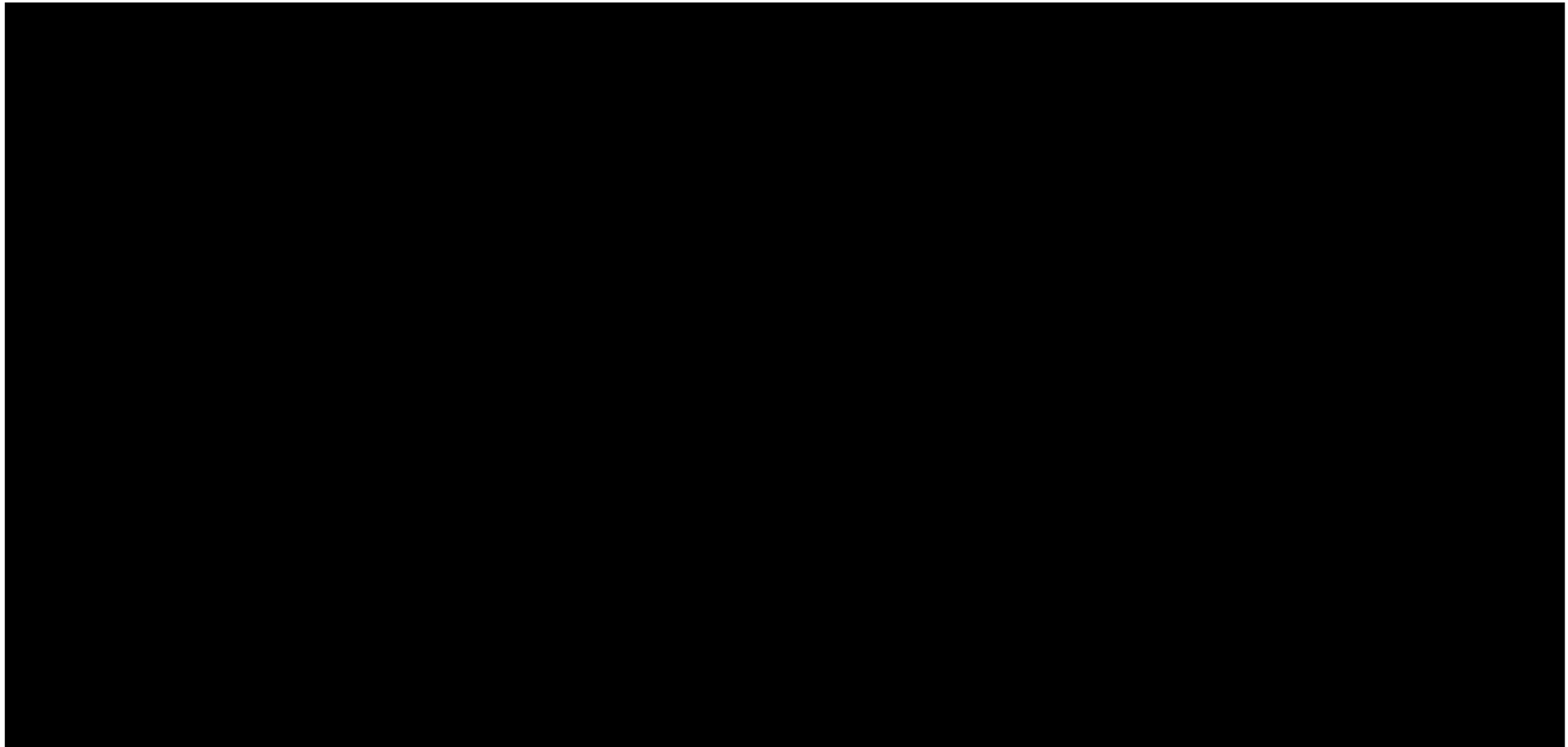


Figure 4: Company's OWSA results (donidalorsen vs berotralstat)

**Table 41: OWSA incremental results for the most impactful parameters
(donidalorsen vs lanadelumab)**

Parameter name	Lower bound incremental costs (£)	Upper bound incremental costs (£)
Donidalorsen dose reduction one-off percentage	██████	██████
Lanadelumab dose reduction one-off percentage	██████	██████
Age	██████	██████
Lanadelumab dose reduction timepoint (cycles)	██████	██████
Donidalorsen dose reduction timepoint (cycles)	██████	██████
Percentage male	██████	██████
Subcutaneous administration cost	██████	██████
Proportion of patients requiring SC injection support	██████	██████
Weighted one-off SC administration training cost per patient in cycle 1 (£)	██████	██████

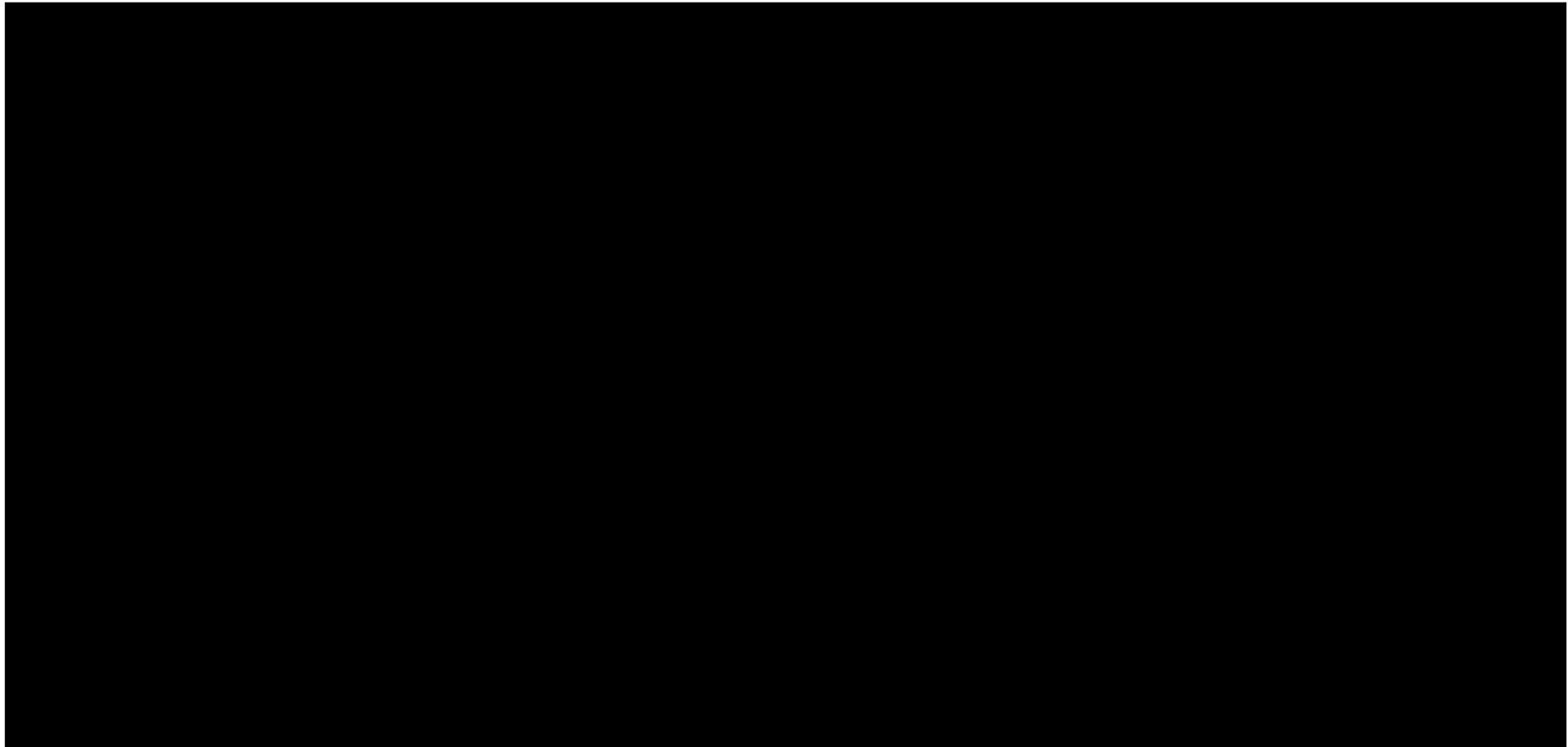


Figure 5: Tornado diagram of the most impactful parameters for donidalorsen vs lanadelumab

**Table 42: OWSA incremental results for the most impactful parameters
(donidalorsen vs C1-INH)**

Parameter name	Lower bound incremental costs (£)	Upper bound incremental costs (£)
C1-INH proportion - Cinryze	██████	██████
Donidalorsen dose reduction one-off percentage	██████	██████
Age	██████	██████
Donidalorsen dose reduction timepoint (cycles)	██████	██████
Intravenous administration cost	██████	██████
Proportion of patients requiring IV injection support	██████	██████
Percentage male	██████	██████
Subcutaneous administration cost	██████	██████
Proportion of patients requiring SC injection support	██████	██████
Weighted one-off IV administration training cost per patient in cycle 1 (£)	██████	██████

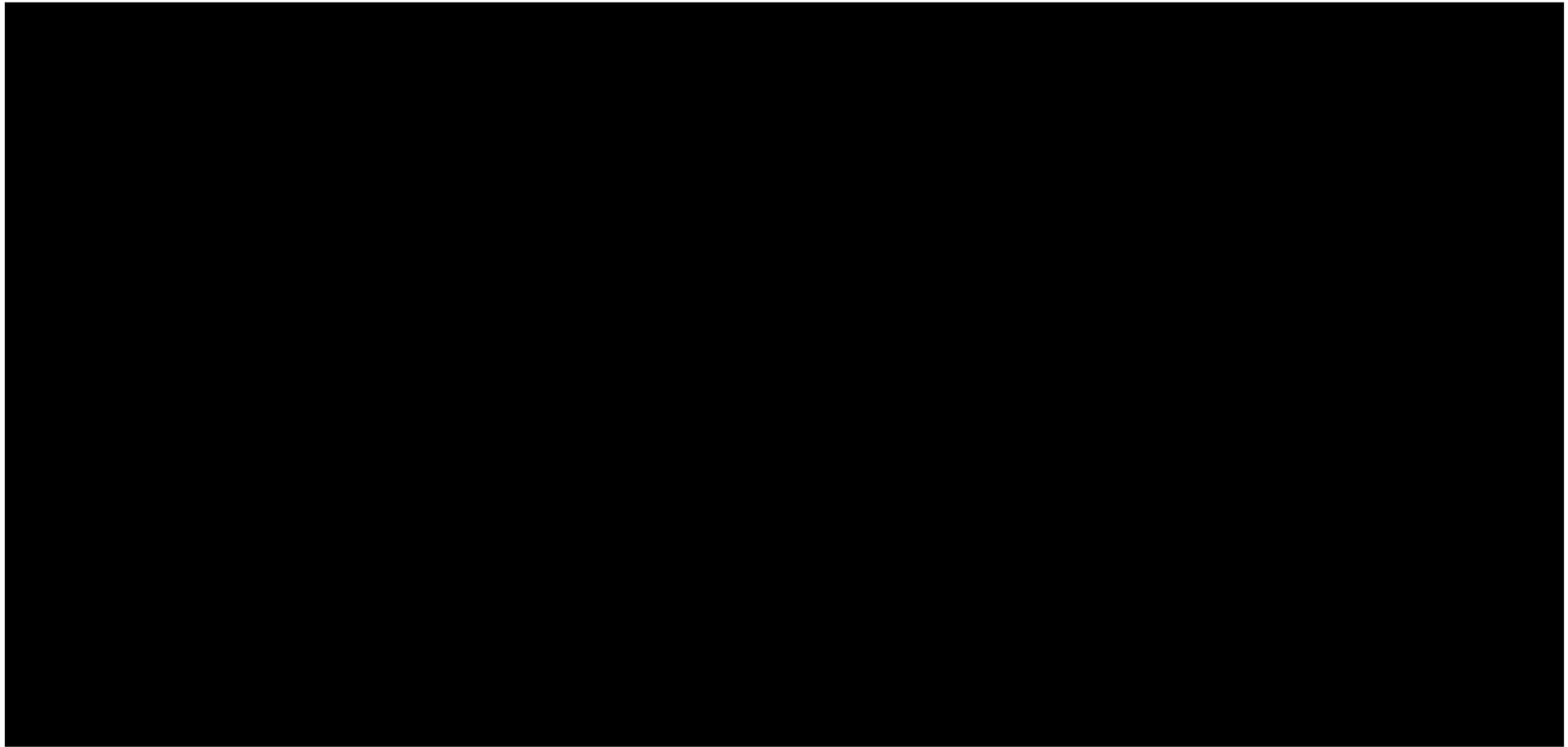


Figure 6: Tornado diagram of the most impact parameters for donidalorsen vs C1-INH

Scenario analysis

The company undertook several scenario analyses to assess the impact to their base-case results. Details of the scenario analyses along with the rationale and results of deterministic and probabilistic scenario analysis was presented. Table 43 presents the scenarios undertaken along with their rationale. In Table 44 - Table 49 we present the results of the deterministic and probabilistic results. The results show that donidalorsen is associated with a cost savings in both deterministic and probabilistic analyses except in the 10-year time horizon deterministic and probabilistic scenario for the ≥ 2 attacks per month population.

Table 43: Company Scenario Analyses

Parameter	Scenario number	Base case	Scenario	Rationale for scenario
Proportion of patients who transfer to donidalorsen Q2M	1	█████%	█████%	This is the proportion of patients who are attack-free for three consecutive months in OASIS-HAE within the European subgroup of patients, as per the post-hoc analysis.
Timepoint at which patients transfer to lanadelumab Q4W	2	After month 12	After month 6	Setting this equal to the dose frequency reduction point for donidalorsen. ^{57, 68}
Treatment discontinuation	3	TTD from the OASIS-HAE trial using an exponential curve	TTD from the OASIS-HAE trial using a log-normal curve	Based on input from UK clinical experts. ⁵⁷
	4		█████% per year	
Time horizon	5	Lifetime (63 years)	10 years	To explore the effect of a range of time horizons.
	6		30 years	
Discount rate for costs	7	3.5%	1.5%	To explore the effect of a range of discount rates on costs.
	8		6%	

Q2M, once every two months; Q4W, once every four weeks

Company's deterministic scenario analysis results

Table 44: Deterministic scenario analysis results for donidalorsen vs berotralstat (≥2 attacks per month), using PAS

Parameter	Scenario	Total costs donidalorsen (£)	Total costs berotralstat (£)	Incremental costs (£)
Proportion of patients who transfer to donidalorsen Q2M	█████%	█████	█████	█████
Timepoint at which patients transfer to lanadelumab Q4W	After month 6	█████	█████	█████
Treatment discontinuation	TTD from the OASIS-HAE trial using a log-normal curve	█████	█████	█████
	█████% per year	█████	█████	█████
Time horizon	10 years	█████	█████	█████
	30 years	█████	█████	█████
Discount rate for costs	1.5%	█████	█████	█████
	6%	█████	█████	█████

HAE, Hereditary angioedema; Q2M, once every two months; Q4W, once every four weeks; TTD, time-to-treatment discontinuation

Table 45: Deterministic scenario analysis results for donidalorsen vs lanadelumab (≥8 attacks per month), with PAS

Parameter	Scenario	Total costs donidalorsen (£)	Total costs lanadelumab (£)	Incremental costs versus donidalorsen (£)
Proportion of patients who transfer to donidalorsen Q2M	■%	■	■	■
Timepoint at which patients transfer to lanadelumab Q4W	After month 6	■	■	■
Treatment discontinuation	TTD from the OASIS-HAE trial using a log-normal curve	■	■	■
	■% per year	■	■	■
Time horizon	10 years	■	■	■
	30 years	■	■	■
Discount rate for costs	1.5%	■	■	■
	6%	■	■	■

HAE, Hereditary angioedema; Q2M, once every two months; Q4W, once every four weeks; TTD, time-to-treatment discontinuation

Table 46: Deterministic scenario analysis results for donidalorsen vs C1-INH (≥ 8 attacks per month), with PAS

Parameter	Scenario	Total costs donidalorsen (£)	Total costs C1-INH (£)	Incremental costs versus donidalorsen (£)
Proportion of patients who transfer to donidalorsen Q2M	████%	████	████	████
Timepoint at which patients transfer to lanadelumab Q4W	After month 6	████	████	████
Treatment discontinuation	TTD from the OASIS-HAE trial using a log-normal curve	████	████	████
	████% per year	████	████	████
Time horizon	10 years	████	████	████
	30 years	████	████	████
Discount rate for costs	1.5%	████	████	████
	6%	████	████	████

C1-INH, C1 esterase inhibitor; HAE, Hereditary angioedema; Q2M, once every two months; Q4W, once every four weeks; TTD, time-to-treatment discontinuation

Company's probabilistic scenario results

Table 47: Probabilistic scenario analysis results for donidalorsen vs berotralstat (≥ 2 attacks per month), with PAS

Parameter	Scenario	Total costs donidalorsen (£)	Total costs berotralstat (£)	Incremental costs versus donidalorsen (£)
Proportion of patients who	████%	████	████	████

Parameter	Scenario	Total costs donidalorsen (£)	Total costs berotralstat (£)	Incremental costs versus donidalorsen (£)
transfer to donidalorsen Q2M				
Timepoint at which patients transfer to lanadelumab Q4W	After month 6			
Treatment discontinuation	TTD from the OASIS-HAE trial using a log-normal curve			
	% per year			
Time horizon	10 years			
	30 years			
Discount rate for costs	1.5%			
	6%			

HAE, Hereditary angioedema; Q2M, once every two months; Q4W, once every four weeks; TTD, time-to-treatment discontinuation

Table 48: Probabilistic scenario analysis results for donidalorsen vs lanadelumab (≥8 attacks per month), with PAS

Parameter	Scenario	Total costs donidalorsen (£)	Total costs lanadelumab (£)	Incremental costs versus donidalorsen (£)
Proportion of patients who transfer to donidalorsen Q2M	%			
Timepoint at which patients transfer to lanadelumab Q4W	After month 6			

Parameter	Scenario	Total costs donidalorsen (£)	Total costs lanadelumab (£)	Incremental costs versus donidalorsen (£)
Treatment discontinuation	TTD from the OASIS-HAE trial using a log-normal curve			
	% per year			
Time horizon	10 years			
	30 years			
Discount rate for costs	1.5%			
	6%			

HAE, Hereditary angioedema; Q2M, once every two months; Q4W, once every four weeks; TTD, time-to-treatment discontinuation

Table 49: Probabilistic scenario analysis results for donidalorsen vs C1-INH (≥8 attacks per month), with PAS

Parameter	Scenario	Total costs donidalorsen (£)	Total costs lanadelumab (£)	Incremental costs versus donidalorsen (£)
Proportion of patients who transfer to donidalorsen Q2M	%			
Timepoint at which patients transfer to lanadelumab Q4W	After month 6			
Treatment discontinuation	TTD from the OASIS-HAE trial using a log-normal curve			
	% per year			
Time horizon	10 years			
	30 years			
	1.5%			

Parameter	Scenario	Total costs donidalorsen (£)	Total costs lanadelumab (£)	Incremental costs versus donidalorsen (£)
Discount rate for costs	6%	████████	████████	████████

HAE, Hereditary angioedema; Q2M, once every two months; Q4W, once every four weeks; TTD, time-to-treatment discontinuation

Cost utility scenario

As previously mentioned, the company undertook a cost-utility analysis as a scenario analysis.

In Table 50, we present the results of the company's CUA deterministic results which shows that treatment with donidalorsen produces a ██████ ICER versus berotralstat in HAE patients experiencing ≥ 2 attacks per month over a lifetime horizon. In patients experiencing ≥ 8 attacks per month, treatment with donidalorsen produces an ICER of ██████ versus lanadelumab and ██████ ICER versus C1-INH. The ██████ results of donidalorsen versus berotralstat and C1-INH explains that donidalorsen is less costly and ██████ than berotralstat and C1-INH. When compared with lanadelumab, the results show that donidalorsen is less costly but also ██████ effective with a cost savings of ██████ and ██████ QALYs gained over the lifetime horizon.

The PSA results presented by the company were like the deterministic results and are reported in Table 51. It shows that while considering joint parameter uncertainty, treatment with donidalorsen is expected to save cost and ██████ when compared to berotralstat for the ≥ 2 attacks per month population. For the ≥ 8 attacks per month population, donidalorsen produces a ██████ ICER versus C1-INH while with lanadelumab majority of the cost and effect pairs were found in the ██████ quadrant which suggests that donidalorsen saves cost ██████ over the life-time horizon.

Table 50: Deterministic cost- utility results

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)	NMB at £20,000	NMB at £30,000
≥2 attacks per month population								
Donidalorsen	██████	22.515	██████	-	-	-	-	
Berotrastat	██████	22.515	██████	██████	██████	██████	██████	██████
≥ 8 attacks per month population								
Donidalorsen	██████	22.515	██████	-	-	-		
Lanadelumab	██████	22.515	██████	██████	██████	██████	██████	██████
C1-INH	██████	22.515	██████	██████	██████	██████	██████	██████

Table 51: PSA cost-utility results

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
≥ 2 attacks per month population					
Donidalorsen	██████	██████	-	-	-
Berotrastat	██████	██████	██████	██████	██████
≥ 8 attacks per month population					

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Donidalorsen	██████	██████	-	-	-
Lanadelumab	██████	██████	██████	██████	██████
C1-INH	██████	██████	██████	██████	██████

C1-INH, C1-esterase inhibitor; ICER, Incremental cost-effectiveness ratio; PSA, Probabilistic sensitivity analysis; QALYs, Quality-adjusted life years; SW, South-west quadrant

Deterministic sensitivity analysis was performed for the CUA. Ten most impactful parameters that have the greatest effect on the net monetary benefit were presented in tornado diagrams (see CS, appendix K figures 1 - 3). The results show that the model was most sensitive to median rate ratio of donidalorsen and respective comparator treatments, the percentage of patients who reduce to the donidalorsen Q2M dosing regimen, the percentage of patients who reduce to the lanadelumab Q4W dosing regimen, and the baseline attack rate.

The company further explored several scenario analyses within the CUA. The results show that donidalorsen has a [REDACTED] ICER versus berotralstat and C1-INH in all scenarios. With lanadelumab, all the scenarios produced ICERs that are in the [REDACTED] quadrant with donidalorsen consistently producing cost savings and [REDACTED] in both deterministic and probabilistic analysis. Table 52 presents the scenarios undertaken along with their rationale. In Table 53- Table 58, we present the deterministic and probabilistic scenario results.

Table 52: Company Scenarios in CUA

Scenario number	Parameter	Base case	Scenario
1	Carer disutilities	Include carer disutilities	Exclude carer disutilities
2	Administration disutilities	Include administration disutilities	Exclude administration disutilities
3	Utility source	Nordenfelt et al. (2024) Attack-free utility: 0.825 Attack base utility: 0.512	Aygören-Pürsün (2016) Attack-free utility: 0.722 Attack base utility: 0.444
4	Proportion of patients who transfer to donidalorsen Q2M	[REDACTED]	[REDACTED]

Scenario number	Parameter	Base case	Scenario
5	Timepoint at which patients transfer to lanadelumab Q4W	After 12 months	After 6 months
6	Treatment discontinuation	Informed by TTD data from the OASIS-HAE trial using an exponential curve	Informed by TTD data from the OASIS-HAE trial using a lognormal curve
7			█% per year, informed by input from UK clinical experts.
8	Time horizon	Lifetime (63 years)	10 years
9			30 years
10	Discount rate for costs and outcomes	3.5%	1.5%
11			6%

Table 53: Deterministic scenario analyses - donidalorsen vs berotralstat (≥2 attacks per month population)

Scenario number	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Base case		█	█	█
1	Exclude carer disutilities	█	█	█
2	Exclude administration disutilities	█	█	█
3	Utility values from Aygören-Pürsün (2016)	█	█	█
4	█% switch to Q2M donidalorsen	█	█	█
6	Treatment discontinuation	█	█	█

Scenario number	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
	distribution - log-normal			
7	█% discontinuation per year	█	█	█
8	10-year time horizon	█	█	█
9	30-year time horizon	█	█	█
10	1.5% discount rate for costs and outcomes	█	█	█
11	6% discount rate for costs and outcomes	█	█	█

ICER, Incremental cost -effectiveness ratio; Q2M, Once every two months; Q4W , Once every four weeks; QALY, Quality adjusted life year.

Table 54: Deterministic scenario analyses - donidalorsen vs lanadelumab (≥8 attacks per month population)

Scenario number	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Base case		█	█	█
1	Exclude carer disutilities	█	█	█
2	Exclude administration disutilities	█	█	█
3	Utility values from Aygören-Pürsün (2016)	█	█	█
4	█% switch to Q2M donidalorsen	█	█	█
5	Timepoint at which patients transfer to lanadelumab Q4W: After month 6	█	█	█

6	Treatment discontinuation distribution - log-normal			
7	% discontinuation per year			
8	10-year time horizon			
9	30-year time horizon			
10	1.5% discount rate for costs and outcomes			
11	6% discount rate for costs and outcomes			

ICER, Incremental cost-effectiveness ratio; Q2M, Once every two months; Q4W, Once every 4 weeks; QALY, Quality adjusted life year; SW, South-west quadrant

Table 55: Deterministic scenario analyses - donidalorsen vs C1-INH (≥8 attacks per month population)

Scenario number	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Base case				
1	Exclude carer disutilities			
2	Exclude administration disutilities			
3	Utility values from Aygören-Pürsün (2016)			
4	% switch to Q2M donidalorsen			
6	Treatment discontinuation distribution - log-normal			

Scenario number	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
7	█% discontinuation per year	██████	██	██████
8	10-year time horizon	██████	██	██████
9	30-year time horizon	██████	██	██████
10	1.5% discount rate for costs and outcomes	██████	██	██████
11	6% discount rate for costs and outcomes	██████	██	██████

C1-INH, C1-esterase inhibitor; ICER, Incremental cost -effectiveness ratio; Q2M, Once every two months; Q4W, Once every 4 weeks; QALY, Quality adjusted life year.

Table 56: Probabilistic scenario analyses - donidalorsen vs berotralstat (≥2 attacks per month population)

Scenario number	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Base case (deterministic)		██████	██	██████
1	Exclude carer disutilities	██████	██	██████
2	Exclude administration disutilities	██████	██	██████
3	Utility values from Aygören-Pürsün (2016)	██████	██	██████
4	█████% switch to Q2M donidalorsen	██████	██	██████

Scenario number	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
6	Treatment discontinuation distribution - log-normal			
7	% discontinuation per year			
8	10-year time horizon			
9	30-year time horizon			
10	1.5% discount rate for costs and outcomes			
11	6% discount rate for costs and outcomes			

ICER, Incremental cost-effectiveness ratio; Q2M, Once every two months; Q4W, Once every four weeks; QALY, Quality adjusted life year.

Table 57: Probabilistic scenario analyses - donidalorsen vs lanadelumab (≥8 attacks per month population)

Scenario number	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
	Base case (deterministic)			
1	Exclude carer disutilities			
2	Exclude administration disutilities			
3	Utility values from Aygören-			

	Pürsün (2016)			
4	■% switch to Q2M donidalorsen	■	■	■
5	Time points at which patients transfer to lanadelumab Q4W: After month 6	■	■	■
6	Treatment discontinuation distribution - log-normal	■	■	■
7	■% discontinuation per year	■	■	■
8	10-year time horizon	■	■	■
9	30-year time horizon	■	■	■
10	1.5% discount rate for costs and outcomes	■	■	■
11	6% discount rate for costs and outcomes	■	■	■

ICER, Incremental cost-effectiveness ratio; Q2M, Once every two months; Q4W, Once every 4 weeks;
QALY, Quality adjusted life year; SW, South-west quadrant.

Table 58: Probabilistic scenario analyses - donidalorsen vs C1-INH (≥8 attacks per month population)

Scenario number	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Base case (deterministic)		■	■	■

Scenario number	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
1	Exclude carer disutilities	██████	████	██████
2	Exclude administration disutilities	██████	████	██████
3	Utility values from Aygören-Pürsün (2016)	██████	████	██████
4	██████% switch to Q2M donidalorsen	██████	████	██████
6	Treatment discontinuation distribution - log-normal	██████	████	██████
7	██████% discontinuation per year	██████	████	██████
8	10-year time horizon	██████	████	██████
9	30-year time horizon	██████	████	██████
10	1.5% discount rate for costs and outcomes	██████	████	██████
11	6% discount rate for costs and outcomes	██████	████	██████

C1-INH, C1-esterase inhibitor; ICER, Incremental cost -effectiveness ratio; Q2M, Once every two months; Q4W, Once every 4 weeks; QALY, Quality adjusted life year.

In summary, the company included suitable model inputs in the PSA with appropriate distributions to assess the impact of joint parameter uncertainty. In the OWSA, a range of parameter inputs were varied to evaluate the impact on the company's base case results. The EAG was able to replicate all scenario analyses, however we consider that other scenarios like varying the proportion of patients taking Cinryze and Berinert and varying the distribution of patients on the two different doses of Berinert could have been explored due to the uncertainties surrounding the data used in the CEM.

5.2 EAG's additional analyses

5.2.1 Model validation and face validity check

According to the CS, the model was validated by both internal (not involved in the initial programming) and external health economist to ensure it works as expected. The model structure, assumptions, inputs and outputs were validated by UK clinical experts at two different meetings.

Model outputs were further compared with relevant clinical trials and previous TAs (NICE TA 606 and TA 738) for validation. The validation against relevant clinical trials included comparing the attack rates used in the model, obtained from the NMA as follows:

- HAE attack per model cycle based on the NMA was found to be like that of the OASIS-HAE trial (■ vs 0.44)
- The median rate ratio derived from the NMA and applied in the model for donidalorsen Q1M versus placebo (■) aligns with the reduction in HAE attack versus placebo observed in OASIS-HAE trial (81%).
- The rate ratios obtained from the NMA presented on Table 31 of the CS all align with the attack rate ratio versus placebo for all comparators as seen in the relevant trials

According to the company submission, model assumptions and outputs were broadly consistent with those used in previous NICE appraisals (TA606 and TA738). For example, total pharmacological costs for on-demand medication in the current appraisal (£1,382.20) were similar to those reported in TA606 for lanadelumab (£1,382.21). However, the EAG's clinical expert noted that estimating healthcare resource use in HAE—particularly on-demand medication costs—is challenging in the absence of real-world data, given variation across LTPs in the proportion of attacks requiring on-demand treatment and substantial inter-patient heterogeneity in resource use.

The EAG undertook a series of “black-box” validation checks of the company’s model, including setting treatment acquisition costs to zero for individual comparators to confirm that ICERs moved in the expected direction, applying an extreme QALY discount rate to test that post–time 0 QALY gains approached zero, and checking consistency of formulas within the Markov traces across donidalorsen and comparator treatments. The EAG also sought clinical validation of key model assumptions and outputs.

5.2.2 EAG’s exploratory analyses using company’s base case

Based on our critique of the company’s economic model, the EAG made changes to the company’s model to explore the impact of individual changes to the company’s base case results. The suggested changes along with the EAG’s justifications are presented in Table 59. Table 60 and Table 61 show the results of these analyses.

Table 59: EAG exploratory analyses

Exploratory analysis number	Company’s base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
1	Baseline attack rate of the run-in period of the placebo arm of the OASIS-HAE trial	Pooled baseline attack rate from the respective trials for all LTPs	EAG experts indicated baseline attack rate is TEM and determines the choice of LTPs.	4.2.5
	■ IV Cinryze, and ■ IV Berinert.	40% IV Cinryze and 60% IV Berinert	Due to the uncertainty in clinical opinion. The proportion	4.2.7

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
			of patients taking C1-INH was informed by the clinical experts the company contacted as part of this appraisal.	
2	Donidalorsen 80mg Q1M, then 80mg Q2M.	Donidalorsen 80mg Q4W, then Q8W.	Differences in the dosing frequency used in trial and that of the MA. To assess the weight of the uncertainty in the dosing frequency of donidalorsen.	4.2.7
3	45% of patients on lanadelumab will switch to Q4W dosing frequency at 12 months	76.9% will switch to Q4W dosing frequency at 12 months	The company used the time point patients switch from TA606 but did not use the corresponding percentage that switch.	4.2.7
4	45% of patients on	45% of patients on lanadelumab 300mg	Clinical experts to the EAG	4.2.7

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
	lanadelumab will switch to Q4W dosing frequency at 12 months	Q2W will switch to Q4W at 3 months	indicated the dosing frequency of lanadelumab is heterogenous with patients switching at different time-points to different dosing frequencies.	
5	No administration cost included for on-demand medications	Administration costs included to the total pharmacological cost of on-demand medications	The company excluded on-demand treatment administration cost but clinical expert to the EAG advised that administration cost should be applied to acute HAE attack treatment.	4.2.7
6	100% compliance assumed in the model	80% compliance assumed	To assess the impact of setting compliance parameter to	4.2.7

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
			80% in the model	
7	Equal efficacy assumed in model	Efficacy differs by treatment and is based on rate ratios derived from the NMA	EAG believes equal efficacy assumption has not been sufficiently justified and degree of separation in point estimates is inconsistent with an assumption of equal efficacy	3.6.6
8	Excludes garadacimab as a comparator	Includes garadacimab as a comparator	Garadacimab is included in the NICE final scope; draft guidance recommending its use was published prior to company submission, and the EAG clinical expert considers its exclusion a major omission.	2.3

TEM, treatment effect modifier; NMA, network meta-analysis

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Table 60: Results of EAG exploratory analyses on company base case

Exploratory analysis number	Scenario applied to company's base case	Total costs (£) Donidalorsen	Total costs (£) Comparator	Incremental costs (£)	Percentage change from base case
Donidalorsen versus Berotralstat (≥ 2 attacks per month population)					
Company base case		██████	██████	██████	-
1	Pooled baseline attack rate (0.82)	██████	██████	██████	██
2	Donidalorsen 80mg Q4W, then Q8W.	██████	██████	██████	████
3	Administration costs for on-demand medications included	██████	██████	██████	██
4	Varying efficacy for all treatments	██████	██████	██████	████
5	80% treatment compliance	██████	██████	██████	████
	90% treatment compliance	██████	██████	██████	████
Donidalorsen versus lanadelumab (≥ 8 attacks per month population)					
Company base case		██████	██████	██████	-
6	Donidalorsen 80mg Q4W, then Q8W	██████	██████	██████	██

Exploratory analysis number	Scenario applied to company's base case	Total costs (£) Donidalorsen	Total costs (£) Comparator	Incremental costs (£)	Percentage change from base case
7	76.9% of patients on lanadelumab 300mg Q2W switch to Q4W at 12 months				
8	45% of patients on lanadelumab 300mg Q2W switch to Q4W at 3 months				
9	Administration costs for on-demand medications included.				
10	80% treatment compliance				
11	90% treatment compliance				
12	Varying efficacy for all treatments				
Donidalorsen versus C1-INH (≥ 8 attacks per month population)					
Company base case					-
13	Donidalorsen 80mg Q4W, then Q8W.				

Exploratory analysis number	Scenario applied to company's base case	Total costs (£) Donidalorsen	Total costs (£) Comparator	Incremental costs (£)	Percentage change from base case
14	40% IV Cinryze and 60% IV Berinert				
15	Administration costs for on-demand medications included				
16	Varying efficacy for all treatments				
17	80% treatment compliance				
18	90% treatment compliance				
Positive percentage change means increase cost savings and negative percentage change means decrease in costs savings of donidalorsen versus the comparator					

Table 61: Cost-utility analysis scenario using EAG rate ratios derived from the NMA

Exploratory analysis number	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
(≥ 2 attacks per month population)							
Donidalorsen	██████	22.515	██████	-	-	-	-
Berotrastat	██████	22.515	██████	-██████	0.000	██████	██████
(≥ 8 attacks per month population)							
Donidalorsen	██████	22.515	██████	-	-	-	-
Lanadelumab	██████	22.515	██████	██████	0.000	██████	██████
C1-INH	██████	22.515	██████	██████	0.000	██████	██████

Exploratory analysis number	Scenario applied to company's base case	Total costs (£) Donidalorsen	Total costs (£) Garadacimab	Incremental costs (£)
	Inclusion of garadacimab as a comparator			

5.2.3 EAG's preferred assumptions

Based on all considerations in Section **Error! Reference source not found.** of this report and further justification for choice of assumptions outlined below, the EAG defined a new tentative base case. The adjustments made to the company model are described below and impact on QALYs and incremental costs summarised in Table 62, Table 63, Table 64, Table 65, Table 66, and Table 67. All results are without a severity modifier (rationale provided in section 5.3.1)

- **Efficacy assumptions for donidalorsen and comparator treatments**

The EAG does not consider it appropriate to assume equal efficacy across treatments based on the presented rate ratios and overlapping credible intervals. Although the 95% credible intervals for the treatment effects versus placebo overlap, these intervals reflect uncertainty in the individual treatment–placebo comparisons and do not provide evidence of equivalence between active treatments. Importantly, the company did not conduct any formal equivalence, non-inferiority, or pairwise comparative analyses between active treatments; the assumption of equal efficacy was based solely on overlapping credible intervals from treatment–placebo comparisons.

The EAG notes that the median rate ratios differ substantially across treatments, ranging from ■■■ for lanadelumab Q2W to ■■■ for berotralstat, indicating heterogeneity in treatment effects. Lanadelumab Q2W and donidalorsen Q4W appear to have notably ■■■ rate ratios than the other comparator treatments, suggesting ■■■ efficacy. This degree of separation in point estimates is inconsistent with an assumption of equal efficacy.

The EAG believes that more appropriate tests of equality would strengthen the company's argument of equal efficacy. Notably, the company could have generated treatment rankings via the NMA (posterior pairwise contrasts) and calculated ranking probabilities (i.e., probabilities of being best). These

outputs provide more appropriate evidence for assessing comparative efficacy than visual inspection of overlapping credible intervals. The EAG therefore considers that any assumption of equal efficacy should be supported by posterior pairwise contrasts showing effects close to unity within a prespecified equivalence margin, as well as by consistent clinical justification.

In the absence of such evidence, the EAG concludes that assuming equal efficacy across treatments is not justified and would risk obscuring clinically meaningful differences in treatment effectiveness. Moreover, at the second committee meeting for garadacimab (TA1101), during discussions on the berotralstat stopping rule, clinical experts noted that although berotralstat can be as effective as lanadelumab in some people, the two treatments should not be considered equivalent. In addition, clinical experts and stakeholders commenting on the draft guidance for garadacimab highlighted the difficulty of directly comparing the efficacy of lanadelumab and berotralstat. Both treatments are active comparators in the company's analysis.

Therefore, the EAG disagrees with the company's choice of a cost-comparison analysis as the base case and believes that a probabilistic cost-utility analysis is the most appropriate method for the reasons outlined above.

- **Garadacimab as a comparator treatment in the population with ≥ 2 attacks per month**

As highlighted throughout this report, the EAG disagrees with the exclusion of garadacimab as a comparator. Thus, in addition to opting for a CUA, the EAG updated the company's NMA to include garadacimab and the CUA includes garadacimab as a comparator.

- **Baseline attack rates**

The EAG prefers to use pooled baseline attack rates in its EAG base case rather than baseline attack rates from OASIS-HAE alone. A full discussion is presented in section 4.2.5.

- **Berotrastat stopping rule**

The EAG prefers to implement a stopping rule for berotrastat. A full discussion is presented in section 4.2.5 .

Table 62. Results using EAG preferred model assumptions in population with ≥ 2 attacks per month

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)	NHB at £30,000
Company's base case (cost-comparison analysis)						
Donidalorsen	██████	N/A	-	N/A	N/A	
Berotrastat	██████	N/A	██████	N/A	N/A	N/A
Garadacimab	N/A	N/A	N/A	N/A	N/A	N/A
EAG01: Efficacy varies by treatment ^a						
Donidalorsen	██████	██████	-	-	-	
Berotrastat	██████	██████	██████	██████	██████	N/A
Garadacimab	N/A	N/A	N/A	N/A	N/A	N/A
EAG02: Garadacimab as comparator						
Donidalorsen	██████	N/A	-	-	-	N/A
Berotrastat	██████	N/A	██████	N/A	N/A	N/A
Garadacimab	██████	N/A	██████	N/A	N/A	N/A
EAG03: Pooled baseline attack rates						
Donidalorsen	██████	N/A	-	N/A	N/A	N/A
Berotrastat	██████	N/A	██████	N/A	N/A	N/A
Garadacimab	██████	N/A	██████	N/A	N/A	N/A
EAG04: Berotrastat stopping rule ^b						
Donidalorsen	██████	██████				
Berotrastat	██████	██████	██████	██████	██████	
Garadacimab	N/A	N/A	N/A	N/A	N/A	N/A
EAG01-04: Cumulative impact of EAG preferred assumptions						
Donidalorsen	██████	██████	██████	██████	██████	██████
Berotrastat	██████	██████	██████	██████	██████	██████
Garadacimab	██████	██████	██████	██████	██████	██████

^a Based on EAG's updated NMA

^b Scenario based on company's cost-utility base case analysis (not cost-comparison analysis) as presented by the company in its clarification (Response B1)

EAG Deterministic cost-effectiveness results: ≥ 2 attacks per month population

In the pairwise comparisons of donidalorsen versus berotralstat and donidalorsen versus garadacimab, donidalorsen [REDACTED] berotralstat (that is, it is both [REDACTED] and [REDACTED]). However, when compared with garadacimab, donidalorsen is associated with [REDACTED] (£[REDACTED] vs. £[REDACTED]) but also generates [REDACTED] ([REDACTED] vs. [REDACTED]) i.e. is [REDACTED] but [REDACTED] (see Table 63). The resulting incremental costs of [REDACTED] and incremental QALYs of [REDACTED] place the ICER for donidalorsen versus garadacimab in the [REDACTED] of the cost-effectiveness plane.

Table 63: EAG deterministic base case cost-effectiveness analysis, ≥ 2 attacks per month population

Technology	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Donidalorsen	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Berotralstat	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Garadacimab	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

EAG Probabilistic cost-effectiveness results: ≥ 2 attacks per month population

The EAG's base case was subjected to a probabilistic sensitivity analysis using 1,000 iterations. The probabilistic incremental costs were [REDACTED] for donidalorsen vs. berotralstat and [REDACTED] for donidalorsen vs. garadacimab. The probabilistic incremental QALYs [REDACTED] and [REDACTED] for donidalorsen vs. berotralstat and donidalorsen vs. garadacimab respectively. The probabilistic results follow the same pattern as the base case deterministic results (Table 64) and the incremental cost-effectiveness scatterplane shows, visually, the distribution of incremental costs and QALYs.

Table 64. Probabilistic cost-effectiveness analysis for donidalorsen vs comparators in population with HAE attacks ≥ 2 per month

	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Cost per QALY (£)

Donidalorsen	██████	████	█	█	██
Berotrastat	██████	████	████	████	████
Garadacimab	██████	████	██████	████	████████

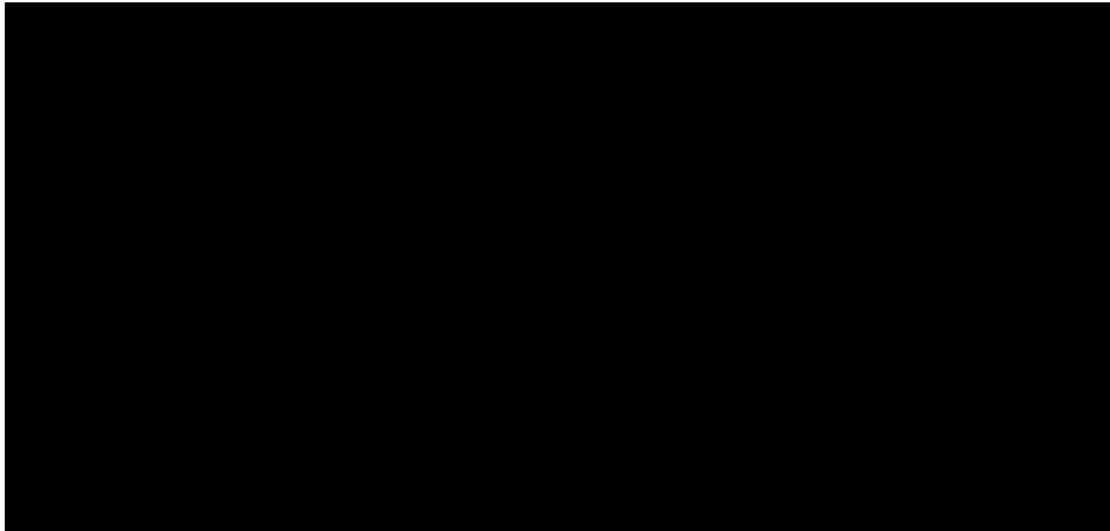


Figure 7: Incremental cost-effectiveness scatterplot, donidalorsen vs. comparators, ≥ 2 HAE attacks per month population

Table 65. Results using EAG preferred model assumptions in population with ≥ 8 attacks per month

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)	NHB at £30,000
Company's base case (cost-comparison analysis)						
Donidalorsen	██████	N/A				
Lanadelumab	██████	N/A	██████	N/A	N/A	N/A
C1-INH	██████	N/A	██████	N/A	N/A	N/A
EAG01: Efficacy varies by treatment ^a						
Donidalorsen	██████	████				
Lanadelumab	██████	████	██████	████	████████	██████
C1-INH	██████	████	██████	████	████████	██████
Cumulative impact of EAG preferred assumptions						
Donidalorsen	██████	████				
Lanadelumab	██████	████	██████	████	████████	██████
C1-INH	██████	████	██████	████	████████	██████

^a Based on EAG's updated NMA

EAG Deterministic cost-effectiveness results: ≥ 8 attacks per month population

In the pairwise comparisons of donidalorsen versus lanadelumab and donidalorsen versus C1-INH, donidalorsen **████████** C1-INH (that is, it is both **████████** and **████████**). However, when compared with lanadelumab, donidalorsen is associated with **████████** (£**██████** vs. £**██████**) but also generates **████████** (**██████** vs. **██████**) i.e. is **████████** but **████████** (see Table 66). The resulting incremental costs of **████████** and incremental QALYs of **██████** place the ICER for donidalorsen versus lanadelumab in the **████████** of the cost-effectiveness plane (Figure 8).

Table 66: EAG Base Case deterministic cost-effectiveness analysis, ≥ 8 HAE attacks per month population

Technology	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)	NHB at £30,000
Donidalorsen	████████	██████				
Lanadelumab	████████	██████	████████	██████	████████	████████
C1-INH	████████	██████	████████	██████	████████	████████

EAG probabilistic cost-effectiveness results: ≥ 8 attacks per month population

The results of the probabilistic analysis are presented below for ≥ 8 attacks per month population

Table 67: EAG Base Case probabilistic cost-effectiveness analysis, ≥8 HAE attacks per month population

Technology	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Donidalorsen	██████	██████			
Lanadelumab	██████	██████	██████	██████	██████
C1-INH	██████	██████	██████	██████	██████

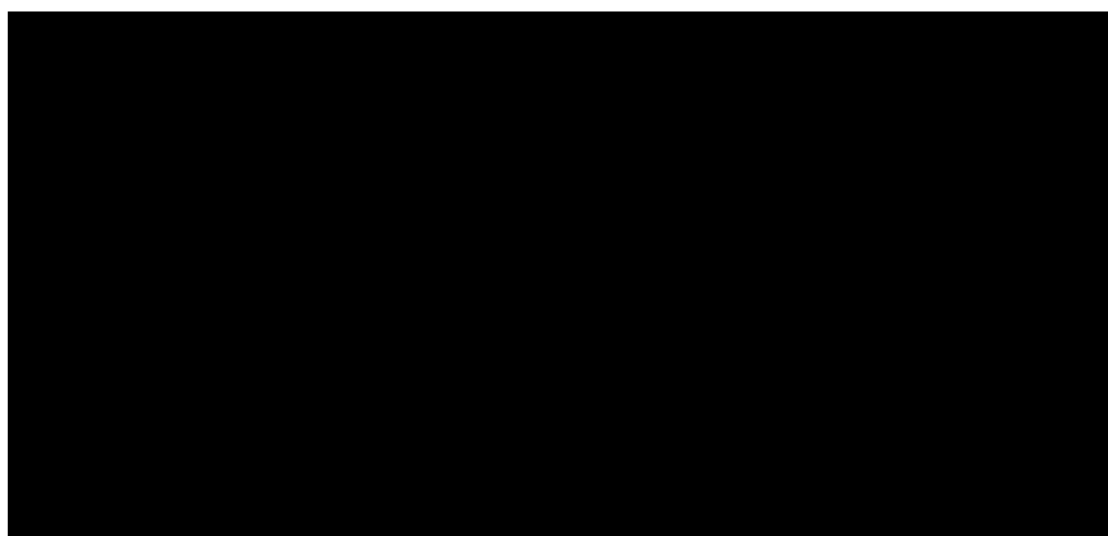


Figure 8: Incremental cost-effectiveness scatterplot, donidalorsen vs. comparators, ≥8 HAE attacks per month population

5.2.4 Scenario analyses using EAG’s preferred assumptions

Table 68 outlines the additional scenario analyses that the EAG has done using the EAG’s preferred base case. Most of the scenario analyses test the impact of company’s preferred assumption on EAG’s base case.

Table 68: Summary of EAG’s scenario analyses using EAG’s preferred assumptions

-	EAG’s base-case assumption	EAG’s scenario
1	Pooled baseline attack rate (0.818)	Baseline attack rate of the run-in period of the placebo arm of QASIS-HAE trial (0.725)
2	Berotrastat stopping rule included	Berotrastat stopping rule excluded
3	Rate ratios based on EAG updated NMA	Rate ratios based on company NMA ^a
4	Include carer disutilities	Exclude carer disutilities
5	Include administration disutilities	Exclude administration disutilities
6	Utilities from Nordenfelt et al. (2024) Attack-free utility: 0.825 Attack base utility: 0.512	Utility values from Aygören-Pürsün (2016) Attack-free utility: 0.722 Attack base utility: 0.444
7	45% of patients on lanadelumab 300mg Q2W switch to Q4W after 12 months.	76.9% of patients on lanadelumab 300mg Q2W switch to Q4W from 12 months.
8	45% of patients on lanadelumab 300mg Q2W switch to Q4W after 12 months.	45% of patients on lanadelumab 300mg Q2W switch to Q4W after 3 months.
9	Time-point at which patients transfer to lanadelumab Q4W - after 12 months.	Time-point at which patients transfer to lanadelumab Q4W – after 6 months
10	100% treatment compliance	80% compliance
11	C1-INH proportion (27% IV Cinryze 73% IV Berinert)	C1-INH proportion (40% IV Cinryze 60% IV Berinert)
12	Dosing frequency of donidalorsen – Donidalorsen 80mg Q1M, then 80mg Q2M	Dosing frequency of donidalorsen - Donidalorsen 80mg Q4W, then Q8W

^a Except garadacimab as rate ratios only derived via EAG’s updated NMA

Table 69: Results of EAG scenario analyses using EAG preferred assumptions (≥2 attacks per month population)

Scenario analysis number	Scenario applied to EAG’s base case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
1	Baseline attack rate of the run-in period of the placebo arm of OASIS-HAE trial (0.73)			
Donidalorsen	-	-	-	-

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
	Berotrastat	████	██	████
	Garadacimab	████	██	████
2 Berotrastat stopping rule excluded				
	Donidalorsen	-	-	-
	Berotrastat	████	██	████
	Garadacimab	NA	NA	NA
3 Rate ratios based on company's NMA				
	Donidalorsen			
	Berotrastat	████	██	████
	Garadacimab	████	██	████
4 Exclude carer disutilities				
	Donidalorsen	-	-	-
	Berotrastat	████	██	████
	Garadacimab	████	██	████
5 Exclude administration disutilities				
	Donidalorsen	-	-	-
	Berotrastat	████	██	████
	Garadacimab	████	██	████
6 Utility values from Aygören-Pürsün (2016) Attack-free utility: 0.722 Attack base utility: 0.444				
	Donidalorsen	-	-	-
	Berotrastat	████	██	████
	Garadacimab	████	██	████
7 80% Treatment compliance				
	Donidalorsen	-	-	-
	Berotrastat	████	██	████
	Garadacimab	████	██	████
8				

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
Donidalorsen 80mg Q4W, then Q8W				
Donidalorsen		-	-	-
Berotrastat		████	██	████
Garadacimab		████	██	████

Table 70: Results of EAG scenario analyses using EAG preferred assumptions (≥ 8 attacks population)

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
1				
Rate ratios based on company's NMA				
Donidalorsen				
Lanadelumab		████	██	████
C1-INH		████	██	████
2				
Exclude carer disutilities				
Donidalorsen		-	-	-
Lanadelumab		████	██	████
C1-INH		████	██	████
3				
Exclude administration disutilities				
Donidalorsen				
Lanadelumab		████	██	████
C1-INH		████	██	████
4				
Utility values from Aygören-Pürsün (2016)				
Attack-free utility: 0.722				
Attack base utility: 0.444				
Donidalorsen		-	-	-
Lanadelumab		████	██	████
C1-INH		████	██	████

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
5				
76.9% of patients on lanadelumab 300mg Q2W switch to Q4W from 12 months.				
Donidalorsen		-	-	-
Lanadelumab		██████	██████	██████████
C1-INH		██	██	██
6				
45% of patients on lanadelumab 300mg Q2W switch to Q4W from 3 months				
Donidalorsen		-	-	-
Lanadelumab		██████	██████	██████████
C1-INH		NA	NA	NA
7				
Time-point at which patients transfer to lanadelumab Q4W – after 6 months				
Donidalorsen		-	-	-
Lanadelumab		██████	██████	██████████
C1-INH		NA	NA	NA
8				
80% treatment compliance				
Donidalorsen		-	-	-
Lanadelumab		██████	██████	██████████
C1-INH		██████	██████	██████████
9				
C1-INH proportion (40% IV Cinryze 60% IV Berinert)				
Donidalorsen		-	-	-
Lanadelumab		NA	NA	NA
C1-INH		██████	██████	██████████
10				
Donidalorsen 80mg Q4W, then Q8W				
Donidalorsen		-	-	-
Lanadelumab		██████	██████	██████████
C1-INH		██████	██████	██████████

5.3 Decision modifiers

5.3.1 QALY weighting for severity

In its submission, the company stated that it did not anticipate that donidalorsen will meet the criteria for the severity weighting modifier. A QALY weight is an additional weight applied to QALY gains in severe diseases. Whether QALY weighting applies depends on both the absolute and proportional QALY shortfalls.

Absolute shortfall: the number of future QALYs lost by people living with the disease on current standard of care.

Proportional shortfall: the proportion of future QALYs lost by people living with the disease on current standard of care.

For example, if the proportional QALY shortfall is ≥ 0.95 , or if the absolute QALY shortfall is ≥ 18 , the incremental QALYs are multiplied by a weighting of 1.7 (see Table 71 Table 72).

Table 71: Severity Modifier Weight Definitions

QALY weight	Proportional shortfall	Absolute shortfall
x1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

The company did not provide a QALY shortfall analysis in its submission for the EAG to verify. Consequently, the EAG derived its own estimates using the QALY shortfall calculator developed by Schneider et al. (Table 72; <https://shiny.york.ac.uk/shortfall/>). The resulting estimates are considered slightly conservative because several input parameters, including age and sex distribution, were rounded (see notes at the bottom of the table).

QALYs for the current standard of care were based on the treatments associated with the lowest QALYs gained in the company's base-case cost–

utility analysis: berotralstat in the population with ≥ 2 attacks per month and C1-INH in the population with ≥ 8 attacks per month. Similar results were obtained when using the EAG base-case values.

Based on this analysis, the EAG agrees with the company's conclusion that QALY weighting does not apply in this appraisal.

Table 72: Parameters used to calculate QALY shortfalls

Parameter	Value	
	≥ 2 attacks per month	≥ 8 attacks per month
Starting age (years)	37 ^a	37 ^a
Percentage female	53 ^b	53 ^b
Discount rate	3.5	3.5
QALYs without disease	18.51	18.51
QALYs with disease (current standard of care)	15 ^c	12 ^c
Absolute QALY shortfall	3.51	6.51
Proportional QALY shortfall	18.98%	35.19%
QALY weight	1	1

^a Actual value in company's economic model is 37.20

^b Actual value in company's economic model is 53.3%

^c Values rounded down; approach favours donidalorsen.

5.3.2 Uncaptured benefits

The company provided other benefits of using donidalorsen that were not captured in their economic evaluation framework. The company claimed that for patients with HAE, donidalorsen can be an easily tolerated, uncomplicated and efficient option of LTPs. It mentioned that the societal costs associated with HAE on patients due to missed work/ school and the indirect impacts on their carers could not be captured in its analysis due to using the NHS/PSS

perspective in accordance with NICE reference case. Therefore, some societal benefits of using donidalorsen was not captured.

Second, donidalorsen SC route reduces the burden of treatment compared to IV C1-INH due to less frequent visits to clinics for injection support - a view the clinical expert to the EAG agreed with, but indicates that the choice of the route of administration is solely dependent on patients preference, and some patients still prefer to use oral treatments than using injectable treatments. Also, they stated that donidalorsen presented in injection pens can be left unrefrigerated for up to 6 weeks in the original carton if stored at less than 30°C providing convenience and less restrictions to patients. The EAG notes that the uncaptured benefits identified by the company were assessed only in relation to the comparators included in the analysis, which excluded garadacimab. Several of the benefits highlighted by the company, such as reduced gastrointestinal side effects and reduced treatment burden associated with subcutaneous administration, would also be expected to apply to garadacimab.

Third, the company claimed donidalorsen is not associated with AEs compared to comparator berotralstat which is associated with GI- related TEAEs and these benefits were not captured within the economic evaluation framework. While the EAG agrees with the company that the use of oral medication results to higher GI-related AEs, the EAG considers that the approach the company has taken for the base-case (cost-comparison analysis), does not allow for all the unique differences in the LTPs to be evaluated. For example, this approach has eliminated the discontinuation rule with berotralstat which does not provide a true evaluation of this treatment as used in clinical practice in comparison with other LTPs.

5.3.3 Health inequalities

The company states that donidalorsen addresses an unmet equality need for patients who, for religious reasons, may decline treatments derived from human plasma, such as intravenous Cinryze and Berinert, and highlights that donidalorsen is not derived from human plasma.

The EAG notes that the same rationale was presented by the company in TA1101 for garadacimab, which, like donidalorsen, is not derived from human plasma. In TA1101, the appraising committee acknowledged that religion is a protected characteristic under the Equality Act 2010 and that some religious groups may be unwilling to receive blood-derived products such as C1-INHs. However, the committee also noted that both garadacimab and lanadelumab are non-plasma-derived alternatives to C1-INHs and concluded that any recommendation would apply equally to all people, regardless of protected characteristics.

The EAG considers that the committee's conclusions in TA1101 are applicable to the current appraisal, as donidalorsen, lanadelumab, and garadacimab are all non-plasma-derived alternatives to C1-INHs.

5.4 Confidential comparator and subsequent treatment prices

All analyses presented in section 5 only consider the donidalorsen PAS. However, there are other confidential discounts that are relevant for this appraisal for the comparator treatments (berotralstat, lanadelumab and garadacimab (an additional comparator in EAG base case)). There are also eMIT prices for Firazyr (an on-demand treatment). A separate confidential appendix (accompanying the EAG report) will be submitted, replicating the: EAG's exploratory analyses (on company's base case); EAG's base case analysis; EAG scenario analyses (on EAG base case); company's base case analysis. The analyses in the confidential appendix will use all confidential

comparator and eMIT prices for on-demand medications relevant to this appraisal.

Table 73: Pharmaceutical products and sources for the EAG cPAS appendix

Name	Form	Dose per unit	Vial/pack size	Source for main report	Source for cPAS appendix
Donidalorsen	SC	80 mg	1	Draft SmPC Donidalorsen	PAS from company
Berotrastat	Oral	150 mg	28	BNF	Fixed price PAS
Lanadelumab	SC	300 mg/2ml	1	BNF	PAS discount
Cinryze	IV	500 IU	2	BNF	None - BNF
Berinert	IV	500 IU	1	BNF	None-BNF
Ruconest	IV	2,100 IU	1	BNF	None-BNF
Firazyr	SC	30 mg/3ml	1	BNF	eMIT
Garadacimab	SC	167 mg/1 ml	1	BNF	Fixed price PAS

5.5 Conclusions of the cost-effectiveness section

The company submitted a de novo economic model that is broadly logical and consistent with structures accepted in previous related appraisals, and the systematic literature review appears comprehensive. However, the EAG identified several key limitations in the cost-effectiveness analysis that introduces uncertainty in the interpretation of the results.

The most important concerns are the exclusion of garadacimab, an approved and relevant comparator, the assumption of equal efficacy across treatments without formal evidence of equivalence, and the omission of a stopping rule for berotralstat, which does not reflect its recommended use in clinical practice. Collectively, these assumptions introduce substantial uncertainty into the estimated costs and QALYs and may bias the results.

Additional unresolved uncertainties include the approach to modelling time to discontinuation, impact of using a different network meta-analysis approach, the impact of concomitant use of androgens and tranexamic acid in a few patients (■■■■) in OASIS-HAE trial, and the lack of exploration of alternative long-term extrapolation assumptions for HAE attacks. The EAG was unable to assess the direction or magnitude of bias associated with these factors.

In the EAG's base case, equal efficacy is not assumed, and the analysis is conducted as a cost-utility analysis. Under these assumptions, donidalorsen is ■■■■ compared with berotralstat and C1-INH but is ■■■■ and ■■■■ than garadacimab and lanadelumab, with ICERs in the ■■■■ quadrant.

The EAG does not agree with the company's use of a cost-comparison analysis as the base case or the exclusion of garadacimab. The EAG concludes that, without inclusion of garadacimab and robust justification for the equal-efficacy assumption, the company's cost-effectiveness results remain highly uncertain, and should be interpreted with caution.

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71. *TAKHZYRO 300 mg solution for injection in pre-filled syringe: Summary of Product Characteristics (SmPC)*. emc; 2025. URL: <https://www.medicines.org.uk/emc/product/12051/smpc> (Accessed 27 January 2026).

72. *Cinryze 500 IU powder and solvent for solution for injection: Summary of Product Characteristics (SmPC)*. emc; 2025. URL: <https://www.medicines.org.uk/emc/product/2808/smpc> (Accessed 27 January 2026).

73. *Berinert 500 IU Powder and solvent for solution for injection / infusion: Summary of Product Characteristics (SmPC)*. emc; 2021. URL: <https://www.medicines.org.uk/emc/product/6523/smpc> (Accessed 27 January 2026).

74. COReC (Care and Outcomes Research Centre). *Unit costs 2022 – 2027: new Unit Costs of Health and Social Care programme*. University of Kent. URL: <https://www.pssru.ac.uk/unitcostsreport/>. (Accessed 27 January 2026).
75. *Ruconest 2100 U powder for solution for injection: Summary of Product Characteristics (SmPC)*. emc; 2023. URL: <https://www.medicines.org.uk/emc/product/8580/smpc> (Accessed 27 January 2026).

7 Appendices

7.1 Additional literature search undertaken by the EAG

Ovid MEDLINE(R) ALL <1946 to January 07, 2026>

Date searched: 08/01/26

- 1 exp Angioedemas, Hereditary/ 1801
- 2 ((familial or hereditary) adj3 (angioedema* or angio* edema* or angio* oedema*)).kf,tw. 3571
- 3 (donidalorsen or Cinryze* or Berinert* or Ruconest or Lanadelumab or Berotralstat or Garadacimab or c1 esterase inhibit* or Plasma-Derived C1-Inhibitor* or "pdc1 INH" or dawnzera* or Takhzyro* or conestat alfa* or Orladeyo* or andembry*).mp. [interventions/comparators in NICE scope] 1663
- 4 (1 or 2) and 3 964
- 5 (2025042* or 2025043* or 202505* or 202506* or 202507* or 202508* or 202509* or 20251* or 2026*).dt,ez,da,ed. 1543927
- 6 4 and 5 92
- 7 (metaanalys* or meta analys* or NMA* or MAIC* or indirect comparison* or mixed treatment comparison*).mp. 409609
- 8 (systematic* adj3 (review* or overview* or search or literature)).mp. 506531
- 9 7 or 8 [SRs / MAs pragmatic filter] 662557
- 10 6 and 9 [systematic reviews etc] 5
- 11 exp randomized controlled trial/ 655976

12 controlled clinical trial.pt. 95759
 13 randomized.ab. 726598
 14 placebo.ab. 265480
 15 clinical trials as topic.sh. 206518
 16 randomly.ab. 477617
 17 trial.ti. 356060
 18 11 or 12 or 13 or 14 or 15 or 16 or 17 1744036
 19 exp animals/ not humans.sh. 5411926
 20 18 not 19 [Cochrane RCTs Highly sensitive search strategy; Sensitivity- and
 precision-maximizing version (2023 revision) for Ovid as found
 here: <https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/rcts>]
 1609602
 21 ("in data review" or in process or publisher or "pubmed not medline").st.
 6920922
 22 (random* or controlled trial* or clinical trial* or rct).ab,kf,ti. 2124829
 23 21 and 22 [filter to pick up RCTs that have not been fully indexed for
 MEDLINE yet] 378859
 24 6 and (20 or 23) [RCTs] 12
 25 Economics/ 27557
 26 exp "Costs and Cost Analysis"/ 284759
 27 Economics, Nursing/ 4015
 28 Economics, Medical/ 9322
 29 Economics, Pharmaceutical/ 3175
 30 exp Economics, Hospital/ 26389
 31 Economics, Dental/ 1922
 32 exp "Fees and Charges"/ 31806
 33 exp Budgets/ 14451
 34 budget*.ti,ab,kf. 41893
 35 (economic* or cost or costs or costly or costing or price or prices or pricing or
 pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or
 expense or expenses or financial or finance or finances or financed).ti,kf. 325456
 36 (economic* or cost or costs or costly or costing or price or prices or pricing or
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expense or expenses or financial or finance or finances or financed).ab. /freq=2
463625

37 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or
outcomes)).ab,kf. 266835

38 (value adj2 (money or monetary)).ti,ab,kf. 3595

39 exp models, economic/ 17132

40 economic model*.ab,kf. 4987

41 markov chains/ 17696

42 markov.ti,ab,kf. 34656

43 monte carlo method/ 35093

44 monte carlo.ti,ab,kf. 69735

45 exp Decision Theory/ 14777

46 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. 55938

47 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
or 40 or 41 or 42 or 43 or 44 or 45 or 46 [economic evaluations & models filter from CDA-
AMC. <https://searchfilters.cda-amc.ca/link/16>] 1062472

48 6 and 47 [cost-effectiveness] 3

49 "Value of Life"/ 5853

50 Quality of Life/ 316437

51 quality of life.ti,kf. 145202

52 ((instrument or instruments) adj3 quality of life).ab. 4358

53 Quality-Adjusted Life Years/ 18788

54 quality adjusted life.ti,ab,kf. 21246

55 (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf. 37001

56 disability adjusted life.ti,ab,kf. 9556

57 daly*.ti,ab,kf. 8728

58 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or
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63 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or
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64 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kf. 29933

65 (hye or hyes).ti,ab,kf. 80

66 (health* adj2 year* adj2 equivalent*).ti,ab,kf. 49

67 (pqol or qls).ti,ab,kf. 528

68 (quality of wellbeing or quality of well being or index of wellbeing or index of well
being or qwb).ti,ab,kf. 859

69 nottingham health profile*.ti,ab,kf. 1300

70 sickness impact profile.ti,ab,kf. 1111

71 exp health status indicators/ 369624

72 (health adj3 (utilit* or status)).ti,ab,kf. 108837

73 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or
score* or weight)).ti,ab,kf. 19518

74 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or
disease or score* or instrument or instruments)).ti,ab,kf. 17453

75 disutilit*.ti,ab,kf. 769

76 rosser.ti,ab,kf. 114

77 willingness to pay.ti,ab,kf. 11274

78 standard gamble*.ti,ab,kf. 956

79 (time trade off or time tradeoff).ti,ab,kf. 1847

80 tto.ti,ab,kf. 1767

81 (hui or hui1 or hui2 or hui3).ti,ab,kf. 2316

82 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.
29059

83 duke health profile.ti,ab,kf. 97

84 functional status questionnaire.ti,ab,kf. 137

85 dartmouth coop functional health assessment*.ti,ab,kf. 14

86 or/49-85 [CADTH filter for Health Utilities/Quality of Life – OVID Medline
<https://www.cadth.ca/strings-attached-cadths-database-search-filters>] 866596

87 6 and 86 [HRQoL] 17
 88 48 or 87 [economics; cost eff or QoL] 19
 89 6 not (10 or 24 or 88) [anything else] 67

Embase <1974 to 2026 January 06>

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 or Orladeyo* or andembry*).kf,tn,tw. [interventions/comparators listed in NICE scope]
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 9 6 or 7 or 8 [added to database since date of company's search] 179
 10 exp randomized controlled trial/ 1138244
 11 controlled clinical trial/ 461197
 12 random\$.ti,ab. 2563372
 13 randomization/ 101788
 14 intermethod comparison/ 318340
 15 placebo.ti,ab. 473134
 16 (compare or compared or comparison).ti,ab. 9010411
 17 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or
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 keyword heading word, floating subheading word, candidate term word] 3700133
 18 (open adj label).ti,ab. 193900

19 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
374704

20 double blind procedure/ 315988

21 parallel group\$1.ti,ab. 54210

22 (crossover or cross over).ti,ab.159290

23 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or
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24 (assigned or allocated).ti,ab. 625027

25 (controlled adj7 (study or design or trial)).ti,ab. 653428

26 (volunteer or volunteers).ti,ab.326717

27 human experiment/ 740377

28 trial.ti. 579424

29 or/10-28 12034391

30 (((random\$ adj sampl\$ adj7 "cross section\$") or questionnaire\$1 or survey\$ or
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31 cross-sectional study/ not (exp randomized controlled trial/ or controlled
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33 systematic review.ti,ab. not (trial or study).ti. 443614

34 (nonrandom\$ not random\$).ti,ab. 21620

35 "random field\$".ti,ab. 3293

36 (random cluster adj3 sampl\$).ti,ab. 1815

37 (review.ab. and review.pt.) not trial.ti. 1363578

38 "we searched".ab. and (review.ti. or review.pt.) 61733

39 "update review".ab. 156

40 (databases adj4 searched).ab. 81851

41 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or
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42 animal experiment/ not (human experiment/ or human/) 2821950

43 or/30-42 6788923

44 29 not 43 [Cochrane Embase RCT filter 2023 revision as found
at [https://sites.google.com/a/york.ac.uk/issg-search-filters-
resource/home/rcts/embase-rct-filter](https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/rcts/embase-rct-filter)] 9941313

45 9 and 44 [RCTs filter] 54

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50 Economics/ 248735

51 Cost/ 67170

52 exp Health Economics/ 1195466

53 Budget/ 38306

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59 Statistical Model/ 184178

60 exp economic model/ 5611

61 economic model*.ab,kw. 7664

62 Probability/ 180445

63 markov.ti,ab,kw. 43647

64 monte carlo method/ 60995

65 monte carlo.ti,ab,kw. 72825

66 Decision Theory/ 1941

67 Decision Tree/ 31959

68 (decision* adj2 (tree* or analy* or model*)).ti,ab,kw. 72257

69 or/50-68 [filter for Economic Evaluations & Models - Embase. CDA-AMC.
<https://searchfilters.cda-amc.ca/link/15.>] 2356623

70 9 and 69 [cost effectiveness] 16

71 socioeconomics/ 184766

72 exp Quality of Life/ 868006

73 quality of life.ti,kw. 217204

74 ((instrument or instruments) adj3 quality of life).ab. 6268

75 Quality-Adjusted Life Year/ 43390

76 quality adjusted life.ti,ab,kw. 32243

77 (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw. 57565

78 disability adjusted life.ti,ab,kw. 11574

79 daly*.ti,ab,kw. 11280

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 sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw. 86

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 sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kw. 614

86 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kw. 49153

87 (hye or hyes).ti,ab,kw. 225

88 (health* adj2 year* adj2 equivalent*).ti,ab,kw.53

89 (pqol or qls).ti,ab,kw. 870

90 (quality of wellbeing or quality of well being or index of wellbeing or index of well
 being or qwb).ti,ab,kw.1100

91 nottingham health profile*.ti,ab,kw. 1835

92 nottingham health profile/ 827

93 sickness impact profile.ti,ab,kw. 1331

94 sickness impact profile/ 2398
 95 health status indicator/ 3710
 96 (health adj3 (utilit* or status)).ti,ab,kw. 143824
 97 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or
 score* or weight)).ti,ab,kw. 31350
 98 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or
 disease or score* or instrument or instruments)).ti,ab,kw. 23533
 99 disutilit*.ti,ab,kw. 1576
 100 rosser.ti,ab,kw. 157
 101 willingness to pay.ti,ab,kw. 16680
 102 standard gamble*.ti,ab,kw. 1281
 103 (time trade off or time tradeoff).ti,ab,kw. 2695
 104 tto.ti,ab,kw. 2732
 105 (hui or hui1 or hui2 or hui3).ti,ab,kw. 3913
 106 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw.
 50584
 107 duke health profile.ti,ab,kw. 129
 108 functional status questionnaire.ti,ab,kw. 194
 109 dartmouth coop functional health assessment*.ti,ab,kw. 14
 110 or/71-109 [Economic - Health Utilities / Quality of Life - Standard - Embase. In:
 CADTH Search Filters Database. Ottawa: CADTH; 2022:
<https://searchfilters.cadth.ca/link/18.>] 1270324
 111 9 and 110 [HRQoL] 40
 112 70 or 111 [economics] 52
 113 9 not (45 or 48 or 112) [anything else] 94

External Assessment Group (EAG) Report Addendum

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Produced by	Centre for Evidence and Implementation Science, University of Birmingham
Authors	Mubarak Patel, Research Fellow II (Statistician), University of Birmingham Christiana Anyebe, Research Associate, University of Birmingham Mubarak Patel, Research Fellow II (Clinical Effectiveness Reviewer), University of Birmingham Angela Mwape, Research Fellow, University of Birmingham Anna Brown, Information Specialist, University of Birmingham Mandy Maredza, Research Fellow II, University of Birmingham
Correspondence to	Dr Mandy Maredza, m.maredza@bham.ac.uk
Date completed	Date completed (04/02/2026)

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Declared competing interests of the authors

None

Copyright statement

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1 Introduction

The purpose of this addendum is to present updated cost-effectiveness results for the population experiencing ≥ 8 hereditary angioedema (HAE) attacks per month, with garadacimab included as a comparator.

In the main EAG report, garadacimab was included as a comparator only in the ≥ 2 attacks per month population, in order to explore the impact that its exclusion would have on the overall interpretation of the results. This addendum has been produced in response to NICE's request to include garadacimab as a comparator in both populations. This request reflects that (i) the company has positioned donidalorsen for use in both populations, and (ii) the committee recommendation in TA1101 states that "garadacimab could be used as an option to prevent recurrent attacks of hereditary angioedema in people aged 12 years and over having 2 or more attacks a month, which includes people having more frequent attacks (that is, 2 or more attacks a week)."

1.1 Deterministic cost-effectiveness results

The updated deterministic EAG base case cost-effectiveness results including garadacimab are shown in Table 1

Table 1: Updated EAG base case deterministic cost-effectiveness results, ≥ 8 attacks per month population, donidalorsen vs. comparators

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)- Donidalorsen versus comparators	NMB at £30,000 WTP
Donidalorsen	██████	██████	█	█	█	█
Lanadelumab	██████	██████	██████	██████	██████	██████
C1-INH	██████	██████	██████	██████	██████	██████
Garadacimab	██████	██████	██████	██████	██████	██████

LYG are similar across all treatments i.e., 22.515 years; NMB, net monetary benefit; WTP, willingness to pay; QALYs, quality adjusted life years; ICER, incremental cost-effectiveness ratio

1.2 Probabilistic cost-effectiveness results

The updated probabilistic EAG base case cost-effectiveness results including garadacimab are shown in Table 2 and incremental cost-effectiveness scatterplot in Figure 1

Table 2: Updated EAG base case probabilistic cost-effectiveness results, ≥8 attacks per month population, donidalorsen vs. comparators

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Cost per QALY (£)
Donidalorsen					
Lanadelumab					
C1-INH					
Garadacimab					

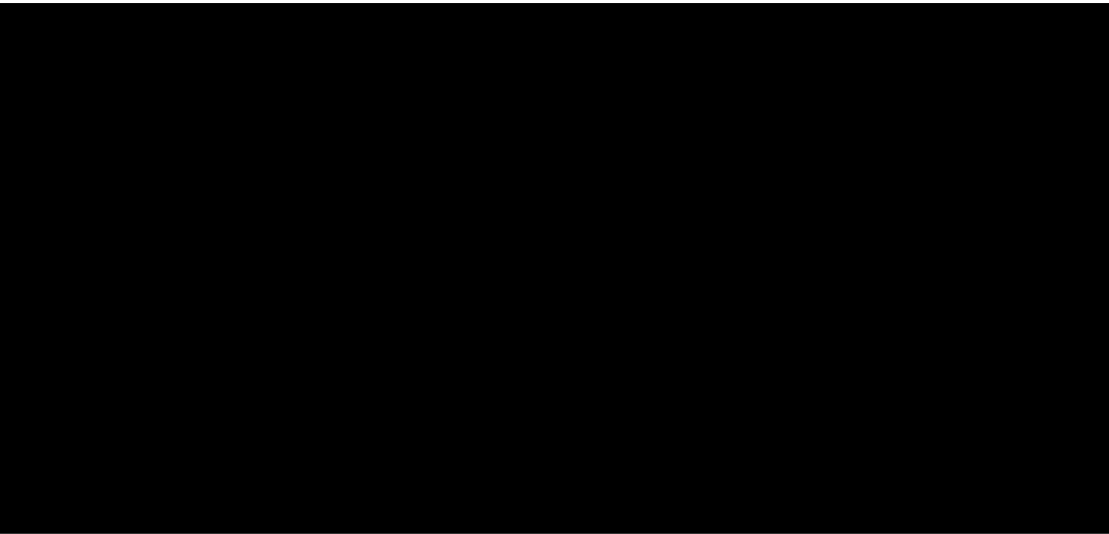


Figure 1: Incremental cost-effectiveness plane, donidalorsen vs. comparators, ≥8 attacks per month population

1.3 Scenario analyses on EAG preferred base case assumptions

Table 3 presents scenario analyses based on the EAG's preferred base case, showing the individual impact of each scenario on incremental costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs).

Table 3: Scenario analyses on EAG preferred base case, ≥8 attacks per month population

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
1				
Rate ratios based on company's NMA				
Donidalorsen				
Lanadelumab				
C1-INH				
Garadacimab		N/A	N/A	N/A
2				
Exclude carer disutilities				
Donidalorsen		-	-	-
Lanadelumab				
C1-INH				
Garadacimab				
3				
Exclude administration disutilities				
Donidalorsen				
Lanadelumab				
C1-INH				
Garadacimab				
4				
Utility values from Aygören-Pürsün (2016)				
Attack-free utility: 0.722				
Attack base utility: 0.444				
Donidalorsen		-	-	-
Lanadelumab				
C1-INH				

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
Garadacimab		██████	██████	██████████
5 76.9% of patients on lanadelumab 300mg Q2W switch to Q4W from 12 months.				
Donidalorsen		-	-	-
Lanadelumab		██████	██████	██████████
C1-INH		██████	██████	██████████
Garadacimab		██████	██████	██████████
6 45% of patients on lanadelumab 300mg Q2W switch to Q4W from 3 months				
Donidalorsen		-	-	-
Lanadelumab		██████	██████	██████████
C1-INH		██████	██████	██████████
Garadacimab		██████	██████	██████████
7 Time-point at which patients transfer to lanadelumab Q4W – after 6 months				
Donidalorsen		-	-	-
Lanadelumab		██████	██████	██████████
C1-INH		██████	██████	██████████
Garadacimab		██████	██████	██████████
8 80% treatment compliance				
Donidalorsen		-	-	-
Lanadelumab		██████	██████	██████████
C1-INH		██████	██████	██████████
Garadacimab		██████	██████	██████████
9 C1-INH proportion (40% IV Cinryze 60% IV Berinert)				
Donidalorsen		-	-	-
Lanadelumab		██████	██████	██████████
C1-INH		██████	██████	██████████
Garadacimab		██████	██████	██████████
10 Donidalorsen 80mg Q4W, then Q8W				
Donidalorsen		-	-	-

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
Lanadelumab		██████	████	████████
C1-INH		██████	████	████████
Garadacimab		██████	████	████████

N/A, rate ratios for garadacimab not included in company analysis

1.4 Uncertainty

Similar sources of uncertainty to those highlighted in the main EAG report apply to this cost-effectiveness analysis. Of note is that the EAG was constrained to using the company's network meta-analysis (NMA) when updating analyses to include garadacimab and was therefore unable to explore the impact of alternative NMA approaches on the results.

Conclusion

The EAG notes that, in TA1101, the committee concluded that for people experiencing two or more attacks per week, garadacimab dominated the relevant comparators and was therefore considered a cost-effective option. In that appraisal, the comparators explored were C1-INHs and lanadelumab. For the current analysis, donidalorsen ██████ C1-INH but is both ██████ and ██████ than garadacimab and lanadelumab. For comparison with garadacimab, the ICERs predominantly lie within the ██████ quadrant of the cost-effectiveness plane. To fully understand the relative cost-effectiveness of donidalorsen within its proposed positioning in the treatment pathway, garadacimab needs to be included as a relevant comparator.

Single Technology Appraisal

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday, 10 February 2026** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [REDACTED] should be highlighted in turquoise and all information submitted as '[REDACTED]' in pink.

Issue 1 Inaccuracies in the EAG's cost-effectiveness model results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>Section 1.6, Table 2, page 21:</i> Key issue 1: Exclusion of garadacimab as a comparator, total costs: “[REDACTED]”	The company requests that the value reported is amended to: “[REDACTED]”	The total costs reported for garadacimab under key issue 1 do not align with the EAG's economic model.	The total costs for garadacimab have been amended to £[REDACTED]
<i>Section 1.6, Table 2, page 21:</i> Key issue 1: Exclusion of garadacimab as a comparator, incremental costs: “[REDACTED]”	The company requests that the value reported is amended to: “[REDACTED]”	The incremental total costs reported for garadacimab under key issue 1 do not align with the EAG's economic model.	The incremental costs for garadacimab have been amended to [REDACTED]
<i>Section 1.6, Table 3, page 23:</i> Company's base case (cost-comparison analysis), C1-INH total costs: “N/A”	The company requests that the value reported is amended to: “[REDACTED]”	The company's base-case analysis in the population of patients experiencing ≥ 8 HAE attacks per month evaluated total costs for C1-INH and therefore should be reported in Table 3.	Apologies for the omission. The total costs are now reported.
<i>Section 1.6, Table 3, page 23:</i> Company's base case (cost-comparison analysis), C1-INH incremental costs:	The company requests that the value reported is amended to: “[REDACTED]”	The company's base-case analysis in the population of patients experiencing ≥ 8 HAE attacks per month evaluated the	Apologies for the omission. The incremental costs for C1-INH are now reported as per company's base

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"N/A"		incremental costs for C1-INH and therefore should be reported in Table 3.	case cost-comparison analysis
<i>Section 4.2.4, page 137:</i> "The scenario analysis shows that the cost savings associated with donidalorsen [REDACTED] by [REDACTED] and [REDACTED] when compared with lanadelumab and C1-INH respectively"	The company requests that text is amended to: "The scenario analysis shows that the cost savings associated with donidalorsen [REDACTED] by [REDACTED] and [REDACTED] when compared with lanadelumab and C1-INH respectively.	The cost savings associated with donidalorsen compared with C1-INH reduce by [REDACTED]% under the scenario using Q4W and Q8W dosing of donidalorsen in comparison to Q1M and Q2M dosing schedules.	The correct value remains [REDACTED] after values for scenario analysis No.13 (table 60, EAG report) were updated
<i>Section 5.2.2, Table 60, page 195:</i> Donidalorsen versus berotralstat (≥ 2 attacks per month population), Exploratory analysis 2, Percentage change from base case: "[REDACTED]"	The company requests that the value reported is amended to: "[REDACTED]"	The percentage change from base case in the EAG's exploratory analysis 2 of donidalorsen Q4W and Q8W dosing schedules compared to Q1M and Q2M schedules is [REDACTED].	Thank you. The percentage change has been amended to [REDACTED]"
<i>Section 5.2.2, Table 60, page 195:</i> Donidalorsen versus berotralstat (≥ 2 attacks per month population), Exploratory analysis 3,	The company requests that the value reported is amended to: "[REDACTED]" and	The total costs for the donidalorsen and berotralstat treatment arms in exploratory analysis 3 do not align with the total costs presented in the EAG's economic model or the company's cost-effectiveness	The total costs for exploratory analysis 3 have been amended as suggested

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Total costs (£) Donidalorsen: “[REDACTED]” Total costs (£) Comparator: “[REDACTED]”	“[REDACTED]”, respectively.	model v2.0 8Dec25 when this scenario is implemented. Furthermore, in the EAG’s model, the application of this scenario includes an administration cost for ‘no treatment’. Patients receiving ‘no treatment’ as an on-demand treatment are not expected to accrue administration costs. Therefore, the company consider this an error in the implementation of this scenario. The proposed amendments to the total costs consider no administration costs are applied to the proportion of patients receiving ‘no treatment’.	
<i>Section 5.2.2, Table 60, page 195:</i> Donidalorsen versus lanadelumab (≥ 2 attacks per month population), Exploratory analysis 9,	The company requests that the value reported is amended to: “[REDACTED]” and	The total costs for the donidalorsen and lanadelumab treatment arms in exploratory analysis 9 do not align with the total costs presented in the EAG’s economic model or the company’s cost-effectiveness	The total costs for exploratory analysis 9 have been amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Total costs (£) Donidalorsen: “[REDACTED]” Total costs (£) Comparator: “[REDACTED]”	“[REDACTED]”, respectively.	model v2.0 8Dec25 when this scenario is implemented. Furthermore, in the EAG’s model, the application of this scenario includes an administration cost for ‘no treatment’. Patients receiving ‘no treatment’ as an on-demand treatment are not expected to accrue administration costs. Therefore, the company consider this an error in the implementation of this scenario. The proposed amendments to the total costs consider no administration costs are applied to the proportion of patients receiving ‘no treatment’.	
<i>Section 5.2.2, Table 6, page 196:</i> Donidalorsen versus C1-INH (≥ 8 attacks per month population), exploratory analysis 12, total costs comparator:	The company requests that the value reported is amended to: “[REDACTED]”	The total costs for the C1-INH treatment arm in exploratory analysis 12 does not align with the total costs presented in the company’s cost-effectiveness model v2.0 8Dec25. Furthermore, as the scenario applies a change	Apologies for the error. The values have been amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
“[REDACTED]”		to only the donidalorsen dosing frequency, the total costs of C1-INH in this scenario are not expected to differ from the total costs of C1-INH in the base-case analysis, which is not replicated in Table 60.	
<i>Section 5.2.2, Table 60, page 196:</i> Donidalorsen versus C1-INH (≥ 8 attacks per month population), exploratory analysis 12, incremental costs: “[REDACTED]”	The company requests that the value reported is amended to: “[REDACTED]”	The incremental costs associated with donidalorsen versus C1-INH under the donidalorsen Q4W and Q8W dosing schedules scenario do not align with the company’s cost-effectiveness model v2.0 8Dec25.	The incremental costs have been amended for this scenario (now renumbered as exploratory analysis No. 13)
<i>Section 5.2.2, Table 60, page 197</i> 40% IV Cinryze and 60% IV Berinert scenario, total costs (£) comparator: “[REDACTED]”	The company requests that the value reported is amended to: “[REDACTED]”	The total costs associated with C1-INH under the 40/60 IV Cinryze/Berinert scenario do not align with the EAG’s economic model or the company’s cost-effectiveness model v2.0 8Dec25.	The total costs have been amended for C1-INH for this scenario (now renumbered exploratory analysis No. 14)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>Section 5.2.2, Table 60, page 197</i> 40% IV Cinryze and 60% IV Berinert scenario, incremental costs (£) comparator: “[REDACTED]”	The company requests that the value reported is amended to: “[REDACTED]”	The incremental costs associated with donidalorsen versus C1-INH under the 40/60 IV Cinryze/Berinert scenario do not align with the EAG’s economic model or the company’s cost-effectiveness model v2.0 8Dec25.	The incremental costs have been amended for C1-INH for this scenario (now renumbered exploratory analysis No. 14)
<i>Section 5.2.2, Table 60, page 195:</i> Donidalorsen versus C1-INH (≥ 8 attacks per month population), Exploratory analysis 14, Total costs (£) Donidalorsen: “[REDACTED]” Total costs (£) Comparator: “[REDACTED]”	The company requests that the value reported is amended to: “[REDACTED]” and “[REDACTED]”, respectively.	The total costs for the donidalorsen and C1-INH treatment arms in exploratory analysis 14 do not align with the total costs presented in the EAG’s economic model or the company’s cost-effectiveness model v2.0 8Dec25 when this scenario is implemented. Furthermore, in the EAG’s model, the application of this scenario includes an administration cost for ‘no treatment’. Patients receiving ‘no treatment’ as an on-demand treatment are not expected to accrue administration	The total costs for exploratory analysis 14 have been amended (now re-numbered as exploratory analysis No.15)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		costs. Therefore, the company consider this an error in the implementation of this scenario. The proposed amendments to the total costs consider no administration costs are applied to the proportion of patients receiving 'no treatment'.	
<i>Section 5.2.3, Table 62, page 202:</i> EAG01: Efficacy varies by treatment, Incremental QALYs “[REDACTED]”	The company requests that the incremental QALYs associated with donidalorsen compared with berotralstat is amended to: “[REDACTED]”	The incremental QALYs associated with donidalorsen compared with berotralstat are [REDACTED], as donidalorsen is [REDACTED] than berotralstat.	The incremental QALYs have been amended
<i>Section 5.2.3, Table 62, page 202:</i> EAG02: Garadacimab as comparator, Garadacimab total costs “[REDACTED]”	The company requests that the value reported is amended to: “[REDACTED]”	The total costs reported for garadacimab under the 'inclusion of garadacimab as a comparator' scenario do not align with the EAG's economic model.	Total costs for EAG02 have been amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>Section 5.2.3, Table 62, page 202:</i> EAG02: Garadacimab as comparator, Garadacimab incremental costs [REDACTED]	The company requests that the value reported is amended to: [REDACTED]	The incremental costs reported for garadacimab under the ‘inclusion of garadacimab as a comparator’ scenario do not align with the EAG’s economic model.	Incremental costs for EAG02 have been amended
<i>Section 5.2.3, Table 62, page 202:</i> EAG03: Pooled baseline attack rates, Garadacimab total costs [REDACTED]	The company requests that the value reported is amended to: [REDACTED]	The total costs reported for garadacimab under the ‘pooled baseline attack rate’ scenario do not align with the EAG’s economic model.	The total costs for garadacimab for EAG03 scenario have been updated
<i>Section 5.2.3, Table 62, page 202:</i> EAG03: Pooled baseline attack rates, Garadacimab total costs [REDACTED]	The company requests that the value reported is amended to: [REDACTED]	The incremental costs reported for garadacimab under the ‘pooled baseline attack rate’ scenario do not align with the EAG’s economic model.	The incremental costs for garadacimab vs. donidalorsen for “EAG03” scenario have been updated
<i>Section 5.2.4, Table 69, page 209:</i>	The company requests that the value reported is amended to:	The incremental costs reported for garadacimab under the ‘80% treatment compliance’ scenario	The incremental costs for treatment compliance

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Scenario number 7 (80% treatment compliance), Garadacimab incremental costs “[REDACTED]”	“[REDACTED]”	do not align with the EAG’s economic model.	scenario for garadacimab have been updated
<i>Section 5.2.4, Table 69, page 209:</i> Scenario number 7 (80% treatment compliance), Garadacimab ICER “[REDACTED]”	The company requests that the value reported is amended to: “[REDACTED]”	The ICER reported for garadacimab under the ‘80% treatment compliance’ scenario does not align with the EAG’s economic model.	The ICER for treatment compliance scenario for garadacimab have been updated

Issue 2 Inaccuracies in the clinical effectiveness section

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>Section 3.2.1, page 51:</i> “The EAG notes that the CS highlights a discrepancy in the number of sites reported, as the publication by Riedl et al. (2024) reports 42 sites whereas the CSR reports 40 sites. The CS reports both 39 and 40 sites.”	The company requests this text is amended to: “The EAG notes that the CS highlights a discrepancy in the number of sites reported, as the publication by Riedl et al. (2024) reports 42 sites	The CSR (Section 2, Section 6.1, and Section 11.4.2.4) consistently reports 39 sites in OASIS-HAE representing the number of sites at which patients were enrolled and received study treatment.	This was not a factual inaccuracy at point of report submission. However, thank you for clarifying the discrepancy. This

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	whereas the CSR reports 39 sites. The CS reports both 39 and 40 sites.” The company requests that the following text is added to clarify the discrepancies in number of trial sites reported: “The company subsequently confirmed that the number of sites that enrolled patients in OASIS-HAE was 39.”	The company notes that discrepancies in the reporting of the number of trial sites across the CSR, Riedl et al. (2024) publication, and the CS arise from differences in whether screening sites or enrolling/treating sites were reported. Specifically: • CSR The CSR reports 39 sites, representing the sites that enrolled patients following screening. • Riedl et al. (2024) The publication reports 42 sites, representing the sites at which patients were screened for the trial. Of these 42 screening centres, 39 centres subsequently enrolled patients.	amendment has been made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		Company submission In Section 2.3.1 of the CS, the number of UK sites was reported as 3, reflecting the number of UK sites that were activated rather than the number that enrolled patients. The text should instead state “2 in the UK”, which is consistent with the CSR. This clarification reconciles the reported figures and confirms that there were 39 enrolling sites in OASIS-HAE.	
<i>Section 3.3.1, Table 10, 12th row, page 72:</i> “Investigator confirmed moderate or severe HAE attacks per 4 weeks (LSM 95% CI); % reduction vs placebo (95% CI)”	The company requests that EAG include an additional row underneath to present the P values for these data, in line with other outcome reported in Table 10 of the EAG report, and with Table 12 of the company submission.	The P value row for this outcome is missing and should be included for consistency and completeness.	Thank you this has now been included.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	The P values missing are as follows: donidalorsen Q4W – <0.001; donidalorsen Q8W – 0.173.		
<i>Section 3.3.1, Table 10, 17th row, page 72:</i> “Participants with a $\geq$ 90% reduction in HAE attack n (%): Donidalorsen Q4W – 37 (82.2)”	The company requests that this value is amended to: “28 (62.2)”	Incorrect data reported.	Thank you this has been amended.
<i>Section 3.3.1, Table 10, 17th row, page 72:</i> “Participants with a $\geq$ 90% reduction in HAE attack n (%): Donidalorsen Q8W – 15 (65.2)”	The company requests that this text is amended to: “11 (47.8)”	Incorrect data reported.	Thank you this has been amended.
<i>Section 3.3.1, Table 10, 17th row, page 72:</i> “Participants with a $\geq$ 90% reduction in HAE attack n (%): Placebo – 4 (18.2)”	The company requests that this value is amended to: “2 (9.1)”	Incorrect data reported.	Thank you this has been amended.
<i>Section 3.3.1, page 75:</i> “The between-group differences versus placebo were –18.56 (-27.67 to	The company requests that this value is amended to:	Incorrect data reported.	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
-9.45) points for the Q4W arm which was statistically significant ($P < 0.001$) and -13.65 (-24.02 to -3.39) points for the Q8W arm which was also statistically significant ($P = 0.010$)..."	"The between-group differences versus placebo were -18.56 (-27.67 to -9.45) points for the Q4W arm which was statistically significant ($P < 0.001$) and -13.65 (-24.02 to -3.29) points for the Q8W arm which was also statistically significant ($P = 0.010$)..."		
<i>Section 3.4.1, page 76:</i> "Patients completing OASIS-HAE were eligible to enrol in OASISplus, with 83 participants entering the OLE cohort.^{7, 52} This represents a selected population enriched for trial completers, potentially favouring patients who tolerated and responded to treatment in the double-blind phase. Such selection limits the generalisability of long-term findings to the broader HAE population."	The company requests that the EAG removes or rephrases these statements as the OASISplus enrolment criteria did not only select for patients who had completed OASIS-HAE. "Patients completing OASIS-HAE were eligible to enrol in OASISplus, with 83 participants entering the OLE cohort.^{7, 52} Patients who withdrew from the OASIS-HAE trial owing to lack of efficacy after week 5 were also eligible to enrol in the	Enrolment into OASISplus was not restricted to patients who had completed OASIS-HAE. As reported in Section 2, Section 9.1, and Section 10.1 of the OASIS-HAE CSR, <i>'Patients who experienced at least 5 attacks/month for 2 consecutive months after Week 5 (considered lack of efficacy) had the opportunity to discontinue from treatment in the current study and either progress to the Post-Treatment Period or enrol in</i>	Thank you for providing clarity for the OASISplus enrolment criteria to include patients who had withdrawn from OASIS-HAE due to a lack of efficacy. The amendments have been made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>Section 3.4.1, page 77:</i> “The EAG notes that as an uncontrolled, unblinded study, OASISplus is inherently subject to multiple sources of bias, including selection bias, expectancy effects, and regression to the mean.” <i>Section 3.4.2, page 78:</i> “While these findings suggest maintenance of effect, interpretation is limited by the lack of a comparator, the enrichment of the cohort with prior responders, and the non-randomised dosing strategy.” <i>Section 3.4.2, page 79:</i> “However, the open-label, uncontrolled design, selective enrolment of trial completers, short follow-up in the switch cohort, limited maturity of long-term data, and	OLE cohort.” This ~~represents a selected population enriched for trial completers, potentially favouring patients who tolerated and responded to treatment in the double-blind phase. Such selection limits the generalisability of long-term findings to the broader HAE population.”~~ “The EAG notes that as an uncontrolled, unblinded study, OASISplus may be subject to multiple sources of bias, including selection bias, expectancy effects, and regression to the mean.” “While these findings suggest maintenance of effect, interpretation may be limited by the lack of a comparator;	<i>the OLE study. If a patient chose to enrol in the OLE study, the patient was to be discontinued from the current study.</i> As presented in Section 2.3.1.1, Table 7 of the company submission (and Table 7 of the OASIS-HAE CSR), five patients discontinued from OASIS-HAE due to lack of efficacy (one in the donidalorsen Q4W group, one in the donidalorsen Q8W group, and three in the placebo group), all of whom enrolled into the OASISplus OLE. Selection for enrolment into OASISplus was therefore not biased toward including only patients who had completed OASIS-HAE, and the OASISplus population was not enriched with prior responders and trial completers from OASIS-HAE.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
incomplete reporting of safety and patient-reported outcomes substantially limit the strength of conclusions that can be drawn.” <i>Section 3.5.2, page 82:</i> “OASISplus provides longer-term safety data for donidalorsen. However, interpretation is limited by its open-label, uncontrolled design and selective enrolment of patients who completed OASIS-HAE.”	~~the enrichment of the cohort with prior responders, and the non-randomised dosing strategy.”~~ “However, the open-label, uncontrolled design, ~~selective enrolment of trial completers,~~ short follow-up in the switch cohort, maturity of long-term data, and the safety and patient-reported outcomes limited to latest cut-off substantially limit the strength of the conclusions that can be drawn.” “OASISplus provides longer-term safety data for donidalorsen. However, interpretation may be limited by its open-label and uncontrolled design ~~and selective enrolment of~~		

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	~~patients who completed OASIS-HAE.~~		
<i>Section 3.4.2, page 78:</i> “The most common reason for early termination from those who switched form lanadelumab was lack of efficacy (n=█; █).”	The company requests that this value is amended to: “The most common reason for early termination from those who switched form lanadelumab was lack of efficacy (n=█; █).”	Incorrect data reported.	Thank you this has been amended.
<i>Section 3.5.1, page 80:</i> “In the Q4W arm, headache was the most common TEAE reported in █ (█) of participants.”	The company requests that this text is amended to: “In the Q4W arm, headache and injection site erythema were the most common TEAEs reported in █ (█) of participants.”	Injection site erythema was also the joint most common adverse event alongside headache in the donidalorsen Q4W arm.	Thank you this has been amended.
<i>Section 3.5.1, Table 11, 8th row, page 81:</i> “Discontinuations due to TEAEs, n (%):	The company requests that these values are amended to:	Incorrect data reported for the donidalorsen Q8W and placebo treatment arms.	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
- Donidalorsen 80mg Q4W (N=45), n(%): [REDACTED] - Donidalorsen 80mg Q8W (N=23), n(%): [REDACTED] - Placebo (N=22), n(%): [REDACTED]	- Donidalorsen 80mg Q4W (N=45), n(%): [REDACTED] - Donidalorsen 80mg Q8W (N=23), n(%): [REDACTED] - Placebo (N=22), n(%): [REDACTED]		
<i>Section 3.6.3.3, Table 16, 25th row, page 95:</i> C1INH-nf -> placebo, Type I: 42 (93.3%)	The company requests that this text is amended to: C1INH-nf -> placebo, Type I: 9 (82.2%)	Incorrect data reported.	Thank you this has been amended.
<i>Section 3.6.3.3, Table 16, 26th row, page 95:</i> C1INH-nf -> placebo, Type II: 42 (93.3%)	The company requests that this text is amended to: C1INH-nf -> placebo, Type II: 2 (18.2%)	Incorrect data reported.	The EAG is unsure of the error
<i>Section 3.6.3.3, Table 16, 33rd row, page 96:</i> Lana Q2W, Previous prophylactic treatment = Yes: 3 (11%)	The company requests that this text is amended to: Lana Q2W, Previous prophylactic treatment	Incorrect data reported.	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	= Yes: Oral: 0 (0%) Combi: 3 (11.1%)		
<i>Section 3.6.3.3, Table 16, 33rd row, page 96:</i> Lana 300mg Q4W, Previous prophylactic treatment = Yes: Oral: 1 (3.5%), Combi 1 (3.5%)	The company requests that this text is amended to: Lana 300mg Q4W, Previous prophylactic treatment = Yes: Oral: 1 (3.4%), Combi 1 (3.4%)	Incorrect data reported.	Thank you this has been amended.
<i>Section 3.6.3.5, Table 17, 6th row, page 102:</i> Mean number of HAE attacks requiring on-demand medication, OASIS-HAE (n=22): “1.90 (1.23 to 2.62)”	The company requests that this text is amended to: “1.80 (1.23 to 2.62)”	Incorrect data reported.	Thank you this has been amended.
<i>Section 3.6.5.1, page 106:</i> “The company’s statement that donidalorsen Q4W demonstrates a [REDACTED] than berotrastat and placebo therefore appears either a misinterpretation of	The company asks that the EAG rephrases or removes these statements as the company considers the interpretation of the results presented for the AE-QoL NMA outcome in the	The company considers the interpretation of the results presented for the AE-QoL NMA outcome in the company submission to be correct. The NMA results present the mean difference in the change from baseline	Thank you for providing additional clarity and supporting text to aid interpretation of the analysis presented in company submission for the AE-QOL outcome.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
the direction of the estimated treatment effects, or an error when analysing this outcome. The change from baseline as presented in Table 19 of the NMA Feasibility Assessment v8.0 report shows both donidalorsen arms are associated with the [REDACTED] in QOL score from baseline, with donidalorsen Q4W being associated with the [REDACTED] in AE-QOL score, suggesting [REDACTED]. The EAG re-ran this analysis on the QOL outcome and produced similar results to the company; therefore, the EAG believes this issue stems from a confusion between the interpretation in the company's write up and how the results are presented. Although the NMA results were presented as positive mean differences relative to donidalorsen Q4W, this reflects the direction of the contrast rather than the superior efficacy of the comparators. AE-QOL improvements are represented by reductions from baseline, therefore the positive mean	company submission to be correct.	in AE-QoL and support the conclusions that donidalorsen has a [REDACTED] [REDACTED] compared to berotralstat. To further clarify the interpretation of the results, the company have provided suggested wording edits to the caption of Table 23 in the company submission and the supporting text, as follows: - Company submission, Table 23 "Mean difference and 95% CrIs from the NMA from the change in AE-QoL score from baseline" - Company submission, Section 2.10.4.7, page 115 "A [REDACTED], as indicated by the CrIs of the	The text has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		<i>“donidalorsen Q4W was associated with a [REDACTED] in AE-QoL compared with berotralstat”.</i> Therefore, the EAG’s conclusion that the company’s NMA reported [REDACTED], with credible intervals [REDACTED] is incorrect. There was no difference observed between the company and EAG NMAs in the comparison between donidalorsen Q4W and berotralstat for the AE-QoL outcome.	

Issue 3 CIC Mark up

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
<i>Section 3.6.5.1, page 106</i>	Results from the company NMA are not published and are considered confidential.	“The company’s statement that donidalorsen Q4W demonstrates a [REDACTED] than berotralstat and placebo therefore appears either a misinterpretation of the direction of the estimated treatment effects, or an error when analysing this outcome.”	Thank you this statement has been amended and confidentiality marking applied.
<i>Section 4.2.3, page 135</i>	The average weight of OASIS-HAE participants is not published and is considered confidential.	“A mean age of 37.2years, with an average weight of [REDACTED] kg and 46.70% males were applied in the economic model.”	Thank you this has been amended.
<i>Section 4.2.4, page 138</i>	The distribution of patients receiving 1000 IU or 1500 IU of Berinert is informed by insights from clinical experts. The clinical validation report is not published and is considered confidential.	“This resulted in implementation of a distribution of patients receiving 1000 IU or 1500 IU of Berinert with an assumption that [REDACTED] of patients take 1000 IU ([REDACTED]) and [REDACTED] of patients take 1500 IU ([REDACTED]).”	Thank you this has been amended.
<i>Section 4.2.4, Table 31, page 144</i>	The distribution of from laryngeal, moderate/severe (excluding laryngeal attacks) and mild HAE attacks in the OASIS-HAE trial	“1%”	Thank you this has been amended.

<i>Section 4.2.7, page 153</i>	The distribution of patients receiving 1000 IU or 1500 IU of Berinert is informed by insights from clinical experts. The clinical validation report is not published and is considered confidential.	“In estimating the cost of C1-INH, the dosage of IV Berinert used in the model was informed by the company’s clinical experts – ■■■ of patients on 1500IU and ■■■ on 1000IU.”	Thank you this has been amended.
<i>Section 5.1.2, page 179</i>	Model results (total costs, QALYs, LYs, incremental costs, NMB and ICERs) are confidential to avoid back-calculation of the confidential Patient Access Scheme. Indirect treatment comparison results have not been published are considered confidential.	“The ■■■■■ results of donidalorsen versus berotralstat and C1-INH explains that donidalorsen is less costly and ■■■■■ than berotralstat and C1-INH.”	Thank you this has been amended.
<i>Section 5.1.2, page 179</i>	Model results (total costs, QALYs, LYs, incremental costs, NMB and ICERs) are confidential to avoid back-calculation of the confidential Patient Access Scheme. Indirect treatment comparison results have not been published are considered confidential.	“When compared with lanadelumab, the results show that donidalorsen is less costly but also ■■■■■ effective with a cost savings of ■■■■■ and ■■■■■ QALYs gained over the lifetime horizon.”	Thank you this has been amended.
<i>Section 5.1.2, page 179</i>	Model results (total costs, QALYs, LYs, incremental costs, NMB and	“It shows that while considering joint parameter uncertainty,	Thank you this has been amended.

	ICERs) are confidential to avoid back-calculation of the confidential Patient Access Scheme.	treatment with donidalorsen is expected to save cost and [REDACTED] when compared to berotralstat for the ≥ 2 attacks per month population.”	
<i>Section 5.1.2, page 179</i>	Model results (total costs, QALYs, LYs, incremental costs, NMB and ICERs) are confidential to avoid back-calculation of the confidential Patient Access Scheme.	“For the ≥ 8 attacks per month population, donidalorsen produces a [REDACTED] ICER versus C1-INH while with lanadelumab majority of the cost and effect pairs were found in the [REDACTED] quadrant which suggests that donidalorsen saves cost [REDACTED] ([REDACTED]) over the life-time horizon.”	Thank you this has been amended.
<i>Section 5.2.1, page 190</i>	The attack rate from the OASIS-HAE trial is published within the Riedl et al. 2024 study and is not considered confidential.	HAE attack per model cycle based on the NMA was found to be like that of the QASIS trial ([REDACTED] vs 0.44)	Thank you this has been amended.

(Please add further lines to the table as necessary)

Issue 4 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, Issue 2, page 15 “3.4.6”	“3.6.6”	The reference to the section within the EAG report is incorrect, the company ask that the EAG amend this to the correct section.	Thank you this has been amended.
Section 1.4, Issue 1, page 19 “3.4.3.3”	“3.6.3.3”	The reference to the section within the EAG report is incorrect, the company ask that the EAG amend this to the correct section.	Thank you this has been amended.
Section 1.6, Page 22: “Berotralstat is [REDACTED] in company base case cost-utility scenario analysis”	The company requests that the text is amended to: “Berotralstat is [REDACTED] in the company’s base case cost-utility scenario analysis”	In the company’s cost-utility scenario, treatment with donidalorsen resulted in a [REDACTED] ICER versus berotralstat.	Thank you this has been amended.
Section 2.1, page 27: “The EAG clinical expert also highlighted that in addition to emotional stress was also a trigger for an attack.”	The company <i>suggests</i> that the text is amended to: “The EAG clinical expert also highlighted that in addition to hormonal factors , emotional	This sentence is incomplete; the opinion of the EAG's clinical expert is unknown to the company, though the context suggests that “hormonal factors” may be the missing text. The	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	stress was also a trigger for an attack."	company asks that the EAG update this sentence to accurately reflect the clinical expert's opinion.	
Section 2.1, page 27: "Symptoms of AK"	"Symptoms of HAE "	The section heading refers a different health condition; the company asks that the EAG update the header to reflect the disease area of this appraisal.	Thank you this has been amended.
Section 2.1, page 33: "For example, while the EAG acknowledge the limitations of berotralstat, including gastrointestinal tolerability concerns and the stopping rule, ^{38, 44} the EAG disagrees with the assertion that berotralstat is the only routinely commissioned oral prophylactic option for patients experiencing ≥ 2 attacks per month."	The company requests that the text is reassessed. The following text is proposed: "For example, while the EAG acknowledge the limitations of berotralstat, including gastrointestinal tolerability concerns and the stopping rule, ^{38, 44} the EAG disagrees with the assertion that berotralstat is the only standard-of-care long-term prophylactic option for patients experiencing ≥ 2 attacks per month."	Berotralstat is the only routinely commissioned <i>oral</i> prophylactic option. Lanadelumab, garadacimab and C1-INHs are administered via SC or IV injection. This is reflected in Table 4 of the EAG's report, where berotralstat is the only LTP SoC option administered orally. The company do not assert that berotralstat is the only routinely commissioned LTP for patients experiencing ≥ 2 attacks per month. However, at the time of the company evidence	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		submission, berotralstat was the only SoC LTP for patients experiencing ≥ 2 attacks per month.	
<i>Section 3.1, Table 6, page 50:</i> “It is also unclear whether the risk of bias assessment Risk of bias were conducted by a single reviewer or two reviewers.”	The company requests that the text is amended to: “It is also unclear whether the risk of bias assessment ~~Risk of bias~~ was conducted by a single reviewer or two reviewers.”	Typographical error. (delete repeated wording)	Thank you this has been amended.
<i>Section 3.2.1, Table 7, page 57:</i> “Disallowed concomitant therapy included: chronic prophylaxis for HAE attacks, except for stable doses of androgens or tranexamic acid. Lanadelumab and berotralstat was also no permitted.”	The company requests that the text is amended to: “Disallowed concomitant therapy included: chronic prophylaxis for HAE attacks, except for stable doses of androgens or tranexamic acid. Lanadelumab and berotralstat was also not permitted.”	Typographical error.	Thank you this has been amended.
<i>Section 3.6.3.3, Table 16, 11th row, page 94:</i> “BMI”	The company requests that the text is amended to: “BMI (SD)”	Typographical error.	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>Section 3.6.4, page 104:</i> “Examination of the NMA inputs suggests that the different estimands used across trials”	The company requests that the text is amended to: “Examination of the NMA inputs suggests that ~~the~~ different estimands were used across trials”	Typographical error.	Thank you this has been amended.
<i>Section 3.6.8, page 110:</i> “The absence of statistically meaningful differences between active treatments in this context reflects limited precision rather than evidence of equals efficacy.”	The company requests that the text is amended to: “The absence of statistically meaningful differences between active treatments in this context reflects limited precision rather than evidence of equal efficacy.”	Typographical error.	Thank you this has been amended.
<i>Section 3.7.2, page 119:</i> “VANGUARD required a minimum recent attack frequency, comparable to the thresholds used in HELP and APeX-2, although CSL312_2001 imposed a higher short-term attack	The company requests that the text is amended to: “VANGUARD required a minimum recent attack frequency, comparable to the thresholds used in HELP and APeX-2, although CSL312_2001 imposed a higher	Typographical error.	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
requirement which may have resulted in a sample with higher disease activity at baseline, and whereas VANGUARD included adolescents aged ≥ 12 years, aligning closely with OASIS-HAE and HELP.”	short-term attack requirement which may have resulted in a sample with higher disease activity at baseline. VANGUARD included adolescents aged ≥ 12 years, aligning closely with OASIS-HAE and HELP.”		
<i>Section 3.7.5, page 123:</i> “Sensitivity analyses were conducted assuming correlations of 0.3 and 0.7 resulted in no meaningful differences.”	The company requests that the text is amended to: “Sensitivity analyses were conducted assuming correlations of 0.3 and 0.7 and resulted in no meaningful differences.”	Typographical error.	Thank you this has been amended.
<i>Section 3.7.8, page 124:</i> “Compared with donidarlosen Q4W (reference treatment), garadacimab 200 mg QM was associated with [REDACTED] RRs for overall HAE attacks...”	The company requests that the text is amended to: “Compared with donidalorsen Q4W (reference treatment), garadacimab 200 mg QM was associated with [REDACTED] RRs for overall HAE attacks...”	Typographical error.	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>Section 4.2.4, page 136:</i> “The EAG notes that there are differences with the dosing frequency stated in the marketing authorisation and that used in the OASIS-HAE trial.”	The company requests that the text is amended to: “The EAG notes that there are differences with the dosing frequency stated in the marketing authorisation and those used in the OASIS-HAE trial.”	Typographical error.	Thank you this has been amended.
<i>Section 4.2.4, page 137:</i> “The company indicated these comparators are in line with NICE scope and established standard of care in the NHSE for patients with HAE, but EAG notes the exclusion of some comparators like Garadacimab, Ruconest and attenuated androgens and antifibrolytics from their analysis.”	The company requests that the text is amended to: “The company indicated these comparators are in line with NICE scope and established standard of care in the NHSE for patients with HAE, but EAG notes the exclusion of some comparators like Garadacimab, Ruconest and attenuated androgens and antifibrinolytics from their analysis”	Typographical error.	Thank you this has been amended.
<i>Section 4.2.4, page 137:</i> “A dose of 150mg once daily of berostralstat was applied in	The company requests that the text is amended to:	Typographical error.	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
the model based on its SmPC."	"A dose of 150mg once daily of berotralstat was applied in the model based on its SmPC."		
<i>Section 4.2.5, Table 30, page 143:</i> The table is missing the note for 'No LTP'* below the table.	The company requests that a note is added below the table: "*'No LTP' is included in this table to show the attack rate patients experience when they discontinue their LTP treatment. 'No LTP' is not a comparator within the economic model."	The table is missing the note for * below the table which provides further clarification for why 'No LTP' is not a comparator in the economic model.	Thank you this has been amended.
<i>Section 4.2.5, page 144:</i> "Laryngeal attacks were estimated from moderate/severe attacks as all attacks that occur in the larynx and can lead to suffocation"	The company requests that the text is amended to: "Laryngeal attacks were estimated from moderate/severe attacks as all attacks that occur in the larynx and can lead to suffocation"	Typographical error.	Thank you this has been amended.
<i>Section 4.2.5, Table 31, page 144: Source column (applies to three rows)</i> "OASIS-HAE, donidalorsen Q4W moderate/severe Weeks 1-25 LSM76"	The company requests that the text is amended to: "OASIS-HAE, donidalorsen Q4W moderate/severe Weeks 1-25 LSM⁷⁶"	The reference used is not superscripted and therefore is not linked to the report reference list.	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>Section 4.2.7, page 151:</i> “Of these studies, 51 were abstracts, 29 full text journal articles and 11 were HTA appraisals.”	The company requests that the text is amended to: “Of these studies, 51 were abstracts, 129 full text journal articles and 11 were HTA appraisals.”	The number of full texts identified in the SLR for cost and resource use is 19.	Thank you this has been amended.
<i>Section 4.2.7, page 152:</i> “The dosing regimen for the LTP comparators (berostralstat, lenadelumab, and C1-INH) used in the model aligns with their` SmPC (Error! Reference source not found.; Error! Reference source not found.).	The company requests that the text is amended to: “The dosing regimen for the LTP comparators (berotralstat, lanadelumab, and C1-INH) used in the model aligns with their SmPC (Error! Reference source not found.; Error! Reference source not found.).	Typographical error.	Thank you this has been amended.
<i>Section 4.2.7, page 154:</i> “The company further stated that implementing the continuation rule would remove acquisition costs for non-responders without	The company requests that the text is amended to: “The company further stated that implementing the discontinuation rule would remove acquisition costs for	Typographical error.	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
capturing the increased attack burden associated with no LTP.”	non-responders without capturing the increased attack burden associated with no LTP.”		
<i>Section 4.2.7, page 158:</i> “No cost was associated with oral treatments (berostralstat) as applicable in standard practice.”	The company requests that the text is amended to: “No cost was associated with oral treatments (berotralstat) as applicable in standard practice.”	Typographical error.	Thank you this has been amended.
<i>Section 4.2.7, page 161:</i> “The company notes, HCRU as rather been applied in the cost utility analysis scenario analysis.”	The company requests that the text is amended to: “The company notes, HCRU h as rather been applied in the cost utility analysis scenario analysis.”	Typographical error.	Thank you this has been amended.
<i>Section 5.1.1, page 164:</i> “The company reported deterministic and sensitivity analysis results for the cost-comparison between donidalorsen and comparators in two subgroups.	The company requests that the text is amended to: ““The company reported deterministic and sensitivity analysis results for the cost-comparison between donidalorsen and comparators in two subgroups. i. Berotralstat for ≥ 2 attacks per month.”	Typographical error.	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
i. Berostralstat for ≥ 2 attacks per month.”			
<i>Section 5.1.1, page 164:</i> “All results reflect the application of a PAS discount of [REDACTED] % for donidalorsen with a net price of £[REDACTED] per 80mg pre-filled pen and list prices for berostsalstat, lanadelumab and C1-INH.”	The company requests that the text is amended to: “All results reflect the application of a PAS discount of [REDACTED] % for donidalorsen with a net price of £[REDACTED] per 80mg pre-filled pen and list prices for berotralstat, lanadelumab and C1-INH.”	Typographical error.	Thank you this has been amended.
<i>Section 5.1.2, page 179:</i> “In patients experiencing ≥ 8 attacks per month, treatment with donidalorsen produces an ICER of [REDACTED] versus lanadelumab and [REDACTED] ICER versus C1-INH.”	The company requests that the text is amended to: In patients experiencing ≥ 8 attacks per month, treatment with donidalorsen produces an ICER of [REDACTED] versus lanadelumab and [REDACTED] ICER versus C1-INH.”	It is important to clarify that the ICER sits in the [REDACTED] of the cost-effectiveness plane, to demonstrate that [REDACTED]. Without this clarification, it may be inferred that donidalorsen is [REDACTED] against lanadelumab.	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>Section 5.1.2, Table 50, page 180:</i> ≥ 8 attacks per month population, ICER incremental (£/QALY): “[REDACTED]”	The company requests that the value reported is amended to: “[REDACTED]”	It is important to clarify that the ICER sits in the [REDACTED] of the cost-effectiveness plane, to demonstrate that [REDACTED]. Without this clarification, it may be inferred that donidalorsen is [REDACTED] against lanadelumab.	Thank you this has been amended.
<i>Section 5.1.2, page 182:</i> “The results show that donidalorsen has a [REDACTED] ICER versus berolstrastat and C1-INH in all scenarios.”	The company requests that the text is amended to: “The results show that donidalorsen has a [REDACTED] ICER versus berotralstat and C1-INH in all scenarios ICER versus “	Typographical error.	Thank you this has been amended.
<i>Section 5.2.1, page 190:</i> “HAE attack per model cycle based on the NMA was found to be like that of the QASIS trial ([REDACTED] vs [REDACTED])”	The company requests that the text is amended to: “HAE attack per model cycle based on the NMA was found to	Typographical error.	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	be like that of the OASIS trial (■■■ vs ■■■)"		
<i>Section 5.2.2, Table 59, Page 191:</i> The left-most column "Exploratory analysis number" in Table 59 is empty.	The company requests that this column in the table is populated with numbers from 1 – 9.	The left-most column numbering the EAG's exploratory analyses is currently empty.	Thank you this has been amended, but from 1 – 8.
<i>Section 5.2.2, Table 59, Page 191:</i> The right-most column "Section in EAG report" in Table 59 is empty.	The company requests that this column in the table is populated with the relevant sections in the EAG report.	The right-most column highlighting the relevant section from the EAG report, in the table presenting the EAG's exploratory analysis, is currently empty.	Thank you this column has been updated. Also, a note has been added under table 32 to allow signposting of scenario No.7. It reads: "100% treatment compliance is assumed for all treatments in the economic model in base case analysis"
<i>Section 5.2.2, Table 59, page 194:</i> 80% compliance scenario, "To assess the impact of setting compliance parameter to 100% in the model"	The company requests that the text is amended to: "To assess the impact of setting the compliance parameter to 80% in the model"	The scenario run by the EAG is setting the compliance to 80% and therefore the justification in the column should specify 80% instead of 100%.	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>Section 5.2.2, Table 59, page 194:</i> Efficacy differs by treatment scenario, “Efficacy differs by treatment and based on rate ratios derived vi the NMA”	The company requests that the text is amended to: “Efficacy differs by treatment and is based on rate ratios derived from the NMA”	Typographical error.	Thank you this has been amended.
<i>Section 5.2.2, Table 60, page 195:</i> “Donidalorsen versus lanadelumab (≥ 2 attacks per month population)”	The company requests that the text is amended to: “Donidalorsen versus lanadelumab (≥ 8 attacks per month population)”	Lanadelumab is reimbursed in the population experiencing ≥8 attacks per month and therefore used in a different analysis to berotralstat, which is reimbursed in the population experiencing ≥2 attacks per month only.	Thank you this has been amended.
<i>Section 5.2.2, Table 60, page 196:</i> Exploratory analysis number 8, incremental costs: “[REDACTED]”	The company requests that the text is amended to: “[REDACTED]”	Typographical error.	Thank you this has been amended.
<i>Section 5.2.2, Table 60, page 196:</i>	The company requests that the EAG amend the left-most column numbering to include row 12 at the ‘Varying efficacy	The numbering of each EAG exploratory analysis is	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The ‘Exploratory analysis number’ column numbering skips one row after number 11, causing subsequent numbering to be misaligned, and merges cells to form number 15, where this should be two separate rows, separately numbered.	for all treatments’ column for donidalorsen versus lanadelumab, which subsequently requires the numbering for donidalorsen versus C1-INH to change as follows: 13: Donidalorsen 80mg Q4W, then Q8W, 14: 40% IV Cinryze and 60% IV Berinert 15: Administration costs for on-demand medications included 16: Varying efficacy for all treatments 17: 80% treatment compliance 18: 90% treatment compliance	misaligned and should be re-numbered from 1 – 18 for clarity.	
<i>Section 5.2.2, Table 61, page 198:</i> ≥ 8 attacks per month population, “Lanadeluumab”	“Lanadelu~~u~~mab”	Typographical error.	Thank you this has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>Section 5.2.3, page 203:</i> “However, when compared with garadacimab, donidalorsen is associated with [REDACTED] (£[REDACTED] vs. £[REDACTED]) but also generates [REDACTED] ([REDACTED] vs. [REDACTED]) i.e. is [REDACTED] but [REDACTED] (see Error! Reference source not found.).”	The company requests that the text is amended to: “However, when compared with garadacimab, donidalorsen is associated with [REDACTED] (£[REDACTED] vs. £[REDACTED]) but also generates [REDACTED] ([REDACTED] vs. [REDACTED]) i.e. is [REDACTED] but [REDACTED] (see Error! Reference source not found.63).”	The table number and therefore cross-reference is missing from the sentence.	Thank you this has been amended.
<i>Section 5.2.4, Table 68, page 207:</i> Left-most column detailing EAG scenario analysis numbering is missing numbers and therefore is misaligned for subsequent rows.	The company requests that the left-most column numbering is amended to follow from 1 – 12, filling in the two missing gaps in the eighth and tenth rows.	The numbering of each EAG exploratory analysis is misaligned and should be re-numbered from 1 – 12 for clarity.	Thank you this has been amended.
<i>Section 5.2.4, Table 69, page 208-209:</i> “Berostralstat” label in the left-most column for each row of scenarios run	The company requests that each row where “Berostralstat” is mentioned is amended to: “Berotralstat”.	Typographical error.	Thank you this has been amended.

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Additional evidence – Company's pairwise analyses of donidalorsen Q4W versus garadacimab

The company would like to thank the National Institute for Health and Care Excellence (NICE) and the Evidence Assessment Group (EAG) for the opportunity to provide further evidence to support the ongoing appraisal of donidalorsen in hereditary angioedema (HAE). In the following document, the company provides additional pairwise network meta-analyses (NMA) to estimate the comparative efficacy between donidalorsen once every four weeks (Q4W), and garadacimab and placebo.

NICE recommended garadacimab (NICE TA1101) on 8 October 2025, 22 days before the company evidence submission (CES). At the time of submission, garadacimab was not considered established clinical practice in England and was therefore not included as a comparator in the clinical or economic analyses.

At the clarification question stage, the company provided a naïve comparison of donidalorsen (OASIS-HAE) and garadacimab (VANGUARD) in response to Question A1. The naïve comparison showed similar mean monthly attack rates for donidalorsen Q4W and garadacimab.

The company acknowledges that the treatment pathway has evolved in the six months since submission, and that garadacimab may now be a relevant comparator. To address the key issue raised by the EAG specifically regarding the inclusion of garadacimab, and to support committee decision-making ahead of the first Appraisal Committee Meeting (ACM1), the company has proactively provided a pairwise NMA comparing donidalorsen Q4W, garadacimab and placebo for both the steady-state and the full trial period.

Methodology

The pairwise NMA was performed to estimate the comparative efficacy of donidalorsen Q4W, garadacimab and placebo, for the mean number of HAE attacks per month outcome. This outcome is the primary outcome used to model the clinical efficacy of donidalorsen and comparators in the economic model.

Following on from the steady-state NMAs for the other LTP comparators provided at the clarification question stage, the company considers a steady-state analysis the most appropriate way to assess the long-term comparative efficacy of donidalorsen Q4W and garadacimab.

Pharmacokinetic analysis showed that garadacimab concentrations appeared to achieve steady-state exposures after the first (loading) dose (i.e. day 1), compared to donidalorsen, which shows a steady-state exposure from week 5.¹ That is, the period when the treatment is assumed to have reached maximum effectiveness. Donidalorsen is expected to reach the steady-state period at approximately 25 to 30 days (i.e. after the first four-week dosing period).^{2,3} Evaluation of efficacy outcomes from Weeks 5–25 in OASIS-HAE reflects the period during which donidalorsen has achieved steady-state plasma kallikrein (PKK) suppression, ensuring that efficacy is assessed under stable pharmacodynamic conditions. A stable reduction in PKK levels is a key marker of efficacy, demonstrating that the treatment has reached a steady-state.^{2,4} Given the time difference for donidalorsen Q4W and garadacimab to reach maximum treatment effectiveness, the company consider a steady-state NMA to be the most appropriate approach for demonstrating a robust comparison between donidalorsen Q4W and garadacimab.

For completeness, the pairwise NMA for the full trial period is also presented. In the company's base-case at the time of submission, the NMA was conducted for the full trial period given the reporting of data in the HELP and APeX-2 clinical trials (for lanadelumab and berotralstat, respectively). As previously noted, the company provided the base-case NMA conducted for the steady-state period in response to Question A23 of the EAG's clarification questions. In the EAG's own NMA, including garadacimab in the network, the analysis was over the full trial period.

Data to inform the pairwise NMA were extracted from the OASIS-HAE trial for donidalorsen Q4W and placebo, covering both the full trial period (baseline to week 25) and the steady-state period (weeks 5 – 25).⁵ Data to inform the pairwise NMA were extracted from the VANGUARD trial (days 1 – 182) for garadacimab and placebo.

All analyses presented below were generated using a random effects (RE) model. The overall methodology of the pairwise NMA aligns with the methodology used in the company's base-case NMA, presented as part of the company's evidence submission. For further details on the NMA methodology, please refer to the CES dated October 2025 or the UK NMA Statistical Analysis Plan (V3.0) provided in the reference pack for the company's response to the EAG's clarification questions.

Results

Steady-state period

Median rate ratios for the mean number of HAE attacks per month and 95% CrIs are shown in Table 1 and the forest plot in Figure 1. No statistically significant differences were observed between the mean number of HAE attacks per month, as informed by the median rate ratios, in treatment with donidalorsen Q4W and garadacimab. The wide and overlapping CrIs observed in the forest plot presented in Figure 1, demonstrate that there is no statistically significant difference between the median rate ratios of donidalorsen Q4W and garadacimab.

A

Table 1: Median rate ratios and 95% CrIs from the pairwise donidalorsen Q4W and garadacimab RE NMA for mean number of HAE attacks per month – steady-state period

Treatment	Median rate ratio (95% CrI)
Garadacimab	
Placebo	

*95% CrI does not include 1 and is therefore considered statistically significant

Abbreviations: CrI – Credible interval; HAE – Hereditary angioedema; NMA – Network meta-analysis; Q4W – Every 4 weeks; RE – Random effects

Figure 1: Forest plot of median rate ratios and 95% CrIs for mean number of HAE attacks per month – steady-state period, RE NMA



Abbreviations: CrI – Credible interval; HAE – Hereditary angioedema; NMA – Network meta-analysis; Q4W – Every 4 weeks; RE – Random effects

Full trial period

Median rate ratios for the mean number of HAE attacks per month and 95% CrIs are shown in Table 2 and the forest plot in Figure 2. No statistically significant differences were observed between the mean number of HAE attacks per month, as informed by the median rate ratios, in treatment with donidalorsen Q4W and garadacimab. The wide and overlapping CrIs observed in the forest plot presented in Figure 1, demonstrate that there is no statistically significant difference between the median rate ratios of donidalorsen Q4W and garadacimab.

A [REDACTED]

Table 2: Median rate ratios and 95% CrIs from the pairwise donidalorsen Q4W and garadacimab RE NMA for mean number of HAE attacks per month – full trial period

Treatment	Median rate ratio (95% CrI)
Garadacimab	[REDACTED]
Placebo	[REDACTED]

*95% CrI does not include 1 and is therefore considered statistically significant

Abbreviations: CrI – Credible interval; HAE – Hereditary angioedema; NMA – Network meta-analysis; Q4W – Every 4 weeks; RE – Random effects

Figure 2: Forest plot of median rate ratios and 95% CrIs for mean number of HAE attacks per month – full trial period, RE NMA



Abbreviations: CrI – Credible interval; HAE – Hereditary angioedema; NMA – Network meta-analysis; Q4W – Every 4 weeks; RE – Random effects

No statistically significant difference was observed between donidalorsen Q4W and garadacimab in the mean number of HAE attacks per month when assessing over the steady-state period or the full trial period. This further supports the assumption of similar efficacy across all LTPs in the company's base-case cost-comparison analysis.

Conclusion

When assessing the steady-state period of donidalorsen and garadacimab, the pairwise NMA demonstrates that [REDACTED] is observed between donidalorsen Q4W and garadacimab for the mean number of HAE attacks per month. This supports the conclusion that donidalorsen is a clinically effective treatment option for patients with HAE, [REDACTED] (median rate ratio [95% CrI]: [REDACTED]).

The results of the pairwise NMA between donidalorsen Q4W and garadacimab support the company's base-case assumption of similar efficacy between donidalorsen and comparator LTPs, including garadacimab. The analysis also provides additional evidence to support the company's conclusion in the response to Question A1 of the EAG's clarification questions that donidalorsen provides a comparable treatment alternative to garadacimab in the management of HAE. This further supports the cost-comparison approach for donidalorsen versus all LTPs, including garadacimab.

Evaluation of efficacy outcomes from Weeks 5–25 in OASIS-HAE reflects the period during which donidalorsen has achieved steady-state PKK suppression (~25–30 days post-initiation), ensuring that

efficacy is assessed under stable pharmacodynamic conditions. This steady-state assessment is consistent with the analytical approach used in other pivotal LTP trials. Accordingly, the Week 5–25 analysis represents an appropriate measure of sustained long-term prophylactic efficacy and likely more representative of the therapeutic response achieved during continued long-term use in clinical practice, given that long-term prophylaxis for HAE is intended for chronic lifelong treatment beyond the initial transition phase. As such, the steady-state NMA presented provides an indirect treatment comparison of donidalorsen Q4W and garadacimab which is more likely to reflect longer-term outcomes in clinical practice.

If it would be helpful for decision making, a full NMA network for the steady-state period for all comparators, including garadacimab, can be provided.

Given the variability of HAE and the importance of individualised treatment in this indication, whereby the disease course varies both from patient to patient, and over time for individual patients, it is important to ensure the availability of alternative treatment options for HAE patients.⁶ Donidalorsen provides a unique mechanism of action, and offers HAE patients a treatment choice for managing such a rare, chronic and potentially life-threatening disease.

The company hopes that that the evidence provided will help facilitate an efficient and well-informed discussion at ACM1, enabling the Committee to reach a robust decision in a time-efficient manner. By proactively providing this material, our intention is to support the sparing use of the Committee's time and contribute constructively to the appraisal process. The company hope that this will assist in expediting the appraisal of donidalorsen and, where appropriate, help ensure timely patient access in HAE.

References

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2. Riedl, M. A. *et al.* Efficacy and Safety of Donidalorsen for Hereditary Angioedema. *N Engl J Med* **391**, 21–31 (2024).
3. IONIS. Data on file. Clinical study report - A Phase 3 Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ISIS 721744 in Patients with Hereditary Angioedema (HAE). [Internal document]. (2024).
4. Singh, P. *et al.* Exposure–Response Analysis of Donidalorsen for the Treatment of Hereditary Angioedema. *Clin Transl Sci* **18**, e70388 (2025).
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6. Metcalfe, A. *et al.* *White Paper Tackling Unmet Need in HAE*. Pdf. <https://www.haeuk.org/wp-content/uploads/2025/07/White-Paper-Unmet-Need-in-HAE-digital-June-min.pdf> (2025).

External Assessment Group (EAG) Review of Company Additional Evidence (pre-ACM1)

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6457]

Produced by	Centre for Evidence and Implementation Science, University of Birmingham
Authors	Mubarak Patel, Research Fellow II (Statistician), University of Birmingham Christiana Anyebe, Research Associate, University of Birmingham Mubarak Patel, Research Fellow II (Clinical Effectiveness Reviewer), University of Birmingham Angela Mwape, Research Fellow, University of Birmingham Anna Brown, Information Specialist, University of Birmingham Mandy Maredza, Research Fellow II, University of Birmingham
Correspondence to	Dr Mandy Maredza, m.maredza@bham.ac.uk
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Declared competing interests of the authors

None

Statistical critique of additional evidence – Company's pairwise analyses of donidalorsen Q4W versus garadacimab

The company provided a pairwise network meta-analysis (NMA) comparing donidalorsen Q4W, garadacimab, and placebo for the mean number of HAE attacks per month, for both the steady-state and full trial periods. The EAG notes the following limitations with this analysis and the company's conclusions.

The analysis is a pairwise NMA comprising only three treatments, with the two long-term prophylaxis (LTP) treatments connected through placebo. The comparison between donidalorsen and garadacimab is therefore solely indirect and does not incorporate the wider evidence base used in either the company's original NMA or the EAG's NMA. The EAG's NMA already included garadacimab within the full network (placebo, donidalorsen Q8W and Q4W, lanadelumab Q2W and Q4W, berotralstat, and C1INH-nf), which represents a more methodologically complete indirect treatment comparison (ITC). The company notes in its additional evidence submission that *"if it would be helpful for decision making, a full NMA network for the steady-state period for all comparators, including garadacimab, can be provided."* The EAG considers that this analysis should have been included in the submission to ensure alignment with the approach taken in the original submission.

The credible intervals from both analyses are [REDACTED], reflecting [REDACTED] in the estimated relative effects. For the steady-state period, the rate ratio for garadacimab versus donidalorsen Q4W was [REDACTED] (95% CrI: [REDACTED]), and for the full trial period, [REDACTED] (95% CrI: [REDACTED]). Credible intervals of these widths are consistent with very wide ranges of plausible relative effects, garadacimab being [REDACTED] to donidalorsen. The EAG noted in the EAG's final report that the absence of a statistically meaningful difference (95% CrI not including 1) reflects imprecision in the estimates rather than the confirmation of equivalent efficacy. The company's conclusion that these results "further support the assumption of similar efficacy" repeats the same inferential error identified in the original submission.

The company presented the steady-state analysis as the primary analysis, and the full trial period for “completeness”. The company’s justification for preferring the steady-state period rests on pharmacokinetic arguments regarding the time taken for each drug to reach maximum effectiveness. However, from a clinical perspective, the pharmacokinetic justification alone is not sufficient to support treating the steady-state period as the primary analysis in place of the full trial period. Therapies included in the network may differ in their onset of action, and garadacimab appears to reach steady state earlier than donidalorsen. Restricting the analysis to weeks 5 – 25 may therefore exclude clinically relevant treatment effects occurring during the early treatment period for garadacimab, while having less impact on donidalorsen. Furthermore, the steady-state analysis may not fully capture the total clinical benefit experienced during the treatment initiation period and could influence the relative treatment effect estimates within the network. Additionally, from a statistical perspective, the EAG notes that the full trial period point estimate is numerically [REDACTED] to garadacimab than the steady-state estimate, meaning the company’s choice of the steady-state analysis is potentially selective without sufficient justification.

The addendum is limited to a single outcome. No comparative results are present for other outcomes included into the company’s NMA in the original submission. The company’s additional analysis therefore provides only a partial comparative picture and is insufficient to substantiate the broader claim of equivalent efficacy across all relevant outcomes when including garadacimab to the company’s NMA.

Cost-effectiveness evidence

In the company’s original submission, a cost-utility scenario analysis was presented alongside the chosen base case cost-comparison analysis. The EAG expected the company to adopt a similar approach in its additional evidence submission by providing cost-utility analyses that included garadacimab. This would have ensured that the committee had access to both the EAG’s analyses and the company’s own cost-utility analyses, thereby facilitating a more efficient and well-informed discussion at ACM1, as the company itself indicated.

Committee Briefing

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Group (EAG) Report. Further detail for each consideration is available within the separate tabs.

The feasibility assessment indicates whether the Managed Access Team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access Team.

Topic name:

Donidalorsen for preventing hereditary angioedema attacks in people 12 years and over

Topic ID:

6457

Managed Access Lead:

Steve Norton

Date of assessment(s):

04/02/2026

Feasibility of successful managed access		Comments / Rationale
No managed access proposal	Rationale for rating	The company has not made a managed access proposal. If Committee or other stakeholder wishes for managed access to be considered, they should contact the Managed Access Team.
	Previous ratings and rationale for change	

Managed Access Proposal	No	
Managed Access Team input at Committee meeting	Low	The Managed Access Team does not expect to actively engage with this topic during committee meetings unless a managed access proposal is made

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	No	Since there is no proposal for managed access and other treatments exist, this technology does not seem to meet the criteria for the IMF
Are there outstanding uncertainties that could be resolved with further data collection?	Low	Without a managed access proposal it is not clear that any of the EAG's identified uncertainties can be resolved through data collection in the IMF.
Can data collection from ongoing clinical trials and RWE sources resolve relevant uncertainties?	Unclear	The pivotal trial has ended The extension phase OASISplus may continue to provide useful data. The company has not so far used data from OASISplus in its model, but has reported that its results support the pivotal OASIS-HAE trial. A managed access proposal would be required to explain whether the extension trial would sufficiently resolve uncertainties present in the evidence base.
Are there any other points to note that suggest RWE data collection may be beneficial or challenging in resolving uncertainties?	Low	As there is no proposal, this has not been investigated in detail
Are there any other substantive issues (excluding price) that are a barrier to a MAA?	Not applicable	As there is no proposal, this has not been investigated in detail

Key questions for committee if Managed Access is considered	
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Highlighted uncertainties, other issues or ongoing Managed Access Team actions	
1	
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