Medicinrådet

Bilag til direkte indplacering af donidalorsen i Medicinrådets evidensgennemgang vedrørende lægemidler til arveligt angioødem

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. donidalorsen til arveligt angioødem
2. Amgros' forhandlingsnotat vedr. donidalorsen til arveligt angioødem
3. Ansøgning vedr. vedr. donidalorsen til arveligt angioødem

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Stockholm, 31-03-2026

Otsuka would like to thank the Danish Medicines Council's (DMC) and the expert committee for the efficient assessment for direct placement of donidalorsen (Dawnzera®) in the treatment guidelines for hereditary angioedema (HAE). Otsuka supports the decision to include donidalorsen in the first-line long-term prophylaxis (LTP) category alongside garadacimab, lanadelumab, and subcutaneous C1-inhibitor.

The DMC acknowledges that donidalorsen is a first-in-class, RNA-targeted antisense oligonucleotide. Otsuka considers that the submitted evidence demonstrates that the RNA-targeting mechanism of donidalorsen enables **durable target suppression and supports an extended-interval dosing strategy[1].** As such, donidalorsen may help address residual disease activity and quality-of-life (QoL) impairments that persist in a proportion of patients despite the availability of current treatments.

Otsuka would like to provide additional context regarding the interpretation of the Week 5–25 analysis window, as summarized by the DMC. The interpretation that the Week 5–25 endpoint window favours the donidalorsen OASIS-trial due to "steady state" considerations is not straightforward. Lanadelumab reaches pharmacokinetic (PK) steady state earlier than donidalorsen, and **PK steady state should not be equated with clinically meaningful stabilization of effect.** As stated in the SmPC[2], donidalorsen shows a gradual reduction in attack rate beginning at Week 1, with maximum effect expected after approximately one month. Given the different mechanisms of action, **analyses of later time periods for donidalorsen reflect biological relevance rather than methodological bias**. Overall, the net impact on comparative efficacy remains uncertain and supports a cautious interpretation rather than favouring one intervention a priori.

Unlike pharmaceutical agents that act directly on circulating proteins, such as antibodies and small molecules, donidalorsen targets prekallikrein (PKK) mRNA in hepatocytes. As a result, existing plasma PKK must undergo natural degradation before the full clinical effect is observed. PKK circulates predominantly in complex with high molecular weight kininogen and a nadir in plasma PKK levels is not expected to occur immediately after treatment initiation but is anticipated to be reached progressively, towards the end of the first 4-week dosing interval. Importantly, the pivotal donidalorsen study (OASIS-HAE) did not include the percentage of attack-free patients during Weeks 1–25 as a primary or secondary endpoint.

Otsuka propose that the evidence submitted shows that donidalorsen **may address unmet clinical needs** within LTP of HAE and provide an **additional clinical benefit** within the current treatment landscape by:

1. **Allowing patients with residual disease activity to transition directly from other LTP therapies** without requiring a washout period and resulting in a reduction in the attack activity.
2. **Improved dosing regimen with the ability to prolong the dosing interval to 8 weeks and** allowing for less frequent dosing than currently approved prophylactic treatments thereby decreasing treatment burden and improving overall convenience

The available evidence demonstrates that donidalorsen provides a **high level of attack prevention** and **clinically meaningful improvements in disease control and patient-reported outcomes** in a substantial proportion of patients. These findings are supported by results from Phase 2[3] and Phase 3[4] clinical studies, including their respective open-label extension studies[5-6], which show durable reductions in attack frequency, high attack-free rates, and sustained improvements in quality of life with extended-interval dosing.

The magnitude of attack reduction observed with donidalorsen is broadly comparable to that reported for established LTPs, while offering the potential for less frequent administration. In addition, data from the OASIS

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open-label extension indicate that patients can transition directly from other prophylactic treatments to donidalorsen without a washout period, with an early and sustained reduction in attack activity and no evidence of increased breakthrough attacks[5].

In the Phase 2 study (ISIS 721744-CS2), **donidalorsen reduced mean monthly HAE attack rates by 97% vs** placebo during Weeks 5–17, with **>90% of patients remaining attack-free** and **clinically meaningful improvements in AE-QoL (≥6 points)** [3].

In the pivotal Phase 3 study (ISIS 721744-CS5), donidalorsen reduced attack rates by **87% vs placebo** over Weeks 5–25; **53% of patients remained attack-free** (vs 9% with placebo), **91% achieved well-controlled disease (AECT ≥10)**, moderate/severe attacks were reduced by **89%**, and attacks requiring acute treatment by **92%**[4].

Long-term data confirm sustained disease control[6] **-** In the OLE cohort of the OASIS-plus study (ISIS 721744-CS7), patients transitioning from Phase 3 maintained attack reductions of **94% (Q4W)** and **95% (Q8W)** after ~1 year, with **AE-QoL improvements of +28** and **≥96% achieving controlled disease on AECT**[5]. These outcomes compare favorably with Phase 3 data for other prophylactic therapies (lanadelumab **87%** and garadacimab **87%** reduction vs placebo), supporting a clinically meaningful benefit with **less frequent dosing**[6].

Sustained benefit was also observed after switching to donidalorsen (updated data in recent publication)[5]**.** Following transition from previous LTPs, mean attack rates decreased from **0.85 to 0.28 attacks per 4 weeks** over the treatment period through 1 year (Weeks 0–52), with consistent reductions across prior therapies. Group-level analysis showed a **–68% overall reduction**, including **–64% prior lanadelumab**, **–83% prior berotralstat**, and **–51% prior C1-INH**. **Patient-reported outcomes improved and were sustained over time.** Following the switch to donidalorsen, the proportion of patients with well-controlled disease increased from **67% to 90%.** These improvements were accompanied by **clinically meaningful gains in AE-QoL**, without an increase in breakthrough attacks or the emergence of new safety signals during the transition.

References:

1. *EMA COMP - Dawnzera ODD assesment report.* EMA/OD/0000262773
2. *Otsuka. Summary of Product Characteristics for Dawnzera. EMA. 2026*
3. *Fijen L et al. N Engl J Med. 2022 (Phase 2)*
4. *Riedl MA et al. N Eng J Med. 2024 (OASIS-HAE)*
5. *Riedl MA et al. Allergy 2026 (OASIS-plus Switch cohort)*
6. *Lumry WR et al. J Asthma Allergy. 2026 (OASIS-plus OLE cohort)*

Please refer to the Medicinrådet report and the published literature for absolute numbers and detailed data.

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31.03.2026

LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.04.2026
Leverandør	Otsuka Pharma
Lægemiddel	Dawnzera (donidalorsen)
Ansøgt indikation	Donidalorsen er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af hereditært angioødem (HAE) hos voksne og unge patienter i alderen 12 år og derover.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Dawnzera (donidalorsen):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Dawnzera	80 mg (1 stk.)	167.454,00	[redacted]	[redacted]

Aftaleforhold

[redacted]

[redacted]

[redacted]

Konkurrencesituationen

Medicinrådet har en gældende behandlingsvejledning vedr. lægemidler til arveligt angioødem, hvor lægemidlerne Berinert (C1-esteraseinhibitor), Andembry (garadacimab) og Takhzyro (lanadelumab) er klinisk ligestillede som 1. valg til forebyggende behandling af patienter med arveligt angioødem. Medicinrådet vurderer aktuelt, om Dawnzera kan ligestilles med førnævnte lægemidler som 1. valg til disse patienter.

[redacted]

Tabel 2 viser lægemiddeludgifter i relation til Berinert, Andembry og Takhzyro baseret på Medicinrådets kliniske sammenligningsgrundlag. I det kliniske sammenligningsgrundlag benyttes en sammenligningsperiode på 8 ugers behandling, der betragtes som et udsnit af et livslangt behandlingsforløb.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient fro 8 ugers behandling

Lægemiddel	Styrke (paknings-størrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 8 ugers behandling (SAIP, DKK)
Dawnzera	80 mg (1 stk.)	50%: 80 mg månedligt, s.c. 50%: 80 mg hver 2. måned, s.c.	[redacted]	[redacted]
Berinert*	2000 IE (1 stk.)	60 IE/kg legemsvægt 2 gange ugentligt, s.c.	[redacted]	[redacted]
Andembry	200 mg (1 stk.)	200 mg månedligt, s.c.	[redacted]	[redacted]
Takhzyro	300 mg (1 stk.)	50%: 300 mg hver 2. uge, s.c. 50%: 300 mg hver 4. uge, s.c.	[redacted]	[redacted]

*Beregnet for en gennemsnitsvægt på 70 kg, jf. opsummering af Medicinrådets evidensgennemgang vedrørende lægemidler til arveligt angioødem

[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til vurdering
England	Under vurdering	Link til status
Sverige	Ikke ansøgt	

Opsummering

[redacted]

[redacted]

Application for the assessment of DAWNZERA (donidalorsen) by updating the treatment guideline for the prophylactic treatment of hereditary angioedema

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

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Abbreviations: N/A = not applicable

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Abbreviations

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
AE	Adverse event
AECT	Angioedema Control Test
AE-QoL	Angioedema Quality of Life
ASO	Antisense oligonucleotide
BMI	Body mass index
CI	Confidence interval
C1-INH	C1-esterase inhibitor
DMC	Danish Medicines Council
DSU	Decision Support Unit guidance
EC	European Commission
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL-5-Dimensions questionnaire
GAD-7	Generalized Anxiety Disorder 7
HAE	Hereditary angioedema
HAE-C1INH-Type1	HAE-C1 inhibitor-Type 1
HAE-C1INH-Type2	HAE-C1 inhibitor-Type 2
HAE-QoL	Health-related quality of life questionnaire for hereditary angioedema
HRQoL	Health-related quality of life
HTA	Heath technology assessment

ITT	Intention-to-treat
IU	International unit
LICA	Ligand-conjugated antisense
LSM	Least Square Mean
LTP	Long-term prophylaxis
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
N/A	Not applicable
OLE	Open-label extension
OR	Odds ratio
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PICO	Population, intervention, comparator, and outcome
PICOS	Population, intervention, comparator, outcome, and study type
PKK	Prekallikrein
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of life
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks

RCT	Randomised controlled trial
RR	Rate ratio
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SEM	Standard error of mean
SLR	Systematic literature review
TEAE	Treatment-emergent adverse event
TEM	Treatment effect modifier
VAS	Visual analogue scale
WPAI	Work Productivity and Activity Impairment

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	DAWNZERA
Generic name	Donidalorsen
Therapeutic indication as defined by EMA	Donidalorsen is indicated for the routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.
Marketing authorization holder in Denmark	Otsuka Pharmaceutical Netherlands B.V.
ATC code	B06AC09
Combination therapy and/or co-medication	No
Date of EC approval	19-01-2026
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes, 19-02-2024
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	0.2 ml stoppered glass vial containing an 80 mg (0.8 ml) dose of solution for single use

Abbreviations: DMC = Danish Medicines Council; EC = European Commission; EMA = European Medicines Agency; HAE = hereditary angioedema.

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Donidalorsen is indicated for the routine prevention of recurrent attacks of HAE in adults and adolescents aged 12 years and older.
Dosage regiment and administration:	The recommended starting dose in adult and adolescent patients is 80 mg donidalorsen administered once monthly, driven by the ligand-conjugated antisense (LICA) conjugation technology and its mechanism of action. The dosing interval can be extended to 80 mg every two months if patients are well controlled (e.g., attack free) for at least three months while receiving donidalorsen. Donidalorsen is administered subcutaneously (SC) via an auto-injector pen, giving patients the ability to self-administer at home. Additionally, donidalorsen does not require a hospital-administered loading dose before starting the treatment regimen.
Choice of comparator [if any]	Takhzyro (lanadelumab) is chosen as the most relevant comparator for Danish medical practice, since it is considered first choice treatment in the "use" category in the current treatment recommendation from September 2025 (1).
Most important efficacy endpoints (Difference/gain compared to comparator)	In OASIS-HAE (NCT05139810), the efficacy and safety of donidalorsen in participants with HAE was evaluated. A total of 90 patients received donidalorsen every 4 weeks (Q4W) (45 patients), donidalorsen every 8 weeks (Q8W) (23 patients), or placebo (22 patients). The least square mean (LSM) time-normalized attack rate was 0.44 (95% confidence interval (CI): 0.27, 0.73) in the 4-week group, 1.02 (95% CI: 0.65, 1.59) in the 8-week group, and 2.26 (95% CI: 1.66, 3.09) in the placebo group. The mean attack rate from week 1 to week 25 was 81% lower (95% CI: 65, 89) in the 4-week group than in the placebo group (P < 0.001) and 55% lower (95% CI: 22, 4) in the 8-week group than in the placebo group (P = 0.004) (2). A network meta-analysis (NMA) was conducted to compare donidalorsen with lanadelumab. Results of the comparison are presented below, with donidalorsen Q4W as the reference treatment. Median odds ratio (OR) for proportion of patients achieving a ≥90% reduction in HAE attacks from baseline (95% credible interval (CrI)): • Donidalorsen 80 mg Q8W: 0.66 (0.14, 3.13) • Lanadelumab 300 mg every 2 weeks (Q2W): 7.26 (0.45, 132.76) • Lanadelumab 300 mg Q4W: 4.34 (0.30, 80.14)

Summary	
	• Placebo: 0.15 (0.02, 0.81)* Median rate ratios (RRs) for mean number of HAE attacks per month (95% CrI): • Donidalorsen 80 mg Q8W: 2.32 (0.67, 8.28) • Lanadelumab 300 mg Q2W: 0.67 (0.11, 4.02) • Lanadelumab 300 mg Q4W: 1.38 (0.23, 8.93) • Placebo: 5.15 (1.48, 18.06)* Median RRs for mean number of moderate or severe HAE attacks per month (95% CrI) • Donidalorsen 80 mg Q8W: 3.24 (0.90, 11.69) • Lanadelumab 300 mg Q2W: 0.91 (0.16, 5.54) • Lanadelumab 300 mg Q4W: 1.44 (0.24, 8.93) • Placebo: 5.61 (1.59, 20.73)* Median mean difference from baseline in Angioedema Quality of Life (AE-QoL score) (95% CrI) • Donidalorsen 80 mg Q8W: 4.82 (-3.91, 13.57) • Lanadelumab 300 mg Q2W: 1.75 (-11.08, 4.56) • Lanadelumab 300 mg Q4W: 5.64 (-7.02, 18.36) • Placebo: 18.35 (9.27, 27.42)*
Most important serious adverse events for the intervention and comparator	In OASIS-HAE, no patient in the donidalorsen Q4W group or donidalorsen Q8W group experienced serious treatment-emergent adverse events (TEAEs). One (4.5%) patient in the placebo group experienced a serious TEAE of limb injury (severe) that required hospitalisation (2). In HELP, 3 (10.3%) patients in the lanadelumab Q4W group, 1 (3.7%) in the lanadelumab Q2W group, and 0 in the placebo group experienced a serious AE (SAE). One (3.4%) patient in the lanadelumab Q4W group had a SAE of pyelonephritis, 1 (3.4%) had a SAE of meniscus injury, and 1 (3.4%) had a SAE of bipolar II disorder. One (3.7%) patient had a SAE of catheter site infection in the lanadelumab Q2W group (3).

Abbreviations: AE = adverse event; AE-QoL = Angioedema Quality of Life; CI = confidence interval; CrI = credible interval; HAE = hereditary angioedema; LICA = ligand-conjugated antisense technology; LSM = least square mean; OR = odds ratio; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; RR = rate ratio; SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse event.
Notes: *95% CrI does not include 1 and is therefore considered statistically significant.

3. The patient population, intervention and relevant outcomes

3.1 The medical condition, patient population, current treatment options and choice of comparator(s)

Currently, there is no formal treatment guideline for the prophylactic treatment of HAE. However, a protocol for development of the treatment guideline (4), an evidence review by the DMC (5), as well as treatment recommendations (1) for HAE exists.

Hereditary angioedema is an inherited, rare, chronic, debilitating genetic disorder characterised by recurrent, unpredictable, painful and potentially life-threatening swelling episodes that most commonly affect the extremities, face, abdomen, genitals, and larynx (6).

Hereditary angioedema is a distinct form of nonallergic angioedema and is in the majority of cases caused by a mutation in the C1-esterase inhibitor gene (C1-INH) *SERPING1*. However, some patients have normal levels and function of C1-INH and in some instances the angioedema is acquired rather than inherited (7). Hereditary angioedema can be categorised into one of three subtypes, based on C1-INH levels and activity, however the disease presents with the same debilitating clinical symptoms and impact (8):

- HAE-C1 inhibitor-Type 1 (**HAE-C1INH-Type1):** Mutations in the *SERPING1* gene cause low levels and functioning of plasma C1-INH; accounts for 80-85% of people with HAE.
- or HAE-C1 inhibitor-Type 2 (**HAE-C1INH-Type2):** Mutations in *SERPING1* causes an individual to produce normal levels of dysfunctional C1-INH; accounts for 15-20% of people with HAE.

HAE-C1INH-Type1 and HAE-C1INH-Type2 are caused by an autosomal dominant inheritance, resulting in a 50% risk of children inheriting the disease from an affected parent. In Denmark, up to 90% of patients with HAE have HAE-C1INH-Type1, while approximately 10% have HAE-C1INH-Type2 (4). Patients with the third subtype of HAE (HAE-nC1INH) have normal levels and function of C1-INH. This form of the disease is extremely rare and affects less than one percent of patients (9,10).

3.1.1 Patient population

Estimates patient numbers in Denmark are provided in Table 1. The prevalence of HAE was estimated based on the DMC stating that the exact prevalence is unknown, but that HAE is estimated to affect approximately 1 per 10,000–50,000 individuals worldwide, with 107 patients registered in Denmark in 2023 (4). A prevalence of 1 per 50,000 was applied to the Danish population for each year from 2020 to 2024, as this corresponds to approximately 119 patients in Denmark in 2023, which is in close agreement with the 107 patients reported by the DMC. The incidence of HAE is unknown. Among the 107 patients registered in Denmark, 47 received prophylactic treatment in 2023 (4).

Table 1 Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024
Prevalence in Denmark	117	117	118	119	119

Note: Although, the estimates concern the full Danish population, the Danish patient population relevant to this application consists of adults and adolescents aged 12 years and above with HAE.
Sources: Danish Medicines Council, 2023 (4); Statistics Denmark, 2025 (11).

3.1.2 Current treatment options and choice of comparator

As indicated in the current treatment recommendation (1), the treatment options in the “use” category include Takhzyro (lanadelumab) and Berinert (C1-INH), with lanadelumab being the first choice of treatment, intended for use in at least 80% of patients. Alternatively, Orladeyo (berotralstat, oral) can be considered if SC treatment — i.e., one of the treatments in the “use” category — is not feasible, or if these treatments must be discontinued due to AEs. Finally, intravenous Cinryze (C1-INH) should be reserved for situations where neither SC nor oral administration is feasible.

Lanadelumab is the chosen comparator because it represents the current standard treatment, being intended for use in at least 80% of patients (1). The DMC has also reported that, among the 47 patients receiving prophylactic treatment, the majority are treated with lanadelumab (4).

3.2 The intervention

Donidalorsen, brand name DAWNZERA, is a first-in-class, ribonucleic acid-targeted antisense oligonucleotide (ASO) 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 and significantly decreasing plasma PKK protein levels and the production of bradykinin (12,13). The GalNAc3 (a triantennary N-acetyl-galactosamine) conjugation to the antisense (ASO) molecule facilitates uptake into hepatic parenchymal cells (2). By preventing PKK protein synthesis and reducing circulating PKK levels, donidalorsen acts directly on limiting the production of kallikrein to inhibit the plasma kallikrein-kinin system. This prevents the production of bradykinin which causes vasodilation and increased vascular permeability, leading to angioedema (14). While other available long-term prophylaxes (LTPs) provide exogenous C1-INH or inhibit PKK directly, donidalorsen employs a post-transcriptional gene-silencing strategy to reduce the synthesis of PKK, decreasing bradykinin levels and mitigating HAE attacks (14).

In donidalorsen, the ASO is conjugated to $GalNAc_3$ via LICA technology, which increases the potency by almost 30, compared to the unconjugated form due to an enhanced uptake into hepatocytes (12,15). This allows donidalorsen to be used in lower doses with less frequent than weekly administrations, offering improved tolerability compared to the parent unconjugated ASO, while still resulting in notable benefits to patients. The increased potency supports an increase in the safety margin of donidalorsen, as the reduced doses that can be used for this new chemical class of ASOs means that peak plasma concentration-related adverse events are likely reduced (16).

An overview of key features of donidalorsen is presented in Table 2 below.

Table 2 Overview of donidalorsen

Overview of intervention	
Therapeutic indication relevant for the assessment	Donidalorsen is indicated for the routine prevention of recurrent attacks of HAE in adults and adolescents aged 12 years and older.
Method of administration	Donidalorsen is administered SC via an auto-injector pen, which gives patients the ability to self-administer at home (after training). Additionally, donidalorsen does not require a hospital-administered loading dose before starting the treatment regimen.
Dosing	The recommended starting dose in adult and adolescent patients is 80 mg donidalorsen administered once monthly, driven by the LICA conjugation technology and its mechanism of action. The dosing interval can be extended to 80 mg every two months if patients are well controlled (e.g., attack free) for at least three months while receiving donidalorsen.
Should the pharmaceutical be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Until loss of efficacy or unacceptable AEs.
Necessary monitoring, both during administration and during the treatment period	Treatment should be initiated under the supervision of a physician experienced in the management of patients with HAE. After proper training on correct SC injection technique, a patient or caregiver may inject donidalorsen if their physician determines it is appropriate.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	0.2 ml stoppered glass vial containing an 80 mg (0.8 ml) dose of solution for single use

Abbreviations: AE = adverse events; HAE = hereditary angioedema; LICA = ligand-conjugated antisense; SC = subcutaneous.
References: Otsuka, 2025 (17).

3.2.1 The intervention in relation to Danish clinical practice

Donidalorsen is indicated for the routine prevention of recurrent attacks of HAE in adults and adolescents aged 12 years and older. The introduction of donidalorsen provides another option for prophylactic treatment to Danish patients with the benefit of less frequent administration than other LTPs (18–21). In addition, donidalorsen offers an easy and convenient administration, as it is administered SC via an easy-to-use auto-injector pen, which gives patients the ability to self-administer at home (22).

Donidalorsen is expected to be used for the indirect comparative efficacy package, be able to fulfil the criteria to be recommended by the DMC as a treatment alternative in the "use" category together with lanadelumab and the C1-INH Berinert.

3.3 Relevant efficacy outcomes

3.3.1 Definition of efficacy outcomes included in the application

The definitions of the efficacy outcomes included in the studies of interest (OASIS-HAE and HELP, presented in section 4) to this application are provided in

Table 3. The included efficacy outcomes correspond to those assessed in the DMC's evidence review (5) of medicines for the prophylactic treatment of HAE.

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition
Attack-free (Included in OASIS-HAE and HELP)	Week 25[a] Week 26[b]	Percentage of Investigator-confirmed HAE attack-free patients from Week 5 to Week 25[a] Proportion of Investigator-confirmed HAE attack-free patients from the 4-week run-in period over the 26-week treatment period[b]
≥90% reduction in attack rate (Included in OASIS-HAE and HELP)	Week 25[a] Week 26[b]	≥90% reduction in time-normalised Investigator-confirmed HAE attack rate (per 4 weeks) from baseline between Week 5 to Week 25[a] ≥90% reduction in Investigator-confirmed HAE attack rate from the 4-week run-in period over the 26-week treatment period[b]
HAE attack rate (Included in OASIS-HAE and HELP)	Week 25[a] Day 182[b]	Time-normalised Investigator-confirmed HAE attack rate (per 4 weeks) from Week 1 to Week 25[a] Investigator-confirmed HAE attack rate (per month) from Day 0 to 182[b]
Moderate or severe HAE attack rate (Included in OASIS-HAE and HELP)	Week 25[a] Day 182[b]	Time-normalised Investigator-confirmed moderate or severe HAE attack rate (per 4 weeks) from Week 5 to Week 25[a] Investigator-confirmed moderate or severe HAE attack rate (per month) from Day 0 to 182[b]
Change from Baseline in AE-QoL questionnaire total score (Included in OASIS-HAE and HELP)	Week 25[a] Day 182[b]	Change from Baseline in AE-QoL questionnaire total score at Week 25[a] Change from Baseline in AE-QoL questionnaire total score from Day 0-182[b]
AE-QoL improvement of at least 6 points (Included in OASIS-HAE and HELP)	Week 25[a] Day 182[b]	Percentage of patients with an AE-QoL improvement of at least 6 points from Baseline at Week 25[a] Percentage of patients with an AE-QoL improvement of at least 6 points from Baseline at Day 182[b]

Abbreviations: AE-QoL = Angioedema Quality of Life; HAE = hereditary angioedema-
Notes: * Time point for data collection used in analysis. [a] Indicates that the information is specific to OASIS-HAE. [b] Indicates that the information is specifc to HELP.
Sources: Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2); Banerji et al. 2018 (3)

4. Overview of literature

Table 4 presents the trials and corresponding studies of interest identified in the systematic literature review (SLR). Although, five publications reporting on OASIS-HAE or HELP (Riedl et al. 2024 (2), Wu & Banerji 2025 (24), Banerji et al. 2018 (3), Lumry et al. 2021 (25), and Riedl et al. 2020 (26)) were identified in the SLR (see Appendix D), only Riedl et al. 2024 (2) and Banerji et al. 2018 (3) are described in detail in this application as these are in focus for the comparison. The publication by Riedl et al. 2025 (27) was not captured in the SLR, as it is a recent study, although it is presented in Table 4 to acknowledge its existence. The inclusion or exclusion of any identified publications due to various reasons that made their findings irrelevant or unapplicable for the NMA as assessed in the feasibility assessment of the NMA are further explained in section 5.2.5 Method of Synthesis.

Table 4 Relevant literature included in the assessment of efficacy and safety

Trial name, NCT identifier and reference (Full citation incl. reference number)	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
OASIS-HAE, NCT05139810 (Riedl et al. 2024 (2), Riedl et al. 2025 (27), and Wu & Banerji 2025 (24))	Phase III, randomised, double-blinded, placebo-controlled study	The study included an up to 8-week Screening¥ Period, a 24-week Treatment Period, and an up to 13-week Post-Treatment Period. Patients could elect to enrol in the open-label extension (OLE) arm of OASISplus (NCT05392114) rather than complete the	Start: 03/12/21 Completion: 09/11/23 Data cut-off: N/A	Patients aged ≥12 years with a confirmed diagnosis of HAE-C1INH-Type1 or HAE-C1INH-Type2, and with at least two investigator-confirmed HAE attacks during the Run-in¥ Period (56 days to one day before randomisation).	Donidalorsen 80 mg administered SC Q4W or donidalorsen 80 mg administered SC Q8W.	Placebo 80 mg administered SC Q4W or placebo 80 mg administered SC Q8W. Data from patients receiving placebo were pooled for analyses; this pooled placebo group is hereafter referred to as the placebo group.	Relevant for clinical question nr. 1 in the protocol for development of the treatment guideline (there is currently no formal treatment guideline) (4).	In the following, primary, secondary, and exploratory outcomes in OASIS-HAE are presented, corresponding to the efficacy outcomes assessed in the DMC's evidence review (5) of medicines for the prophylactic treatment of HAE. The following primary and secondary outcomes are included: Percentage of Investigator-confirmed HAE attack-free patients from Week 5 to Week 25, Percentage of patients with Attack Rate Reduction of ≥ 90% between Week 5 and 25, Time-normalised number of Investigator-confirmed HAE attacks (per 4 weeks) from Week 1 to Week 25, Time-normalised number of moderate or severe

Trial name, NCT identifier and reference (Full citation incl. reference number)	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
		Post-Treatment Period.						Investigator-confirmed HAE attacks (per 4 weeks) from Week 5 to Week 25, and Change from Baseline in AE-QoL questionnaire total score at Week 25. The exploratory outcome Percentage of patients with an AE-QoL improvement of at least 6 points from Baseline is included in this application. The safety outcome Percentage of patients who discontinued treatment permanently due to AEs is included in this application as well as a qualitative review of the safety profile of donidalorsen.
HELP, NCT02586805 (Banerji et al. 2018 (3), Lumry	Phase III, randomised, double-blinded,	4-week run-in period (preceded by a ≥2-week washout	Start: 03/03/16 Completion: 13/14/17	Patients aged ≥12 years with HAE type 1 or 2, and with at	Lanadelumab 150 mg Q4W$^{\Omega\pi}$, lanadelumab 300 mg Q4W$^{\Omega}$,	Placebo Q2W	Relevant for clinical question nr. 1 in the protocol for development of the treatment guideline	The following presents the primary, secondary, and exploratory outcomes in HELP, corresponding to the efficacy

Trial name, NCT identifier and reference (Full citation incl. reference number)	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
et al. 2021 (25), and Riedl et al. 2020 (26))	placebo-controlled study	of any long-term prophylactic therapy if applicable) followed by a 26-week treatment period. At the end of the treatment period, patients could enter either an OLE study (HELP Study Extension, NCT02741 596 (28)) or an 8-week safety follow-up.	Data cut-off: N/A	least one HAE attack during the 4-week run-in period.	or lanadelumab 300 mg Q2W.		(there is currently no formal treatment guideline) (4).	outcomes assessed in the DMC's evidence review (5). Included primary and secondary outcomes: Rate of investigator confirmed HAE attacks during treatment period (mean number of attacks per month) and Rate of Moderate or Severe Investigator Confirmed HAE Attacks. Included exploratory outcomes: Percentage of patients with ≥90% reduction in attack-rate, Mean change from baseline in AE-QoL score, and Proportion of patients with at least a 6-point improvement from baseline in AE-QoL score. The safety endpoint "Percentage of patients who discontinued treatment due to AEs" is included as well. Additionally, a

Trial name, NCT identifier and reference (Full citation incl. reference number)	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
								qualitative review of the safety profile of lanadelumab is included.

Abbreviations: AE = Adverse event; AE-QoL = Angioedema Quality of Life; DMC = Danish Medicines Council; HAE = hereditary angioedema; HAE-C1INH-Type1 = HAE-C1 inhibitor-Type 1; HAE-C1INH-Type2 = HAE-C1 inhibitor-Type 2; N/A = not applicable; OLE = open-label extension; PICO = population, intervention, comparator, and outcome; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.

Notes: [¥] Screening Period and Run-in Period are used interchangeably to describe the same study phase in OASIS-HAE. [Ω] To maintain the study blind, subjects were given placebo injections every other 2 weeks when they were not receiving drug. [π] The 150 mg Q4W treatment arm is not included in this application, as this dosage is intended for patients under 40 kg, which is assumed to not be applicable to most adults or adolescents over 12 years old.

Sources: ClinicalTrials.gov, 2021 (29); Ionis Pharmaceuticals, Inc., 2024 (23); Banerji et al. 2018 (3); ClinicalTrials.gov, 2016 (30).

5. Clinical question 1

5.1 Efficacy of donidalorsen compared to lanadelumab for patients aged 12 years and older with HAE

5.1.1 Relevant studies

All studies relevant to donidalorsen and lanadelumab that are included in the NMA (see section 5.2.5) are listed in Table 4.

OASIS-HAE is a phase 3, double-blind, randomised, placebo-controlled trial assessing the efficacy and safety of donidalorsen. In the study, patients with HAE were assigned to receive donidalorsen (80 mg SC) or placebo once every 4 or 8 weeks. The primary endpoint was the time-normalised number of Investigator-confirmed HAE attacks per 4 weeks (attack rate) from Week 1 to Week 25 (2).

HELP is a phase 3, double-blind, randomised, placebo-controlled trial assessing the efficacy and safety of lanadelumab. In the study, patients with HAE were assigned to receive lanadelumab 150 mg SC Q4W (not of interest in this application), 300 mg Q4W, 300 mg Q2W, or placebo. The primary efficacy endpoint was the number of investigator-confirmed attacks of HAE over the treatment period (26 weeks) (3).

In addition to OASIS-HAE and HELP, OASISplus along with selected efficacy and safety results are presented in section 5.2.3. OASISplus is not included throughout this application, as it is an ongoing OLE study including both patients from OASIS-HAE, as well as a switch cohort who entered the study following a stable dose of another prophylactic treatment than donidalorsen. Moreover, only randomised treatment periods were included in the NMA.

5.1.2 Comparability of studies

5.1.2.1 Comparability of efficacy outcomes

The efficacy outcomes measurements in the OASIS-HAE study were chosen to best reflect the drug's mechanism of action. As stated in the SmPC, donidalorsen shows *gradual* reduction in attack rate beginning at Week 1, with *maximum effect expected after approximately one month*. Relative to pharmaceutical agents which act directly on proteins, such as antibodies and small molecules, donidalorsen targets prekallikrein (PKK) mRNA in hepatocytes. Existing plasma PKK must degrade before the onset of the clinical effect. The estimated plasma half-life of PKK, which is complexed with high molecular–weight kininogen, is approximately 5 days. A nadir in the PKK levels during the first dosing period is not expected to be immediate and only expected to be reached towards the end of the first 4-week dosing period. Because of the pharmacodynamic profile of donidalorsen, the first four weeks are not considered representative.

A patient may experience an attack during the initial weeks, before pre-existing circulating plasma PKK has been degraded and the drug reaches full effect, and remain attack-free thereafter. In a case with delayed onset of a treatment a binary outcome can misrepresent its true therapeutic benefit. A single attack early in the treatment period will classify the patient as "not attack-free" for the entire interval. Due to the binary nature of the attack-free metric, the period of Week 5 to Week 25 was chosen as a more clinically meaningful time-period for evaluation to avoid misleading interpretations.

Early-treatment attacks are incorporated into more appropriate and established clinically meaningful efficacy measures such as HAE attack rate per 4 weeks, which normalises data across time and avoids binary distortions, was measured and reported for the entire treatment period. These are considered to also represent donidalorsen true therapeutic benefit and better reflect the treatment's expected trajectory and provide a more clinically meaningful assessment of long-term efficacy.

Although the proportion of attack-free patients over the treatment period is still a clinically meaningful and important outcome measure relevant for the application, these were measured over different time-periods in the two studies. Patients who are attack-free from Day 0 to 180 was only reported for HELP. For donidalorsen, the investigators in OASIS-HAE chose to measure the percentage of attack-free patients from Week 5 to Week 25. This difference in assessment periods should be kept in mind when interpreting the results.

Both studies do report the proportion of patients who experience a ≥90% reduction in the number of HAE attacks compared to baseline. However, this was also assessed between Week 5 to 25 in OASIS-HAE, while it was assessed for the full treatment period in HELP. This difference in assessment periods should also be kept in mind when interpreting the results of this outcome.

HAE attack rate was measured similarly in OASIS-HAE and in HELP. In both studies, an HAE attack had to be investigator confirmed and the attack rate was measured per month during the treatment period. However, the method used to calculate the attack rates varies across the studies. OASIS-HAE report the outcome as a LSM, and the LSM estimates were based on a regression which included treatment groups, baseline rate, and the interaction of trial group with baseline rate as covariates. The HELP study calculated the mean attacks per month using a Poisson regression. Results are from a Poisson regression model account for overdispersion; treatment group and the normalised baseline attack rate were fixed effects. While the methods used to calculate the monthly attack rate vary per study, only data from the randomised part of the trials are included. This means the randomisation should have balanced confounding factors, reducing the bias of comparing different measures for the mean monthly attack rate. The consistent evaluation of mean number of attacks per month provides sufficient evidence to compare rate ratios across the two trials.

Attack severity was also explored over different timepoints for each study. OASIS-HAE reported the number of moderate or severe attacks per month from week 5 to week 25. This excludes the first four weeks of the study meaning the results cannot be compared directly with HELP that report this outcome over the entire treatment period. The inclusion of data from week 5 onwards in this analysis period in OASIS-HAE, after which patients were expected to achieve a steady-state concentration of donidalorsen and therefore achieve improved absolute and relative efficacy in the mean number of moderate/severe attacks per month, may bias results of a future NMA in favour of donidalorsen. An analysis of the percentage reduction in the severity of attacks vs baseline was also explored, however this is not feasible as there was insufficient data reported across the studies to conduct an NMA. Although the time periods for measuring attack severity vary across trials, the consistent evaluation of mean number of attacks per month provides sufficient evidence to compare rate ratios across the two trials.

In OASIS-HAE, the AE-QoL total score is evaluated at Week 25 (Day 169), while in the HELP trial the AE-QoL total score is evaluated at Day 182. Although the time periods for measuring scores vary slightly across trials, the consistent evaluation of total score changes provides sufficient evidence to compare mean change from baseline AE-QoL across the two trials.

Finally, patients with at least 6-point improvement (reduction) from baseline in AE-QoL total score were considered as responders in both OASIS-HAE and HELP. This was measured at Week 25 in OASIS-HAE and at Day 182 in HELP.

5.1.2.2 Comparability of study design

Both OASIS-HAE and HELP are phase 3, double-blinded, placebo-controlled and randomised trials. Additionally, OASIS-HAE includes a 24-week treatment period that is fully randomised and placebo-controlled similar to HELP, which includes a 26-week treatment period that is fully randomised and placebo-controlled. Moreover, the number of patients lost to follow-up was low in both trials (zero in OASIS-HAE and one patient in the 300 mg Q4W group in the HELP trial).

The eligibility criteria of the HELP study are broadly aligned with the OASIS-HAE study, with the only extra inclusion criteria mentioned for the HELP study stating details on requirements for males and females who were fertile and sexually active during the study (see 0). These additional inclusion criteria are not expected to introduce any bias. Both trials included participants aged ≥12 years with a documented diagnosis of HAE type I or type II. The requirement for diagnosis confirmation was consistent, with each study mandating a documented clinical history that aligns with HAE. Both studies required C1 inhibitor functional levels <40% for most patients, but patients with levels between 40% and 50% could still be enrolled if they met further requirements, such as having complement factor C4 levels below the lower limit of normal or possessing a known pathogenic mutation in the *SERPING1* gene (2,3). Moreover, OASIS-HAE and HELP excluded patients with a concurrent diagnosis of any other type of recurrent angioedema. Finally, in the OASIS-HAE study participants must experience a minimum of two HAE investigator-confirmed attacks during the 8-week screening period (broadly equivalent to at least one attack per month). Similarly, patients must have experienced a baseline attack rate of ≥1 investigator-confirmed HAE attack per 4 weeks in the HELP study.

The treatment arms, dosing, and regimens included in the OASIS-HAE and HELP study are compared in the following. Patients received a fixed 80 mg dose of donidalorsen SC Q4W or Q8W in the OASIS-HAE trial. In HELP, the mode of administration is consistent with the OASIS-HAE trial (SC). However, HELP had three treatment arms with different timing and dosages: 150 mg and 300 mg doses of lanadelumab Q4W, and a 300 mg dose Q2W. All patients received an injection Q2W, with those in the 4-week group receiving a placebo in between active treatment. The lower dose of 150 mg is intended for patients under 40 kg, which is assumed to not be applicable to most adults or adolescents over 12 years old. Therefore, the 150 mg treatment arm is not included in this application.

5.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

Table 5 presents the baseline characteristics of patients included in OASIS-HAE and HELP, respectively. Within OASIS-HAE, demographic and baseline characteristics were generally similar across the three treatment groups. The mean patient age at informed consent was 39.6 years in patients randomised to receive donidalorsen 80 mg Q4W, 34.1 years in patients randomised to receive donidalorsen 80 mg Q8W, and 35.4 years in the placebo group. Seven patients were aged between 12 and 17 years. Of these 7 (7.8%) patients, 4 (8.9%) were in the Q4W group, and 3 (13.0%) were in the Q8W group. No patients aged between 12 and 17 years were randomly assigned to placebo. The proportions of male patients enrolled in the donidalorsen treatment groups (37.8% and 47.8% in the Q4W and Q8W groups, respectively) were lower compared with the placebo group (63.6%). Across all treatment groups, the majority of patients were white (93.3%, 95.7%, and 81.8% for the Q4W, Q8W, and placebo groups, respectively). Mean body mass index (BMI) was high across all treatment groups (28 and 27 kg/m^2 for the Q4W and Q8W groups, respectively, and 29 kg/m^2 for the placebo group).

Moreover, the HAE history was generally similar across the three treatment groups within OASIS-HAE with the exception of an imbalance in the historical number of HAE attacks over the prior 12-month period between the placebo and donidalorsen treatment groups. Patients in the placebo group had historically fewer observed HAE attacks over the prior 12-month period, with a mean (standard deviation (SD)) number of attacks of 29.1 (21.13) compared with 45.7 (43.04) for the Q4W group and 33.3 (21.95) for the Q8W group. As expected, the majority of patients across all treatment groups had HAE-1 (93.3% and 95.7% for the Q4W and Q8W groups, and 90.9% in the placebo group) and had not received a predefined prophylactic therapy (86.7% and 78.3% for Q4W and Q8W groups, and 77.3% in the placebo group). The majority of patients (86.7%) had a family history of HAE. The mean age at symptom onset was 11.7 years among all patients (not shown in Table 5). A history of laryngeal angioedema attacks experienced was reported in approximately 50% of patients; however, the majority of patients experienced peripheral (>90%) or abdominal (>90%) attacks. Similar to what was observed for the historical number of HAE attacks, the mean (SD) HAE attack rate was lower for the placebo group during the Run-in Period per 4 weeks (2.90 [1.657]) compared with the Q4W group (3.61 [2.236]) and the Q8W group (3.18 [2.147]). This disparity may indicate that patients who were randomly assigned to placebo had more mild disease as determined by HAE attack rate/frequency of attacks than those assigned to donidalorsen treatment groups. Finally, prior and concomitant medication use was generally similar across the three treatment groups in OASIS-HAE.

Within HELP (Table 5), baseline characteristics were generally similar across treatment arms (lanadelumab 300 mg Q2W, lanadelumab 300 mg Q4W, and placebo), with some differences noted by the DMC in their assessment of lanadelumab (Takhzyro) for HAE (31). Specifically, 55.6% of patients in the lanadelumab 300 mg Q2W arm were female versus 82.9% in the placebo arm, although the DMC assessed that there is no reason to expect the treatment effect to differ by sex. Historical attack frequency (preceding 12 months) also varied between groups, but this was less evident during the run-in period, where attack frequency appeared more comparable across treatment arms. Consequently, the historical difference was considered clinically relevant (31).

As evident from Table 5, baseline characteristics of patients were generally similar across OASIS-HAE and HELP, although, the sex distribution in the placebo arms were different between the two studies with 63.6% males in OASIS-HAE and 17.1% males in HELP. It appears that a larger proportion of patients had no prior prophylactic treatment in OASIS-HAE than in HELP, presumably due to differences in how prior prophylactic treatment use was captured across studies. Family history of HAE, some HAE attack types, and other prior treatments were not reported in HELP and therefore could not be compared to OASIS-HAE. Moreover, concomitant treatments were categorised differently across studies.

Overall, the trial populations are comparable to Danish patients eligible for treatment (the DMC recommends prophylactic treatment for patients with HAE type I or II who are at least 12 years of age, have significantly impaired quality of life (QoL), and experience at least four attacks per month). Hereditary angioedema most often manifests during the early teenage years, but in some cases already in childhood (4), which is in alignment with the age at symptom onset among patients in OASIS-HAE and HELP (range 10.9–15.0 years). Moreover, up to 90% of patients have HAE-C1INH-Type1, while approximately 10% have HAE-C1INH-Type2 (4), in line with the included trials.

Table 5 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

<table>
<tr><th></th><th colspan="3">OASIS-HAE</th><th colspan="3">HELP</th></tr>
<tr><th></th><th>Placebo
(N = 22)</th><th>Donidalorsen 80 mg Q4W
(N = 45)</th><th>Donidalorsen 80 mg Q8W
(N = 23)</th><th>Lanadelumab 300 mg Q2W
(N = 27)</th><th>Lanadelumab 300 mg Q4W
(N = 29)</th><th>Placebo
(N = 41)</th></tr>
<tr><td>Age in years, mean (SD)</td><td>35.4
(11.03, 2.35)</td><td>39.6
(15.23, 2.27)</td><td>34.1
(13.22, 2.76)</td><td>40.3 (13.3)</td><td>39.5 (12.8)</td><td>40.1 (16.8)</td></tr>
<tr><td colspan="7">Age group (years), n (%)</td></tr>
<tr><td>12 to 17</td><td>0</td><td>4 (8.9)</td><td>3 (13.0)</td><td>2 (7.4)[Ω]</td><td>3 (10.3)[Ω]</td><td>4 (9.8)[Ω]</td></tr>
<tr><td>18 to 39</td><td>15 (68.2)</td><td>19 (42.2)</td><td>12 (52.2)</td><td rowspan="2">25 (92.6)[Ω]</td><td rowspan="2">26 (89.7)[Ω]</td><td rowspan="2">35 (85.4)[Ω]</td></tr>
<tr><td>40 to 64</td><td>7 (31.8)</td><td>21 (46.7)</td><td>7 (30.4)</td></tr>
<tr><td>≥ 65</td><td>0</td><td>1 (2.2)</td><td>1 (4.3)</td><td>0[Ω]</td><td>0[Ω]</td><td>2 (4.9)[Ω]</td></tr>
<tr><td colspan="7">Sex, n (%)</td></tr>
<tr><td>Male</td><td>14 (63.6)</td><td>17 (37.8)</td><td>11 (47.8)</td><td>12 (44.4)</td><td>10 (34.5)</td><td>7 (17.1)</td></tr>
<tr><td>Female</td><td>8 (36.4)</td><td>28 (62.2)</td><td>12 (52.2)</td><td>15 (55.6)</td><td>19 (65.5)</td><td>34 (82.9)</td></tr>
</table>

	OASIS-HAE			HELP		
	Placebo (N = 22)	Donidalorsen 80 mg Q4W (N = 45)	Donidalorsen 80 mg Q8W (N = 23)	Lanadelumab 300 mg Q2W (N = 27)	Lanadelumab 300 mg Q4W (N = 29)	Placebo (N = 41)
Ethnicity, n (%)						
American Indian or Alaskan Native	2 (9.1)	0	1 (4.3)	N/A	N/A	N/A
Asian	0	1 (2.2)	0	0	0	0
Black or African American	1 (4.5)	1 (2.2)	0	1 (3.7)	6 (20.7)	2 (4.9)
White	18 (81.8)	42 (93.3)	22 (95.7)	26 (96.3)	23 (79.3)	39 (95.1)
Multiple	1 (4.5)	0	0	N/A	N/A	N/A
Other	0	1 (2.2)	0	N/A	N/A	N/A
BMI (kg/m^2), mean (SD)	28.88 (9.216)	28.03 (6.738)	26.97 (5.396)	31.0 (7.8)	28.1 (5.1)	27.5 (7.7)
Family history of HAE, n (%)						

	OASIS-HAE			HELP		
	Placebo (N = 22)	Donidalorsen 80 mg Q4W (N = 45)	Donidalorsen 80 mg Q8W (N = 23)	Lanadelumab 300 mg Q2W (N = 27)	Lanadelumab 300 mg Q4W (N = 29)	Placebo (N = 41)
Yes	17 (77.3)	41 (91.1)	20 (87.0)	N/A	N/A	N/A
No	5 (22.7)	4 (8.9)	3 (13.0)	N/A	N/A	N/A
No. of attacks in the 12 months before screening, median (25th percentile, 75th percentile)	24.0 (12.0, 47.0)	36.0 (15.0, 57.0)	36.0 (14.0, 40.0)	20 (8-36)	24 (12-50)	30 (17-59)
Age of symptoms onset in years, mean (SD)	12.9 (7.19)	11.6 (9.85)	10.9 (7.73)	15.0 (8.7)	14.6 (11.2)	11.2 (8.2)
HAE type, n (%)						
HAE-C1INH-Type1	20 (90.9)	42 (93.3)	22 (95.7)	23 (85.2)	27 (93.1)	38 (92.7)
HAE-C1INH-Type2	2 (9.1)	3 (6.7)	1 (4.3)	4 (14.8)	2 (6.9)	3 (7.3)

	OASIS-HAE			HELP		
	Placebo (N = 22)	Donidalorsen 80 mg Q4W (N = 45)	Donidalorsen 80 mg Q8W (N = 23)	Lanadelumab 300 mg Q2W (N = 27)	Lanadelumab 300 mg Q4W (N = 29)	Placebo (N = 41)
History of HAE types of attacks experienced, n (%)						
Peripheral	20 (90.9)	43 (95.6)	22 (95.7)	N/A	N/A	N/A
Abdominal	20 (90.9)	43 (95.6)	22 (95.7)	N/A	N/A	N/A
Laryngeal	12 (54.5)	22 (48.9)	13 (56.5)	20 (74.1)	17 (58.6)	27 (65.9)
Run-In Period HAE Attack Rate (attacks/month), mean (SD)	2.90 (1.657)[a]	3.61 (2.236)[a]	3.18 (2.147)[a]	3.5 (2.3)	3.7 (2.5)	4.0 (3.3)
Previous prophylactic treatment, n (%)						
Yes	Any predefined prophylactic therapy use: 5 (22.7)[b]	Any predefined prophylactic therapy use: 6 (13.3)[b]	Any predefined prophylactic therapy use: 5 (21.7)[b]	Oral therapy: 0 Combination therapy: 3 (11.1) C1-INH: 11 (40.7)	Oral therapy: 1 (3.4) Combination therapy: 1 (3.4) CI-INH: 18 (62.1)	Oral therapy: 1 (2.4) Combination therapy: 1 (2.4) C1-INH: 22 (53.7)

	OASIS-HAE			HELP		
	Placebo (N = 22)	Donidalorsen 80 mg Q4W (N = 45)	Donidalorsen 80 mg Q8W (N = 23)	Lanadelumab 300 mg Q2W (N = 27)	Lanadelumab 300 mg Q4W (N = 29)	Placebo (N = 41)
No	17 (77.3)[b]	39 (86.7)[b]	18 (78.3)[b]	13 (48.1)	9 (31.0)	17 (41.5)
Prior C1-INH treatment, n (%)[π]	7 (31.8)	22 (48.9)	13 (56.5)	N/A	N/A	N/A
Other prior treatments, n (%)[π]	Icatibant acetate: 11 (50.0) Icatibant: 5 (22.7) Paracetamol: 1 (4.5)	Icatibant acetate: 21 (46.7) Icatibant: 6 (13.3) Paracetamol: 9 (20.0)	Icatibant acetate: 9 (39.1) Icatibant: 5 (21.7) Paracetamol: 3 (13.0)	N/A	N/A	N/A
Concomitant medication, n (%)[¥]	C1-INH: 11 (50.0) Icatibant acetate: 11 (50.0) Icatibant: 6 (27.3) Paracetamol: 7 (31.8) Ibuprofen: 5 (22.7)	C1-INH: 15 (37.8) Icatibant acetate: 15 (35.6) Icatibant: 9 (22.2) Paracetamol: 10 (24.4) Ibuprofen: 9 (22.2)	C1-INH: 11 (52.2) Icatibant acetate: 8 (39.1) Icatibant: 3 (13.0) Paracetamol: 7 (34.8) Ibuprofen: 7 (34.8)	Any on-demand medication[†]: 23 (85.2) Ecallantide: 1 (3.7) Icatibant: 13 (48.1) Nanofiltered/plasma-derived C1 inhibitor: 12 (44.4)	Any on-demand medication[†]: 27 (93.1) Ecallantide: 6 (20.7) Icatibant: 13 (44.8) Nanofiltered/plasma-derived C1 inhibitor: 14 (48.3)	Any on-demand medication[†]: 37 (90.2) Ecallantide: 2 (4.9) Icatibant: 22 (53.7) Nanofiltered/plasma-derived C1 inhibitor: 22 (53.7)

	OASIS-HAE			HELP		
	Placebo (N = 22)	Donidalorsen 80 mg Q4W (N = 45)	Donidalorsen 80 mg Q8W (N = 23)	Lanadelumab 300 mg Q2W (N = 27)	Lanadelumab 300 mg Q4W (N = 29)	Placebo (N = 41)
				Any supportive treatment: 4 (14.8)	Any supportive treatment: 2 (6.9)	Any supportive treatment: 5 (12.2)

Abbreviations: BMI = Body mass index; C1-INH = C1-esterase inhibitor; HAE = Hereditary angioedema; HAE-C1INH-Type1 = HAE-C1 inhibitor-Type 1; HAE-C1INH-Type2 = HAE-C1 inhibitor-Type 2; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SD = standard deviation.
Notes: [Ω] The age groups in HELP were: <18, 18 to <65, and ≥65. [π] Percentages presented for OASIS-HAE for are based on the number of patients with at least one prior medication (21 in the placebo group, 44 in the Q4W group, and 23 in the Q8W group). [¥] Percentages presented for OASIS-HAE for are based on the number of patients with at least one concomitant medication (22 in the placebo group, 41 in the Q4W group, and 21 in the Q8W group). [†] Detailed list of on-demand medications used in the HELP trial can be found in eTable 7 in the supplementary appendix of Banerji et al. 2018 (3). [a] The 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. [b] First-line prophylactic agents and excluded attenuated androgens and tranexamic acid.
References: Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2); Banerji et al. 2018 (3).

5.2 Comparative analyses of efficacy and safety

5.2.1 Efficacy and safety – results per OASIS-HAE

The number and proportion of patients that discontinued the study in the different treatment arms and the primary reason for discontinuation are presented Table 6.

Table 6 Discontinuation in OASIS-HAE

Patient disposition	Placebo (N=22) n (%)	Donidalorsen 80 mg Q4W (N=46) n (%)	Donidalorsen 80 mg Q8W (N=23) n (%)
Patients randomised[a]	22	46	23
Patients dosed[b]	22 (100)	45 (97.8)	23 (100)
Patients who completed the study treatment	18 (81.8)	44 (95.7)	21 (91.3)
Patients who terminated early from the study treatment	4 (18.2)	2 (4.3)[b]	2 (8.7)
Primary reason for early termination of study treatment			
Voluntary withdrawal	0	1 (2.2)[b]	0
Pregnancy	1 (4.5)	0	0
AE or SAE	0	0	1 (4.3)[d]
Lack of efficacy[c]	3 (13.6)	1 (2.2)	1 (4.3)
Patients who completed post-treatment follow-up	0	1 (2.2)	3 (13.0)
Patients who terminated early from post-treatment follow-up	22 (100)	45 (97.8)	20 (87.0)
Primary reason for early termination from post-treatment follow-up			
Voluntary withdrawal	2 (9.1)	1 (2.2)	0

Pregnancy	1 (4.5)	0	0
Rolled over to OLE arm of ISIS 721744-CS7	19 (86.4)	44 (95.7)	20 (87.0)

Abbreviations: AE = adverse event; HAE = Hereditary angioedema; OLE = open-label extension; Q4W = every 4 weeks; Q8W = every 8 weeks; SAE = serious adverse event.
Notes: [a] The denominator of the percentages in the table are the number of randomised patients. [b] One patient in the 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 Q8W group discontinued due to an AE of alanine aminotransferase increased. Although the stopping rule was not met by the patient, study drug was permanently discontinued due to the AE per Investigator's decision.
Source: Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2).

In the following sections, efficacy results from OASIS-HAE are presented. Efficacy assessments were measured for the period of Week 1 to Week 25 or for the period of Week 5 to Week 25. A nadir in the PKK levels during the first dosing period is not expected to be immediate and only expected to be reached towards the end of the first 4-week dosing period. Therefore, the period of Week 5 to Week 25 was chosen as a more clinically meaningful time period for evaluation in addition to Week 1 to Week 25. A Nordic clinical expert also confirmed that inclusion of the Week 5 to Week 25 assessment period is clinically meaningful and provides a fair estimate of the treatment effect of donidalorsen, given the anticipated delay before clinical benefit becomes evident (32). The results are presented for the Full Analysis Set, which includes all randomised patients who received at least one dose of study drug (donidalorsen or placebo).

5.2.1.1 Attack-free patients from Week 5 to 25

The response rate analysis on the percentage of Investigator-confirmed HAE attack-free patients from Week 5 to Week 25 is presented in Table 7. Of the 45 patients in the Q4W group, 24 (53.3%) were HAE attack-free from Week 5 to Week 25, compared with 2 of 22 (9.1%) patients in the placebo group; this difference was statistically significant (p = 0.003). Although a larger percentage of patients (8 of 23 [34.8%]) in the Q8W group were HAE attack-free from Week 5 to Week 25 compared with the placebo group, the difference between these groups did not reach statistical significance (p = 0.240).

Table 7 Response rate analysis on percentage of Investigator-confirmed HAE attack-free patients from Week 5 to Week 25 (Full Analysis Set)

Response rate analysis	Placebo (N = 22)	Donidalorsen 80 mg Q4W (N = 45)	Donidalorsen 80 mg Q8W (N = 23)
HAE attack-free patients from Week 5 to Week 25, n (%)	2 (9.1)	24 (53.3)	8 (34.8)

HAE non-attack-free patients from Week 5 to Week 25, n (%)	20 (90.9)	21 (46.7)	15 (65.2)
OR (95% CI)[a]	--	11.79 (2.34, 59.36)	3.23 (0.46, 22.85)
Nominal p-value	--	0.003	0.240

Abbreviations: CI = confidence interval; HAE = Hereditary angioedema; OR = odds ratio; Q4W = every 4 weeks; Q8W = every 8 weeks.
Notes: The percentages were based on the observed patients in the specific category. [a] The OR, its 95% Cis, 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 a covariate.
Source: Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2).

5.2.1.2 ≥90% reduction in attack rate

The response rate analysis ≥90% reduction in time-normalised Investigator-confirmed HAE attack rate (per 4 weeks) from baseline between Week 5 to Week 25 is presented in Table 8. The percentage of patients ≥ 90% reduction from Baseline in Investigator-confirmed HAE attacks from Week 5 and Week 25 was 62.2% and 47.8% for the Q4W and Q8W groups, respectively, compared with 9.1% in the placebo group (nominally significant, p = < 0.001 and p = 0.014, respectively).

Table 8 Response rate analysis on ≥90% reduction in time-normalised Investigator-confirmed HAE attack rate from baseline between Week 5 to Week 25 (Full Analysis Set)

Response rate analysis on ≥90% 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 Attack Rate Reduction ≥ 90%, n (%)	2 (9.1)	28 (62.2)	11 (47.8)
Patients with Attack Rate Reduction < 90%, n (%)	20 (90.9)	17 (37.8)	12 (52.2)
OR (95% CI)[c]	--	17.04 (3.36, 86.42)	8.70 (1.56, 48.52)
Nominal p-value	--	< 0.001	0.014

Abbreviations: CI = confidence interval; HAE = Hereditary angioedema; OR = odds ratio; Q4W = every 4 weeks; Q8W = every 8 weeks.
Notes: [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 OR, its 95% CI, 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.
Sources: Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2).

5.2.1.3 Time-normalised number of Investigator-confirmed HAE attacks (per 4 weeks) from Week 1 to Week 25

An analysis of the time-normalised Investigator-confirmed HAE attack rate from Week 1 to Week 25 is presented in Table 9. The mean (SD, standard error of mean (SEM)) time-normalised HAE attack rate (per 4 weeks) from Week 1 to Week 25 was 0.89 (1.851, 0.276) for the Q4W group and 1.19 (1.629, 0.340) for the Q8W group, compared with 2.29 (1.807, 0.385) for the placebo group. The LSM time-normalised Investigator-confirmed HAE attack rate (per 4 weeks) from Week 1 to Week 25 was 0.44 (95% CI: 0.265, 0.727) for the Q4W group, 1.02 (95% CI: 0.651, 1.594) for the Q8W group, and 2.26 (95% CI: 1.657, 3.085) for the placebo group, representing an 81% (95% CI: -89.3%, -64.9%) reduction relative to placebo for the Q4W group (statistically significant, $p < 0.001$) and a 55% reduction (95% CI: -73.9%, -22.3%) relative to placebo for the Q8W group (statistically significant, $p = 0.004$).

Analysis of time-normalised, Investigator-confirmed HAE attack rates (per 4 weeks) over successive 4-week periods for the Q4W group showed an early response to donidalorsen with a marked reduction in attack rate observed during Weeks 1 to 5, which was sustained over the 25-week treatment period (Figure 1). For the Q8W group, the reduction in HAE attacks progressively became larger over time and approached that of the Q4W group by Week 25 (Figure 1). This delay to peak effect may be due to the longer time necessary for the drug to achieve steady state for the longer time between doses (8 weeks) compared with Q4W.

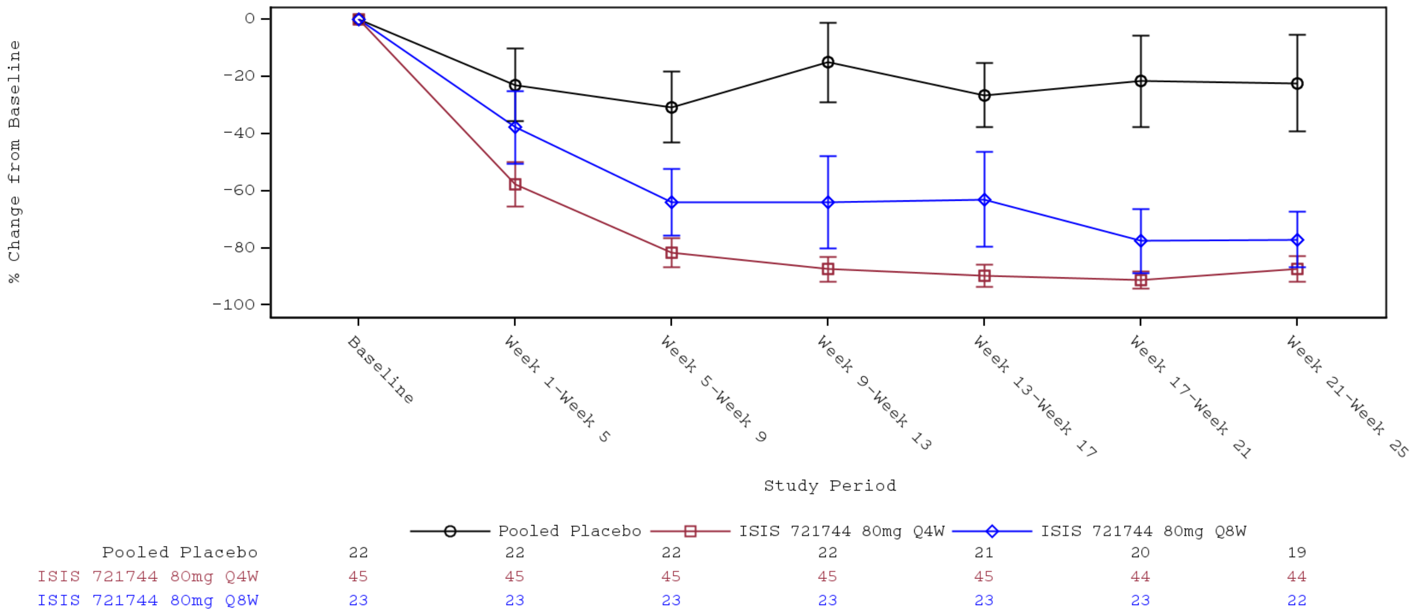
Table 9 Analyses of time-normalised Investigator-confirmed HAE attack rate (per 4 weeks) from Week 1 to Week 25 (Full Analysis Set)

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, SEM)	2.90 (1.657, 0.353)	3.61 (2.236, 0.333)	3.18 (2.147, 0.448)
Time-normalised HAE attack rate from Week 1 to Week 25[b], mean (SD, SEM)	2.29 (1.807, 0.385)	0.89 (1.851, 0.276)	1.19 (1.629, 0.340)
Poisson regression[c]			
LSM rate (95% CI)	2.26 (1.657, 3.085)	0.44 (0.265, 0.727)	1.02 (0.651, 1.594)
Model adjusted mean RR (95% CI)	--	0.19 (0.107, 0.351)	0.45 (0.261, 0.777)

Wald chi-square p-value	--	< 0.001	0.004
Percentage difference (95% CI)[d]	--	-81% (-89.3%, -64.9%)	-55% (-73.9%, -22.3%)

Abbreviations: CI = confidence interval; HAE = Hereditary angioedema; LSM = least square mean; Q4W = every 4 weeks; Q8W = every 8 weeks; RR = rate ratio; SD = standard deviation; SEM = standard error of mean.
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 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 RR -1). Similarly, the estimated upper and lower confidence limits for the mean RR can be transformed by subtracting 1 and multiplying by 100% to calculate 95% Cis for the percentage change.
Source: Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2).

Figure 1 Percent change from Baseline mean (± SEM) of Investigator-confirmed HAE attack rate (per 4 weeks) over successive 4-week periods from Week 1 to Week 25 (Full Analysis Set)



Abbreviations: HAE = Hereditary angioedema; Q4W = every 4 weeks; Q8W = every 8 weeks; SEM = standard error of mean.
Notes: For Investigator-confirmed HAE attacks, the baseline rate, (i.e., Run-in Period Investigator-confirmed HAE attack rate), was calculated for each patient as the number of Investigator-confirmed HAE attacks that occurred during the Run-in Period divided by the number of days contributed to the Run-in Period multiplied by 28 days. The per 4-week HAE attack rate was calculated for each patient as number of HAE attacks occurring during each 4-week period divided by the number of days the patient contributed to the period multiplied by 28. Week 1 to Week 5 starts from Day 1 to Day 28; Week 5 to Week 9 starts from Day 29 to Day 56; Week 9 to Week 13 starts from Day 57 to Day 84; Week 13 to Week 17 starts from Day 85 to Day 112, and so on. Error bars indicate the SEM. ISIS 721744 = donidalorsen.
Source: Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2).

5.2.1.4 Time-normalised number of moderate or severe Investigator-confirmed HAE attacks (per 4 weeks) from Week 5 to Week 25

Analyses of the time-normalised Investigator-confirmed moderate or severe HAE attack rate (per 4 weeks) from Week 5 to Week 25 for the Full Analysis Set are provided in Table 10. The mean (SD, SEM) time-normalised Investigator-confirmed moderate or severe HAE attack rate (per 4 weeks) from Week 5 to Week 25 was 0.37 (1.026, 0.153) and 0.90 (1.617, 0.337) for the Q4W and Q8W groups, respectively, compared with 1.35 (1.707, 0.364) for the placebo group. The LSM time-normalised Investigator-confirmed moderate or severe HAE attack rate (per 4 weeks) from Week 5 to Week 25 was 0.12 (95% CI: 0.044, 0.351) for the Q4W group and 1.15 (95% CI: 0.718, 1.831) for the placebo group, representing a reduction of 89% (95% CI: -96.5%, -66.1%) in the moderate or severe HAE attack rate (per 4 weeks) relative to placebo for the Q4W group (statistically significant, $p < 0.001$). For the Q8W group, the LSM time-normalised Investigator-confirmed moderate or severe HAE attack rate (per 4 weeks) from Week 5 to Week 25 was 0.68 (95% CI: 0.372, 1.229). While the percent difference relative to the placebo group in the moderate or severe HAE attack rate (per 4 weeks) for the Q8W group was a reduction of 41% (95% CI: -72.4%, 26.0%), (nominal $p = 0.173$).

Analysis of time-normalised, Investigator-confirmed moderate or severe HAE attack rate (per 4 weeks) over successive 4-week periods showed that the early response to donidalorsen observed in Weeks 1 to Week 5 was sustained over the Week 5 to Week 25 period, as presented in Figure 2.

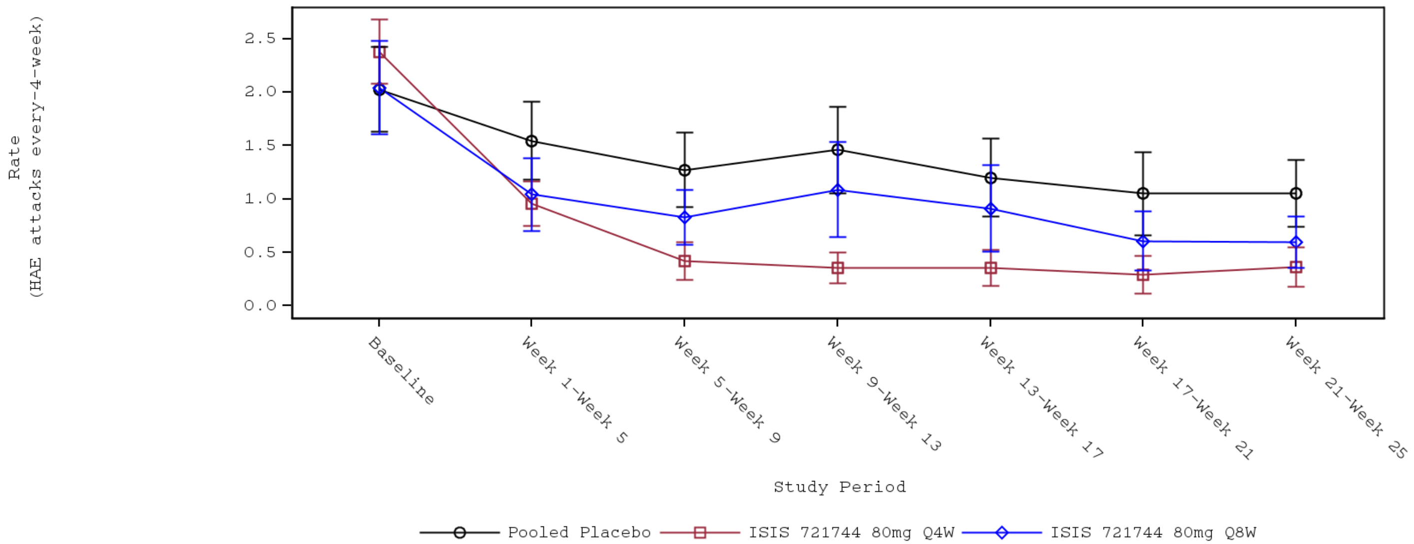
Table 10 Analyses of time-normalised Investigator-confirmed moderate or severe HAE attack rate (per 4 weeks) from Week 5 to Week 25 (Full Analysis Set)

	Placebo (N = 22)	Donidalorsen 80 mg Q4W (N = 45)	Donidalorsen 80 mg Q8W (N = 23)
Run-In Period moderate or severe HAE attack rate[a], mean (SD, SEM)	2.03 (1.854, 0.395)	2.38 (2.023, 0.302)	2.04 (2.095, 0.437)
Time-normalised moderate or severe HAE attack rate from Week 5 to Week 25[b], mean (SD, SEM)	1.35 (1.707, 0.364)	0.37 (1.026, 0.153)	0.90 (1.617, 0.337)
Poisson regression[c]			
LSM rate (95% CI)	1.15 (0.718, 1.831)	0.12 (0.044, 0.351)	0.68 (0.372, 1.229)

Model adjusted mean RR (95% CI)	--	0.11 (0.035, 0.339)	0.59 (0.276, 1.260)
Wald chi-square P-value	--	< 0.001	0.173
Percentage difference (95% CI)[d]	--	-89% (-96.5%, -66.1%)	-41% (-72.4%, 26.0%)

Abbreviations: CI = confidence interval; HAE = Hereditary angioedema; LSM = least square mean; Q4W = every 4 weeks; Q8W = every 8 weeks; RR = rate ratio; SD = standard deviation; SEM = standard error of mean.
Notes: [a] The Run-In Period (Screening) HAE attack rate for each patient was calculated as number of Investigator-confirmed HAE attacks 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 was calculated as number of Investigator-confirmed 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 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 per 4 weeks that each patient was observed from Week 5 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 was calculated as 100% * (mean RR -1). Similarly, the estimated upper and lower confidence limits for the mean RR can be transformed by subtracting 1 and multiplying by 100% to calculate 95% CIs for the percentage change.
Source: Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2).

Figure 2 Absolute value mean (± SEM) of time-normalised Investigator-confirmed moderate or severe HAE attack rate (per 4 weeks) over successive 4-week periods from Week 1 to Week 25 (Full Analysis Set)



Pooled Placebo	22	22	22	22	21	20	19
ISIS 721744 80mg Q4W	45	45	45	45	45	44	44
ISIS 721744 80mg Q8W	23	23	23	23	23	23	22

Abbreviations: HAE = Hereditary angioedema; Q4W = every 4 weeks; Q8W = every 8 weeks; SEM = standard error of mean.
Notes: For Investigator-confirmed HAE attacks, the baseline rate, i.e., Run-in Period Investigator-confirmed HAE attack rate, was calculated for each patient as the number of Investigator-confirmed HAE attacks that occurred during the Run-in Period divided by the number of days contributed to the Run-in Period multiplied by 28 days. The per 4-week HAE attack rate was calculated for each patient as number of HAE attacks occurring during each 4-week period divided by the number of days the patient contributed to the period multiplied by 28. Week 1 to Week 5 starts from Day 1 to Day 28; Week 5 to Week 9 starts from Day 29 to Day 56; Week 9 to Week 13 starts from Day 57 to Day 84; Week 13 to Week 17 starts from Day 85 to Day 112, and so on. Error bars indicate the SEM. ISIS 721744 = donidalorsen.
Source: Ionis Pharmaceuticals, Inc., 2024 (23).

5.2.1.5 Change from Baseline in AE-QoL questionnaire total score at Week 25

Analysis of the AE-QoL questionnaire total score (scores range from 0 to 100, with a score of 100 indicating the worst possible QoL) is presented in Table 11. Overall, the change from Baseline in AE-QoL questionnaire total score at Week 25 showed a clinically meaningful (i.e., ≥ 6 points) improvement in QoL for patients treated with donidalorsen compared with patients treated with placebo. The LSM reduction (improvement) from Baseline (values rounded as analysis of points) in the AE-QoL total score at Week 25 was 24.8 points (95% CI: -29.9, -19.7) for patients in the Q4W group and 19.9 points (95% CI: -27.0, -12.7) for patients in the Q8W group, compared with an LSM reduction of 6.2 points (95% CI: -13.7, 1.4) for patients in the placebo group. The LSM improvement relative to the placebo group in the AE-QoL total score was 18.6 points (95% CI: -27.7, -9.5) and 13.7 points (95% CI: -24.0, -3.3) for the Q4W and Q8W groups, respectively; this difference was statistically significant for the Q4W group ($p < 0.001$) and nominally significant for the Q8W group ($p = 0.010$) compared with the placebo group.

Table 11 Analysis of AE-QoL questionnaire total score at Week 25 (Full Analysis Set)

Change from Baseline to Week 25 Day 169	Placebo (N = 22)	Donidalorsen 80 mg Q4W (N = 45)	Donidalorsen 80 mg Q8W (N = 23)
n	18	42	22
Mean (SD, SEM)	-8.09 (18.083, 4.262)	-24.69 (15.895, 2.453)	-21.29 (22.719, 4.844)
LSM (95% CI)[a]	-6.19 (-13.737, 1.353)	-24.76 (-29.860, -19.652)	-19.85 (-26.960, -12.734)
Treatment Difference in LSM (95% CI)	--	-18.56 (-27.673, -9.454)	-13.65 (-24.024, -3.286)
Nominal P-Value	--	< 0.001	0.010

Abbreviations: AE-QoL = Angioedema Quality of Life; CI = confidence interval; LSM = least square mean; Q4W = every 4 weeks; Q8W = every 8 weeks; SD = standard deviation; SEM = standard error of mean.
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: Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2).

5.2.1.6 Percentage of patients with an AE-QoL improvement of at least 6 points from Baseline

Responder analysis of the AE-QoL questionnaire total score at Week 25 is summarised in Table 12. In the Q4W group and the Q8W group, the percent of AE-QoL responders (i.e., patients with a reduction in AE-QoL total score ≥ 6 points) was higher than in the placebo group (37 of 42 patients [88.1%] and 15 of 21 patients [71.4%] compared with 9 of 20 patients [45.0%], respectively). The difference in percent of responders was nominally significant for the Q4W group (OR [95% CI]: 12.22 [2.75, 54.27]; nominal p < 0.001), but not for the Q8W group (odds ratio [95% CI]: 3.45 [0.83, 14.29]; nominal p = 0.087).

Table 12 Responder analysis of AE-QoL questionnaire total score at Week 25 (Full Analysis Set)

	Placebo (N = 22)	Donidalorsen 80 mg Q4W (N = 45)	Donidalorsen 80 mg Q8W (N = 23)
Responders or non-responders at Week 25, n	20	42	21
Responders at Week 25[a], n (%)	9 (45.0)	37 (88.1)	15 (71.4)
Non-responders at Week 25, n (%)	11 (55.0)	5 (11.9)	6 (28.6)
Early termination due to reasons of AEs or lack of efficacy, n (%)	3 (15.0)	1 (2.4)	1 (4.8)
OR (95% CI)[b]	--	12.22 (2.75, 54.27)	3.45 (0.83, 14.29)
P-value[b]	--	<0.001	0.087

Abbreviations: AE = adverse event; AE-QoL = Angioedema Quality of Life; CI = confidence interval; OR = odds ratio; Q4W = every 4 weeks; Q8W = every 8 weeks.
Notes: [a] Patients with at least 6-point improvement (reduction) from Baseline in AE-QoL total score at Week 25 are considered as responders. Patients who early discontinued Treatment period due to reasons of AEs or lack of efficacy are considered as non-responders; due to other reasons, patients are considered as missing. [B] The OR, its 95% CI, and p-value are calculated on a logistic regression with the Baseline and the Treatment-by-Baseline interaction as covariate.
Source: Ionis Pharmaceuticals, Inc., 2024 (23).

5.2.2 Efficacy and safety – results per HELP

Section 5.2.2 presents results from the HELP study (3), which investigated the efficacy of lanadelumab compared with placebo. The number and proportion of patients that discontinued the study in the different treatment arms and the primary reason for discontinuation are presented in
Table 13.

Table 13 Discontinuation in HELP

Patient disposition	Placebo (N = 41)	Lanadelumab 300 mg Q2W (N = 27)	Lanadelumab 300 mg Q4W (N = 29)

Patients randomised	41	27	29
Received treatment as randomised	41	27	29
Discontinued			
Withdrew	3	2	1
AE	2	0	1
Lost to follow-up	0	0	1
Withdrawn by physician	1	0	0
Entered the OLE study	33	25	25

Abbreviations: AE = adverse event; OLE = open-label extension; Q2W = every 2 weeks; Q4W = every 4 weeks.
Notes: All patients received injections Q2W, with those in the Q4W groups receiving placebo in between active treatments.
Source: Banerji et al. 2018 (3).

5.2.2.1 Attack-free patients from 4-week run-in period to Week 26

The response rate analysis on the percentage of Investigator-confirmed HAE attack-free patients from the 4-week run-in period to Week 26 is presented in Table 14. Of the 27 patients in the Q2W group, 12 (44.4%) were HAE attack-free over the 26 week treatment period, compared with 1 of 41 (2.4%) patients in the placebo group; this difference was statistically significant ($p < 0.001$). Although a lower percentage of patients (9 of 29 [31.0%]) in the Q4W group were HAE attack-free over the 26 week treatment period compared with the Q2W group, this difference was statistically significant ($p = 0.001$) compared with the placebo group..

Table 14 Response rate analysis on percentage of Investigator-confirmed HAE attack-free patients from 4-week run-in period to Week 26

Responder analysis	Placebo (N = 41)	Lanadelumab 300 mg Q2W (N = 27)	Lanadelumab 300 mg Q4W (N = 29)
HAE attack-free patients over the 26 weeks[a], n (%)	**1 (2.4)**	**12 (44.4)**	**9 (31.0)**
Difference (95% CI)[b]	--	**42.0 (18.1, 61.8)**	**28.6 (5.0, 50.0)**
P-value[c]	--	**<0.001**	**0.001**

Abbreviations: CI = confidence interval; HAE = Hereditary angioedema; Q2W = every 2 weeks; Q4W = every 4 weeks.
Notes: [a] Proportion of attack free patients is defined as the percentage of subjects with a percentage reduction of 100% from the run-in period in the HAE attack rate. [b] The difference vs placebo was analysed using Fisher

exact test. [c] P-values shown for exploratory endpoints were not adjusted for multiplicity. All patients received injections Q2W, with those in the Q4W groups receiving placebo in between active treatments.
Source: Banerji et al. 2018 (3).

5.2.2.2 ≥90% reduction in attack rate

The responder analysis on ≥90% reduction in rate of Investigator-confirmed HAE attacks over the 26-week treatment period is presented in Table 15**Error! No bookmark name given.**. Reductions of 90% or more were observed in 66.7% of patients treated with lanadelumab Q2W and 55.2% of patients treated with lanadelumab Q4W (p <0.001 in both groups) compared with 4.9% of patients in the placebo group.

Table 15 Responder analysis of ≥90% reduction in rate of Investigator-confirmed HAE attacks over the 26-week treatment period (exploratory endpoint)[a]

Responder analysis	Placebo (N = 41)	Lanadelumab 300 mg Q2W (N = 27)	Lanadelumab 300 mg Q4W (N = 29)
≥90% reduction in HAE attack rate[b], n (%)	2 (4.9)	18 (66.7)	16 (55.2)
Difference (95% CI) [c]	--	61.8 (39.5, 78.8)	50.3 (27.7, 68.8)
P-value[a]	--	<0.001	<0.001

Abbreviations: CI = confidence interval; HAE = Hereditary angioedema; Q2W = every 2 weeks; Q4W = every 4 weeks.
Notes: [a] P-values shown for exploratory endpoints were not adjusted for multiplicity. All patients received injections Q2W, with those in the Q4W groups receiving placebo in between active treatments. [b] Achievement of a prespecified reduction from the run-in period in the HAE attack rate. The percentage reduction was calculated as the run-in period attack rate minus the treatment period attack rate divided by the run-in period attack rate, multiplied by 100. [c] The difference vs placebo was analysed using Fisher exact test.
Source: Banerji et al. 2018 (3).

5.2.2.3 Investigator-confirmed HAE attacks (per month) from Day 0 to Day 182

An analysis of the Investigator-confirmed HAE attack rate from Day 0 to 182 is presented in Table 16. All lanadelumab treatment regimens were more effective than placebo. The model-based mean number of attacks per month from days 0 through 182 was 1.97 (95% CI: 1.64, 2.36) in the placebo group compared with 0.26 (95% CI: 0.14, 0.46) in the 300 mg Q2W group and 0.53 (95% CI: 0.36, 0.77) in the 300 mg Q4W group. There were statistically significant reductions in attack rates per month; the mean difference in the lanadelumab groups vs the placebo group was -1.71 (95% CI: -2.09, -1.33) in the 300 mg Q2W group and -1.44 (95% CI: -1.84, -1.04) in the 300 mg Q4W group (adjusted p <0.001 for both comparisons). The mean RR relative to placebo was 0.13 (95% CI: 0.07, 0.24) for the 300 mg Q2W group and 0.27 (95% CI: 0.18, 0.41) for the 300 mg Q4W group (adjusted p <0.001 for both comparisons).

Table 16 Investigator-confirmed HAE attacks (per month) from Day 0 to Day 182[a]

	Placebo (N = 41)	Lanadelumab 300 mg Q2W (N = 27)	Lanadelumab 300 mg Q4W (N = 29)
Attacks per month[b, c], mean (95% CI)	1.97 (1.64, 2.36)	0.26 (0.14, 0.46)	0.53 (0.36, 0.77)
Difference (95% CI)[d]	--	-1.71 (-2.09, -1.33)	-1.44 (-1.84, -1.04)
P-value	--	<0.001	<0.001
RR (95% CI)[c]	--	0.13 (0.07, 0.24)	0.27 (0.18, 0.41)
P-value[e]	--	<0.001	<0.001

Abbreviations: CI = confidence interval; HAE = Hereditary angioedema; Q2W = every 2 weeks; Q4W = every 4 weeks; RR = rate ratio.
Notes: [a] All patients received injections Q2W, with those in the Q4W groups receiving placebo in between active treatments. [b] Attack rates are model-based mean attacks per month, defined as 4 weeks. [c] Results are from a Poisson regression model accounting for overdispersion; treatment group and normalised baseline attack rate were fixed effects. The logarithm of time (days) each patient was observed during the treatment period was an offset variable. All p-values (Wald test) reported vs placebo. [d] Estimated from a nonlinear function of the model parameters. All p-values (Wald test) reported vs placebo. [e] P-value adjusted for multiple testing.
Source: Banerji et al. 2018 (3).

5.2.2.4 Investigator-confirmed moderate or severe HAE attacks (per month) from Day 0 to Day 182

An analysis of the Investigator-confirmed moderate or severe HAE attack rate from Day 0 to 182 is presented in Table 17. The mean difference vs placebo was -1.01 (95% CI: -1.32, -0.71) for the 300 mg Q2W group and -0.89 (95% CI: -1.20, -0.58) for the 300 mg Q4W group. These differences were statistically significant (p <0.001 for both comparisons).

Table 17 Investigator-confirmed moderate or severe HAE attacks (per month) from Day 0 to Day 182 [a]

	Placebo (N = 41)	Lanadelumab 300 mg Q2W (N = 27)	Lanadelumab 300 mg Q4W (N = 29)
Attacks per month[b, c], mean (95% CI)	1.22 (0.97, 1.52)	0.20 (0.11, 0.39)	0.32 (0.20, 0.53)
Difference (95% CI)[d]	--	-1.01 (-1.32, -0.71)	-0.89 (-1.20, -0.58)
P-value	--	<0.001	<0.001
RR (95% CI)[c]	--	0.17 (0.08, 0.33)	0.27 (0.16, 0.46)

P-value[e]	--	<0.001	<0.001

Abbreviations: CI = confidence interval; HAE = Hereditary angioedema; Q2W = every 2 weeks; Q4W = every 4 weeks; RR = rate ratio.
Notes: [a] All patients received injections Q2W, with those in the Q4W groups receiving placebo in between active treatments. [b] Attack rates are model-based mean attacks per month, defined as 4 weeks. [c] Results are from a Poisson regression model accounting for overdispersion; treatment group and normalised baseline attack rate were fixed effects. The logarithm of time (days) each patient was observed during the treatment period was an offset variable. All p-values (Wald test) reported vs placebo. [d] Estimated from a nonlinear function of the model parameters. All p-values (Wald test) reported vs placebo. [e] P-value adjusted for multiple testing.
Source: Banerji et al. 2018 (3).

5.2.2.5 Change from Baseline in AE-QoL questionnaire total score at Day 182

Analysis of the AE-QoL questionnaire total score is presented in Table 18. Patients experienced a significant improvement in QoL total scores over 26 weeks in the lanadelumab treatment groups compared with placebo. The mean change in total score vs placebo was -16.57 (95% CI: -28.53, -4.62) for the 300 mg Q2W group and -12.66 (95% CI: -24.51, -0.80) for the 300 mg Q4W group.

Table 18 Analysis of AE-QoL questionnaire total score from Day 0-182[a]

	Placebo (N = 41)	Lanadelumab 300 mg Q2W (N = 27)	Lanadelumab 300 mg Q4W (N = 29)
Number of patients	38	26	27
Change in total score, from Day 0-182[b], LSM (95% CI)	-4.72 (-10.46, 1.02)	-21.29 (-28.21, -14.37)	-17.38 (-24.17, -10.58)
Change vs placebo, mean (95% CI)	--	-16.57 (-28.53, -4.62)	-12.66 (-24.51, -0.80)
P-value[c]	--	0.003	0.03

Abbreviations: AE-QoL = Angioedema Quality of Life; CI = confidence interval; LSM = least square mean; Q2W = every 2 weeks; Q4W = every 4 weeks.
Notes: [a] All patients received injections Q2W, with those in the Q4W groups receiving placebo in between active treatments. [b] Change in AE-QoL scores is controlled for baseline scores and are LSMs. [c] Analysis of covariance post hoc pairwise comparison (Tukey-Kramer) vs placebo.
Source: Banerji et al. 2018 (3).

5.2.2.6 Percentage of patients with an AE-QoL improvement of at least 6 points from Baseline

Responder analysis of the AE-QoL questionnaire total score at Day 182 is summarised in Table 19. A higher proportion of patients treated with lanadelumab (80.8% in the 300 mg Q2W group [p = 0.001] and 63.0% in the 300 mg Q4W group [p = 0.07]) achieved the minimal clinically important difference in total QoL score compared with placebo (36.8%). This corresponded to patients treated with lanadelumab having a significantly greater likelihood of achieving a minimal clinically important difference (OR: 7.2 in the 300 mg Q2W group [p = 0.001] and OR: 2.9 in the 300 mg Q4W group [p = 0.04]) compared with placebo.

Table 19 Responder analysis of AE-QoL questionnaire total score at Day 182[a]

	Placebo (N = 41)	Lanadelumab 300 mg Q2W (N = 27)	Lanadelumab 300 mg Q4W (N = 29)
Number of patients	38	26	27
Responded to therapy[b], %	36.84	80.77	62.96
P-value	--	0.001	0.07
OR (95% CI)	--	7.20 (2.22, 23.37)	2.91 (1.05, 8.10)
P-value	--	0.001	0.04

Abbreviations: AE-QoL = Angioedema Quality of Life; CI = confidence interval; OR = odds ratio; Q2W = every 2 weeks; Q4W = every 4 weeks.
Notes: [a] All patients received injections Q2W, with those in the Q4W groups receiving placebo in between active treatments. [b] Patients who were considered to have responded (responders) to the therapy were defined as achieving an improvement greater than or equal to the minimal clinically important difference of –6 for total scores from days 0 through 182. The questionnaire consisted of four domains (functioning, fatigue and mood, fears and shame, and nutrition) and 17 questions that were taken together for a total score. Total raw scores were transformed to a linear scale of 0 to 100, with lower scores indicating lower impairment or higher health–related QoL. ORs represent times the odds (vs not) to achieve a responder definition compared with placebo.
Source: Banerji et al. 2018 (3).

5.2.3 Efficacy and safety – results per OASISplus

OASISplus (NCT05392114) is an ongoing phase 3 study expected to complete in March 2027 (33). It evaluates the long-term safety and efficacy of donidalorsen and includes, among others, patients from OASIS-HAE. Following completion of the double-blind OASIS-HAE study, 83 of 88 eligible patients rolled over to the OLE cohort in the OASISplus as of February 28, 2024, with two withdrawals due to family planning and voluntary withdrawal (34). All patients who received donidalorsen 80 mg Q4W in OASIS-HAE continued to receive this dosing in OASISplus (n=44), while patients already receiving donidalorsen 80 mg Q8W in OASIS-HAE received the donidalorsen 80 mg Q4W (n=6) or Q8W (n=14) dosing in OASISplus. Patients randomised to receive placebo in OASIS-HAE rolled over to donidalorsen 80 mg Q4W dosing (n=19). Patient were treated for up to 156 weeks. Patients who had been selected for the OLE study and experienced at least five attacks per month for two consecutive months were withdrawn from the OASIS-HAE trial. . In addition to the OLE cohort (patients who rolled over from OASIS-HAE), a switch cohort was enrolled in OASISplus to receive donidalorsen 80 mg Q4W following a stable dose of prophylactic treatment for at least 12 weeks prior to the screening period. A total of 64 patients enrolled in the switch cohort, following a stable dose of lanadelumab (N = 31), berotralstat (N = 11), or C1-INH (N = 22).

The primary objective of the switch and OLE cohorts was to evaluate the safety of long-term dosing with donidalorsen in patients with HAE, with the primary endpoint being the incidence and severity of TEAEs, in addition to the secondary objectives to evaluate the long-term efficacy and effects of donidalorsen on number of HAE attacks and QoL. Secondary endpoints include Time-normalised number of HAE attacks per month (Weeks 1–53) and AE-QoL total score over 53 weeks. The primary outcome was assessed in the safety population, which is defined as all patients enrolled in OASISplus who received at least one dose of donidalorsen. Secondary outcomes were performed on 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.

5.2.3.1 Study results - OASISplus switch cohort

In the following, a summary of results for Week 16 related to the primary and secondary objectives is provided for the switch cohort (35). Results for the switch cohort will be presented for the overall population or only for patients who previously received lanadelumab.

The safety and full analysis sets included the 64 patients who received donidalorsen in OASISplus, who had previously received prophylactic treatment with: lanadelumab (n = 31), C1-INH (n = 22), and berotralstat (n = 11). At week 16, 45 of 64 patients who received doses (70%) reported TEAEs, and most (93%) reported only mild or moderate TEAEs. Of all reported TEAEs, most patients (62%) only reported TEAEs that were unrelated to the study drug. The most frequently reported TEAEs were upper respiratory tract infection (16%), nasopharyngitis (11%), injection-site erythema (11%), and headache (9%). No serious TEAEs were related to the study drug. One patient discontinued owing to a serious AE (ongoing congestive heart failure) that was considered to be unrelated to the study drug. Overall safety data do not indicate that treatment with donidalorsen was associated with any clinically meaningful effects on vital signs, electrocardiogram parameters, or changes in other chemistry or haematology parameters (35).

Overall, patients switching from any prior LTP had a mean 62% reduction in HAE attacks from baseline (with the prior LTP) after switching to donidalorsen Q4W for 16 weeks. At baseline, mean (SD) monthly HAE attack rates were 0.69 (1.09) for patients who were taking stable doses of lanadelumab. After switching to donidalorsen, mean (SD) monthly HAE attack rates were 0.24 (0.33), corresponding to a mean HAE attack rate reduction from baseline of 65% for patients switching from lanadelumab. Furthermore, most individual patients either improved or maintained low mean HAE attack rates from baseline to week 16 of donidalorsen treatment. Improvements were highest among those who entered the study with the highest baseline HAE attack rates. Importantly, there were no notable transient increases in mean HAE attack rates overall in patients during the two months after the transition from patients' prior LTP to donidalorsen (35).

At week 16, patients reported improvements in QoL. Total mean (SD) change in AE-QoL total score from baseline to week 16 was -10.4 (12.6), exceeding the clinically meaningful change threshold of 6 points for patients who switched from any prior LTPs. For patients taking stable doses of lanadelumab at baseline, the mean (SEM) total AE-QoL score was 33.6 (3.8) at baseline. After switching to donidalorsen, the mean (SEM) total AE-QoL score was reduced to 24.5 (3.6) at Week 16 (35).

5.2.3.2 Study results - OASISplus OLE cohort

In total, 69 patients received donidalorsen 80 mg Q4W, while 14 patients received donidalorsen 80 mg Q8W.

The incidence and severity of TEAEs are shown in Table 20. 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, showing that the favourable safety profile of donidalorsen is sustained in long-term treatment. Fewer patients experienced both any TEAEs and any TEAEs related to the study drug in the Q8W group compared to the Q4W group and placebo.

Table 20 Incidence and severity of TEAEs (OLE dosing cohort)

	Donidalorsen 80 mg Q4W (N = 69)	Donidalorsen 80 mg Q8W (N = 14)	All patients (N = 83)
Any TEAE, n (%)	56 (81)	10 (71)	66 (80)
Any TEAE related to study drug, n (%)	16 (23)	2 (14)	18 (22)
Any TEAE leading to discontinuation, n (%)	0	0	0
Any serious TEAE, n (%)	4 (6)	0	4 (5)
Any serious TEAE related to study drug, n (%)	0	0	0
Severity of TEAEs related to study drug, n (%)			
Mild	14 (20)	2 (14)	16 (19)
Moderate	2 (3)	0	2 (2)
Severe	0	0	0

Abbreviations: OLE = open-label extension; Q2W = every 2 weeks; Q4W = every 4 weeks; TEAE = treatment-emergent adverse event.
Source: Tachdjian et al. 2024 (34).

A reduction in time-normalised number of HAE attacks per month (from Week 1 to 53) was observed for both donidalorsen Q4W and donidalorsen Q8W dosing groups, with a reduction of 92% and 93%, respectively. These results show that the efficacy of donidalorsen does not deteriorate in long-term treatment, for both dosing regimens (34).

Patients in both donidalorsen dosing groups reported clinically meaningful improvements in AE-QoL total score, with a reduction of ≥6 points, and ≥90% of patients reported well-controlled disease based on Angioedema Control Test (AECT) scores. Patients indexed to placebo experienced a mean improvement in health-related quality of life questionnaire for hereditary angioedema (AE-QoL) total scores by 24 points from OASIS-HAE baseline (36).

5.2.4 Please provide a qualitative description of safety data. Differences in definitions of outcomes between studies

In section 5.2.4.1 and 5.2.4.2, descriptions of safety data are provided.

Differences in definitions of outcomes between the studies are not described here in section 5.2.4. Instead, please refer to section 5.1.2 for a description of the comparability between studies, which also includes a comparison of outcomes.

5.2.4.1 Safety data from OASIS-HAE

The safety objective was to evaluate the safety and tolerability of donidalorsen in patients with HAE. The safety endpoints included assessment of the number, type, severity, and dose-relationship of AEs; clinical laboratory parameters, vital signs and electrocardiograms. In the Safety Set (all randomised patients who received at least one dose of study drug (donidalorsen or placebo)), the proportion of patients who experienced at least one TEAE was higher in the placebo group than the Q4W group, with 73.3% of patients in the Q4W group experiencing a TEAE, 60.9% in the Q8W group and 81.8% in the placebo group. More patients in the placebo group (27%) experienced a TEAE related to the study drug than in the Q8W group (17%). No deaths were reported during this study. These data demonstrate that donidalorsen is well tolerated among patients, which is key to ensuring there is minimal impact due to treatment on patient’s health-related quality of life (HRQoL) – a key factor for patient satisfaction. An overview of the observed AEs is presented in Table 21.

Table 21: Adverse events (Safety Set)

Parameter	Placebo (N = 22) n (%)	Donidalorsen 80 mg Q4W (N = 45) n (%)	Donidalorsen 80 mg Q8W (N = 23) n (%)
Patients with any AE	19 (86.4)	33 (73.3)	15 (65.2)

Patients with any TEAE[a]	18 (81.8)	33 (73.3)	14 (60.9)
Patients with any TEAE related to study drug[b]	6 (27.3)	19 (42.2)	4 (17.4)
Patients with any TEAE by maximum severity			
Mild	7 (31.8)	17 (37.8)	5 (21.7)
Moderate	9 (40.9)	15 (33.3)	7 (30.4)
Severe	2 (9.1)	1 (2.2)	2 (8.7)
Patients with any TEAE related to study drug by maximum severity			
Mild	5 (22.7)	15 (33.3)	3 (13.0)
Moderate	1 (4.5)	3 (6.7)	1 (4.3)
Severe	0	1 (2.2)	0
Patients with any SAE	1 (4.5)	0	0
Patients with any SAE related to study drug	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	0	1 (4.3)
Patients with any TEAE leading to permanent treatment discontinuation related to study drug	0	0	1 (4.3)

Abbreviations: AE = adverse event; Q4W = every 4 weeks; Q8W = every 8 weeks; SAE = serious adverse event; 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).
Source: Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2).

The majority of TEAEs were mild or moderate in severity. A full breakdown on the type of TEAE observed in >5% of patients is provided below in Table 22. The most commonly reported TEAEs in the Q4W group were headache (13.3%), injection site reactions (13.3%), and nasopharyngitis (11.1%). In the placebo group there were no injection site reactions however, the headache (18.2%) rates and nasopharyngitis (18.2%) rates were higher. The most commonly reported AEs in the Q8W group were influenza (17.4%), nasopharyngitis (13.0%), and headache (8.7%).

Table 22: Treatment-emergent adverse event in >5% of patients (Safety Set)

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]	18 (81.8)	33 (73.3)	14 (60.9)
Headache	4 (18.2)	6 (13.3)	2 (8.7)
Injection site erythema	0	6 (13.3)	1 (4.3)
Nasopharyngitis	4 (18.2)	5 (11.1)	3 (13.0)
Upper respiratory tract infection	1 (4.5)	4 (8.9)	2 (8.7)
Urinary tract infection	0	4 (8.9)	2 (8.7)
Injection site discolouration	0	3 (6.7)	1 (4.3)
Injection site pruritus	0	3 (6.7)	0
Injection site pain	0	3 (6.7)	0
Abdominal discomfort	0	3 (6.7)	0
Influenza	2 (9.1)	2 (4.4)	4 (17.4)
Abdominal pain	2 (9.1)	1 (2.2)	0
Covid-19	2 (9.1)	1 (2.2)	0
Gastroenteritis	2 (9.1)	1 (2.2)	1 (4.3)
Dyspepsia	2 (9.1)	0	0

Limb injury	4 (18.2)	0	1 (4.3)
Oral herpes	0	0	2 (8.7)
Sinusitis	2 (9.1)	0	0
Vomiting	1 (4.5)	0	2 (8.7)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; Q4W = every 4 weeks; Q8W = every 8 weeks; TEAE - treatment-emergent adverse event.
Note: The table was sorted by the frequency of TEAEs in the "donidalorsen 80 mg Q4W" column in descending order. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 26.1. [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: Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2).

5.2.4.2 Safety data from HELP

In the following, safety data from the phase III HELP trial are assessed in a pooled analysis across all three lanadelumab treatment arms (150 mg Q4W, 300 mg Q2W, and 300 mg Q4W). The most commonly reported TEAEs (excluding HAE attacks) in patients treated with lanadelumab during the entire treatment period were injection site pain (42.9%), viral upper respiratory tract infection (23.8%), headache (20.2%), injection site erythema (9.5%), injection site bruising (7.1%), and dizziness (6.0%). Most TEAEs (98.5%) were mild to moderate in severity. The most commonly reported TEAEs in patients treated with lanadelumab that were considered related to treatment were injection site pain (41.7%), injection site erythema (9.5%), injection site bruising (6.0%), and headache (7.1%). There were no deaths or related serious TEAEs (3).

In total, two patients who received placebo withdrew from the study due to TEAEs of tension headache and HAE attack, which were of moderate severity. One patient in the lanadelumab 300 mg Q4W group with metabolic syndrome, fatty liver, and multiple concomitant suspect medications withdrew due to isolated, asymptomatic, and transient elevation of alanine transaminase (140 U/L) and aspartate transaminase (143 U/L) classified as related and severe on day 139 (3).

Table presents adverse events in the individual treatment arms of interest (placebo, lanadelumab 300 mg Q2W, and lanadelumab 300 mg Q4W), as well as across all three lanadelumab treatments arms (150 mg Q4W, 300 mg Q2W, and 300 mg Q4W).

Table 23: Adverse events[a]

Adverse events[b]	Placebo (N = 41) n (%)	Lanadelumab 300 mg Q2W (N = 27) n (%)	Lanadelumab 300 mg Q4W (N = 29) n (%)	All lanadelumab treatment arms* (N = 84) n (%)

Any AE	31 (75.6)	26 (96.3)	25 (86.2)	76 (90.5)
Injection site pain	12 (29.3)	14 (51.9)	9 (31.0)	36 (42.9)
Viral upper respira-tory tract infection	11 (26.8)	10 (37.0)	7 (24.1)	20 (23.8)
Headache	8 (19.5)	9 (33.3)	5 (17.2)	17 (20.2)
Injection site				
Erythema	1 (2.4)	2 (7.4)	2 (6.9)	8 (9.5)
Bruising	0	1 (3.7)	2 (6.9)	6 (7.1)
Dizziness	0	1 (3.7)	3 (10.3)	5 (6.0)
Any TEAE[c]	14 (34.1)	19 (70.4)	14 (48.3)	50 (59.5)
Injection site				
Pain	11 (26.8)	14 (51.9)	9 (31.0)	35 (41.7)
Erythema	1 (2.4)	2 (7.4)	2 (6.9)	8 (9.5)
Bruising	0	1 (3.7)	2 (6.9)	5 (6.0)
Headache	1 (2.4)	3 (11.1)	2 (6.9)	6 (7.1)
Any SAE	0	1 (3.7)	3 (10.3)	4 (4.8)
Any related SAE	0	0	0	0
Any AE leading to dis-continuation	1 (2.4)[d]	0	1 (3.4)	1 (1.2)

Abbreviations: AE = adverse event; Q2W = every 2 weeks; Q4W = every 4 weeks; TEAE = treatment-emergent adverse event; SAE = serious adverse event.
Notes: * All lanadelumab treatment arms include 150 mg Q4W, 300 mg Q2W, and 300 mg Q4W. [a] All patients received injections Q2W, with those in the Q4W groups receiving placebo in between active treatments. [b] TEAEs that were reported at the Preferred Term level in 5% or more of patients in the total lanadelumab-treated group and excludes HAE attack–reported events. Adverse events were collected over the entire treatment period and were assigned to the treatment group without regard to the type of injection (i.e., placebo or active drug in the 300 mg Q4W group). [c] Adverse events that were judged by the investigator to be related to the use of the investigational product. [d] One patient withdrew due to a hereditary angioedema attack and is not included.
Source: Banerji et al. 2018 (3).

5.2.5 Method of synthesis

5.2.5.1 Network meta-analysis: objective and network of relevant studies

There are no head-to-head studies comparing donidalorsen with other LTPs; therefore, an indirect comparison was necessary, and an NMA was selected as the most appropriate method given the availability of multiple licensed treatments and therapies seeking regulatory approval across European markets. The methodology of the NMA is described briefly here in the subsections of section 5.2.5, while Appendix C provides additional information on the methodology and associated trials.

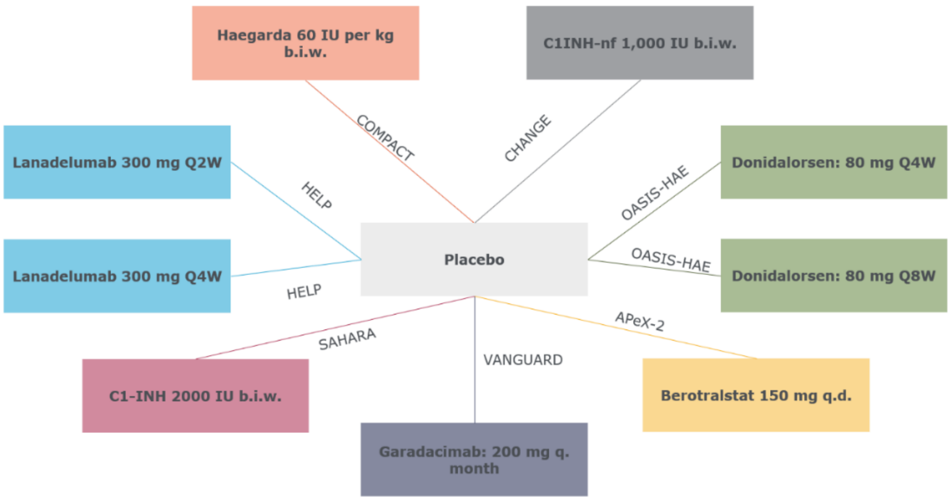
For the purpose of the NMA, a clinical SLR was undertaken on the 22nd of April 2025 (NMA was based on the original SLR with cut-off date 6th of June 2024, but no additional relevant publications were identified in SLR update with cut-off date 22nd of April 2025) to identify all relevant efficacy and safety data in studies conducted with HAE types I and II, for patients aged 12 years or older (the SLR is presented in Appendix D).

5.2.5.2 Feasibility assessment

Following the clinical SLR, a feasibility assessment was undertaken to evaluate whether an NMA of the randomised controlled trials (RCTs) is feasible. The assessment followed standard guidelines, including those by National Institute for Health and Care Excellence (NICE) Decision Support Unit guidance (DSU) and the Cochrane Handbook, to estimate the relative effect of two or more interventions when there are no direct head-to-head studies comparing the treatments directly (37).

The identified studies provided a connected network of evidence such that donidalorsen is indirectly connected to the comparators of interest as presented in Figure 3.

Figure 3 Connected evidence network



Abbreviations: b.i.w. = twice a week; C1-INH = C1-esterase inhibitor; C1INH-nf = nano filtered C1 inhibitor; IU = international units; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 4 weeks; q.d. = every day; q. month = every month.

All identified studies and associated LTP treatments are presented in Table 24 as they reflect the licensed LTP treatments across different European markets, although OASIS-HAE (2) and HELP (3) are the studies of interest in this application.

Table 24 NMA treatment comparators

Trial	Intervention dose	Dosing frequency	Route	Source
OASIS-HAE	**Donidalorsen 80 mg**	**Q4W** **Q8W**	**SC**	**Riedl et al. 2024 (2)**
HELP	**Lanadelumab 300 mg**	**Q2W** **Q4W**	**SC**	**Banerji et al. 2018 (3)**
VANGUARD	Garadacimab 200 mg	Every month	SC	Craig et al. 2023 (42)
APeX-2	Berotralstat 150 mg	Everyday	Oral	Zuraw et al. 2021 (43)
COMPACT	C1-INH 60 IU/kg (Haegarda*)	Q2W	SC	Longhurst et al. 2017 (46)
CHANGE	C1-INH n.f. (Cinryze) 1,000 IU	Q2W	IV	Zuraw et al. 2010 (38)
SAHARA	Pd C1-INH 2,000 IU	Q2W	SC	Lumry et al. 2019 (39)

Abbreviations: C1-INH = C1-esterase inhibitor; IU = international unit; IV = intravenous; n.f. = nanofiltered Pd = Plasma derived; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Notes: *Marketed as Berinert in the United Kingdom.

The feasibility assessment concluded that a total of four studies, alongside OASIS-HAE (2), met the inclusion criteria for the NMA; HELP (3), VANGUARD (42), APeX-2 (43) and COMPACT (46). Notably, the CHANGE (38) and SAHARA (39) studies were excluded from the network due to the lack of a washout period, which may introduce bias. Key findings from the feasibility assessment of all studies are summarised in Appendix C.

It was concluded that it is feasible to conduct NMAs for the following outcomes of interest:

- the mean monthly attack rate,
- percentage of patients who achieved ≥90% reduction in attacks from baseline,
- mean monthly moderate or severe attack rate, and
- change in total AE-QoL scores.

The feasibility of the outcomes of interest were validated by two HAE clinical experts (40,41).

Data for all five studies included in the network per outcome was included as follows:

- To compare the proportion of patients achieving ≥90% reduction in HAE attacks from baseline, placebo data is based on OASIS-HAE (2), VANGUARD (42), HELP (3), and APeX-2 (43) studies.
- For the mean number of attacks per month, placebo data is based on all included studies: OASIS-HAE (2), VANGUARD (42), HELP (3), APeX-2 (43) and COMPACT (46).
- To compare the mean number of moderate or severe HAE attacks, placebo data is based on OASIS-HAE (2), VANGUARD (42), and HELP (3) studies.
- For the change in total AE-QoL score from baseline, placebo data is based on with the OASIS-HAE (2), VANGUARD (42), HELP (3), and APeX-2 (43) studies.

In this application, we focus the comparison of donidalorsen (based on OASIS-HAE (2)) and lanadelumab (based on HELP (3)) as lanadelumab is the relevant comparator. A detailed comparison of the two studies is provided in section 5.1.2. The primary objective of the comparison is to estimate the comparative efficacy and QoL of donidalorsen Q4W against donidalorsen Q8W, lanadelumab Q2W, and lanadelumab Q4W.

5.2.5.3 Statistical analyses

Random effects models account for heterogeneity between studies whilst fixed effects models do not and therefore may be considered less relevant and can lead to artificially narrow CrIs. Therefore, the random effects model is considered as the most relevant model in this analysis and were run for each outcome as recommended by the Multi-parameter Evidence Synthesis Research Group (44).

The analysis included three endpoints: count, binary, and continuous outcomes. Donidalorsen Q4W was used as the reference treatment for these analyses. For count data endpoints, namely mean number of HAE attacks per month and mean number of moderate or severe HAE attacks per month, reported data on numbers of attacks, were analysed to synthesise RRs and CrIs, assuming a Poisson distribution for the total number of attacks reported within each study. The binary outcome, namely proportion of patients experiencing ≥90% reduction in attacks from baseline, was analysed to synthesise ORs, assuming a binomial distribution for the numbers of patients achieving the ≥90% reduction reported within each study. The continuous endpoint, namely mean change from baseline in AE-QoL score, was analysed to synthesise the mean change from baseline in this score, along with CrIs, assuming a normal distribution for the change from baseline in AE-QoL reported within each study.

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:

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

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. A summary of the assumptions and calculations are highlighted in Appendix C (Table 3535).

5.2.6 Results from the comparative analysis

Table 25 presents a summary of the results from the NMA for the two treatments in focus for this application; donidalorsen (based on OASIS-HAE (2)) and lanadelumab (based on HELP (3)) as lanadelumab is the relevant comparator. Donidalorsen Q4W is the reference treatment for all analyses, such that results are presented as the treatment effect of donidalorsen Q4W versus comparators. Each outcome was analysed in the ITT population. Complete results versus all comparators included in the NMA are presented in the following sections.

A statistically significant higher proportion of patients achieving a ≥90% reduction in attacks was associated with donidalorsen Q4W compared with placebo. No statistically significant differences in the proportion of patients achieving a ≥90% reduction in attacks were observed between donidalorsen Q4W, donidalorsen Q8W, and both lanadelumab regimens (Q2W and Q4W). The proportion of patients achieving a ≥90% reduction in HAE attacks from baseline treatment effects is depicted in Figure 4.

A statistically significant lower mean number of HAE attacks per month was associated with donidalorsen Q4W compared with placebo. No statistically significant differences in mean monthly HAE attacks were observed between donidalorsen Q4W, donidalorsen Q8W, and both lanadelumab regimens. The mean number of HAE attacks per month is depicted in

Figure 5.

Donidalorsen Q4W was associated with a statistically significant lower mean number of moderate/severe attacks vs placebo. No statistically significant differences in mean number of moderate/severe attack rates were observed between donidalorsen Q4W, donidalorsen Q8W, and both lanadelumab regimens. The mean number of moderate/severe attacks per month is depicted in Figure 6.

Donidalorsen Q4W was associated with a statistically significant higher mean difference from baseline in AE-QoL score vs placebo. No statistically significant differences were observed in mean difference from baseline in AE-QoL score between donidalorsen Q4W and either lanadelumab regimens. The mean differences from baseline in AE-QoL scores are depicted in Figure 7.

Table 25 Results from the comparative analysis of donidalorsen vs. lanadelumab for adults and adolescents patient aged 12 years and older with HAE

Outcome measure	Donidalorsen 80 mg Q8W	Lanadelumab 300 mg Q2W	Lanadelumab 300 mg Q4W	Placebo
Median OR for proportion of patients achieving a ≥90% reduction in HAE attacks from baseline (95% Crl)	0.66 (0.14, 3.13)	7.26 (0.45, 132.76)	4.34 (0.30, 80.14)	0.15 (0.02, 0.81)*
Median RRs for mean number of HAE attacks per month (95% Crl)	2.32 (0.67, 8.28)	0.67 (0.11, 4.02)	1.38 (0.23, 8.93)	5.15 (1.48, 18.06)*
Median RRs for mean number of moderate or severe HAE attacks per month (95% Crl)	3.24 (0.90, 11.69)	0.91 (0.16, 5.54)	1.44 (0.24, 8.93)	5.61 (1.59, 20.73)*
Median mean difference from baseline in AE-QoL score (95% Crl)	4.82 (-3.91, 13.57)	1.75 (-11.08, 4.56)	5.64 (-7.02, 18.36)	18.35 (9.27, 27.42)*

Abbreviations: AE-QoL = Angioedema Quality of Life; Crl = credible interval; HAE = hereditary angioedema; OR = odds ratio; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; RR = rate ratio.

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

5.2.6.1 Proportion of patients achieving ≥90% reduction in HAE attacks

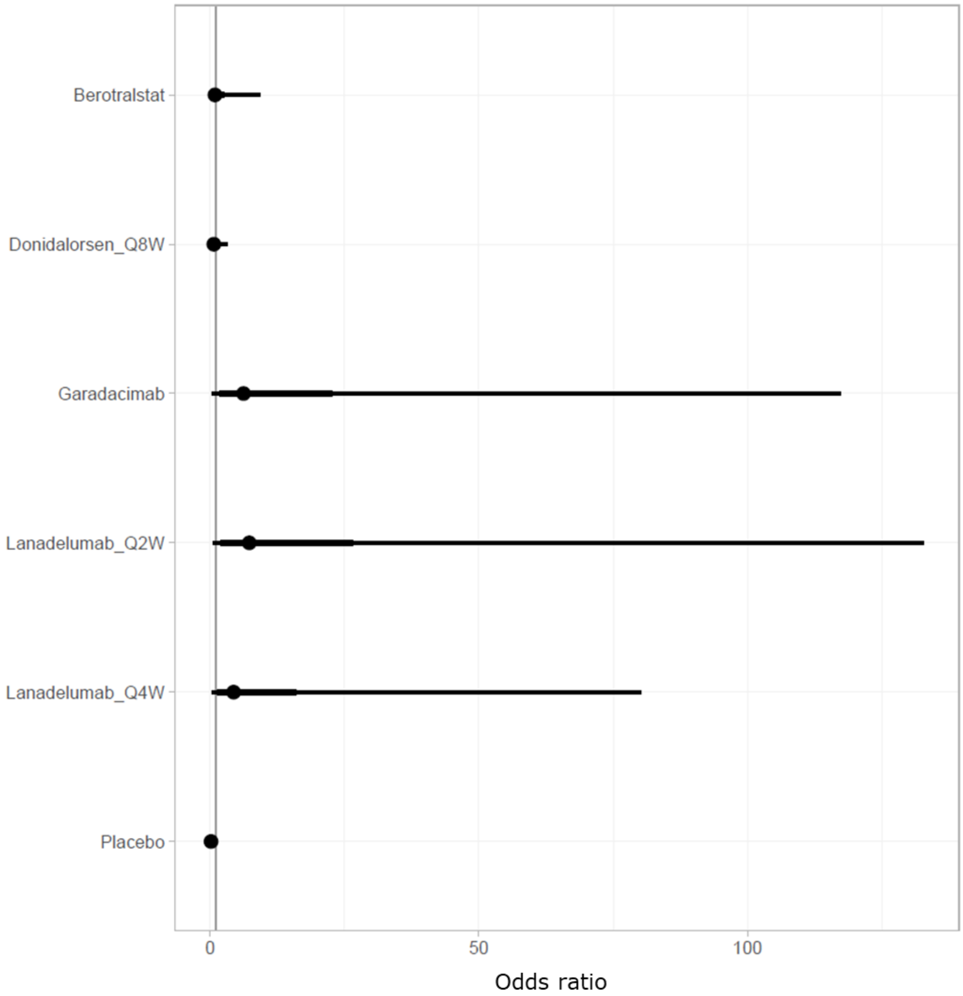
Median odds ratios and 95% CrIs from the RE model are shown in Table 26 and the forest plot in Figure 4. No statistically significant differences were observed between donidalorsen Q4W and berotralstat, donidalorsen Q8W, garadacimab, or both lanadelumab regimens for the proportion of patients achieving a ≥90% reduction in attacks from baseline; the corresponding 95% credible intervals for the median odds ratios all included 1. Donidalorsen Q4W was associated with a numerically higher median odds ratio for the proportion of patients achieving a ≥90% reduction in attacks compared with berotralstat, and donidalorsen Q8W; donidalorsen Q4W was associated with a numerically lower median odds ratio for the proportion of patients achieving a ≥90% reduction in attacks compared with garadacimab and both lanadelumab regimens.
Donidalorsen Q4W was associated with a statistically significant higher median odds ratio for the proportion of patients achieving a ≥90% reduction in attacks compared with placebo, as the 95% credible interval for the odds ratio lay entirely below 1.

Table 26 Median odds ratios and 95% CrIs for proportion of patients achieving a ≥90% reduction in HAE attacks from baseline

Treatment	Median odds ratio (95% CrI)
Berotralstat	0.88 (0.07, 9.29)
Donidalorsen_Q8W	0.66 (0.14, 3.13)
Garadacimab	6.19 (0.40, 117.28)
Lanadelumab_Q2W	7.26 (0.45, 132.76)
Lanadelumab_Q4W	4.34 (0.30, 80.14)
Placebo	0.15 (0.02, 0.81)*

*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; RE – Random effects.

Figure 4 Forest plot – proportion of patients achieving a ≥90% reduction in HAE attacks from baseline treatment effects



Abbreviations: HAE – Hereditary angioedema; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks; RE – Random effects.

5.2.6.2 Mean number of HAE attacks per month

Rate ratios and 95% CrIs from the Random Effects model are shown in Table 27 and the forest plot in Figure 5. No statistically significant differences were observed between donidalorsen Q4W and donidalorsen Q8W, both lanadelumab regimens, berotralstat, garadacimab, or Haegarda for the mean number of HAE attacks per month; the corresponding 95% credible intervals for the median rate ratios all included 1. Donidalorsen Q4W was associated with a numerically lower median rate ratio for the mean number of HAE attacks per month compared with berotralstat, and donidalorsen Q8W, and lanadelumab Q4W; donidalorsen Q4W was associated with a numerically higher median rate ratio for the mean number of HAE attacks per month compared with garadacimab, Haegarda, and lanadelumab Q2W.

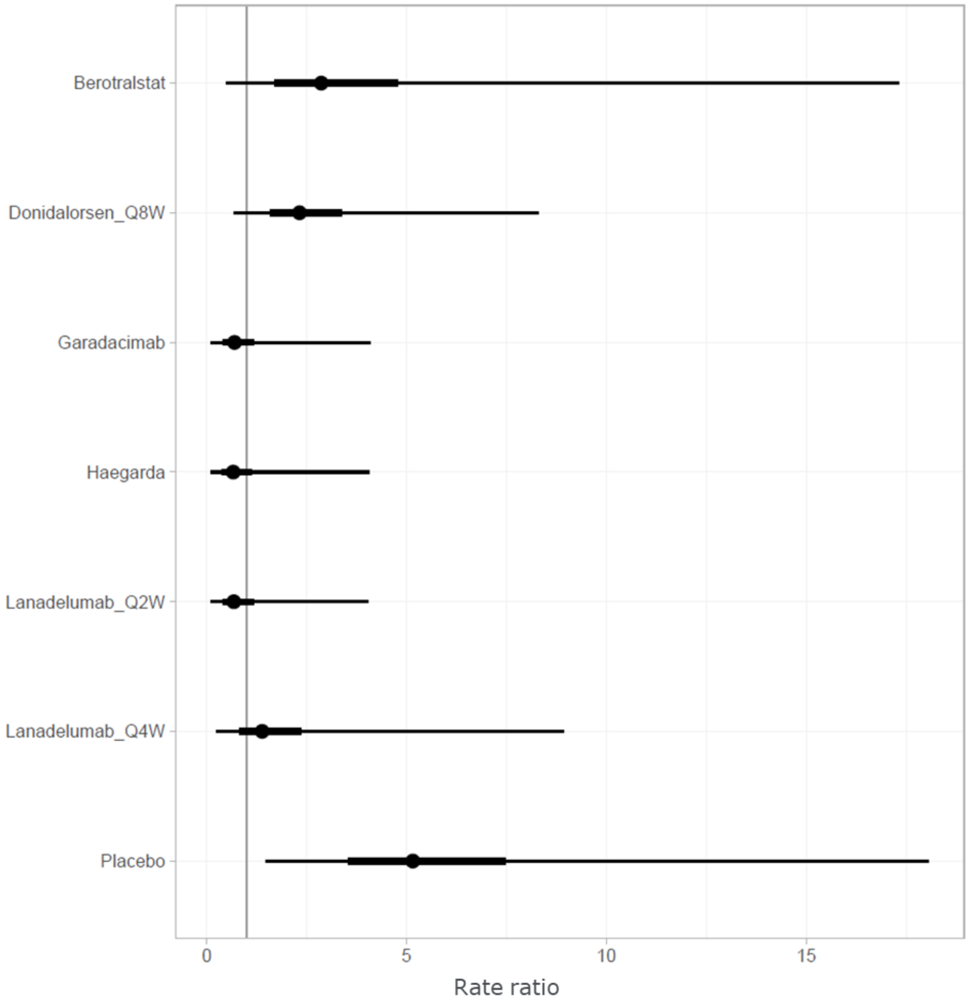
Donidalorsen Q4W was associated with a statistically significant lower median rate ratio for the mean number of HAE attacks per month compared with placebo, as the 95% credible interval for the rate ratio lay entirely above 1.

Table 27 Median rate ratios and 95% CrIs for mean number of HAE attacks per month

Treatment	Median rate ratio (95% CrI)
Berotralstat	2.86 (0.49, 17.32)
Donidalorsen_Q8W	2.32 (0.67, 8.28)
Garadacimab	0.69 (0.11, 4.09)
Haegarda	0.66 (0.11, 4.07)
Lanadelumab_Q2W	0.67 (0.11, 4.02)
Lanadelumab_Q4W	1.38 (0.23, 8.93)
Placebo	5.15 (1.48, 18.06)*

*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 – median rate ratios and 95% CrIs – endpoint: mean number of HAE attacks per month treatment effects



Abbreviations: HAE = hereditary angioedema; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks.

5.2.6.3 Mean number of moderate or severe HAE attacks per month

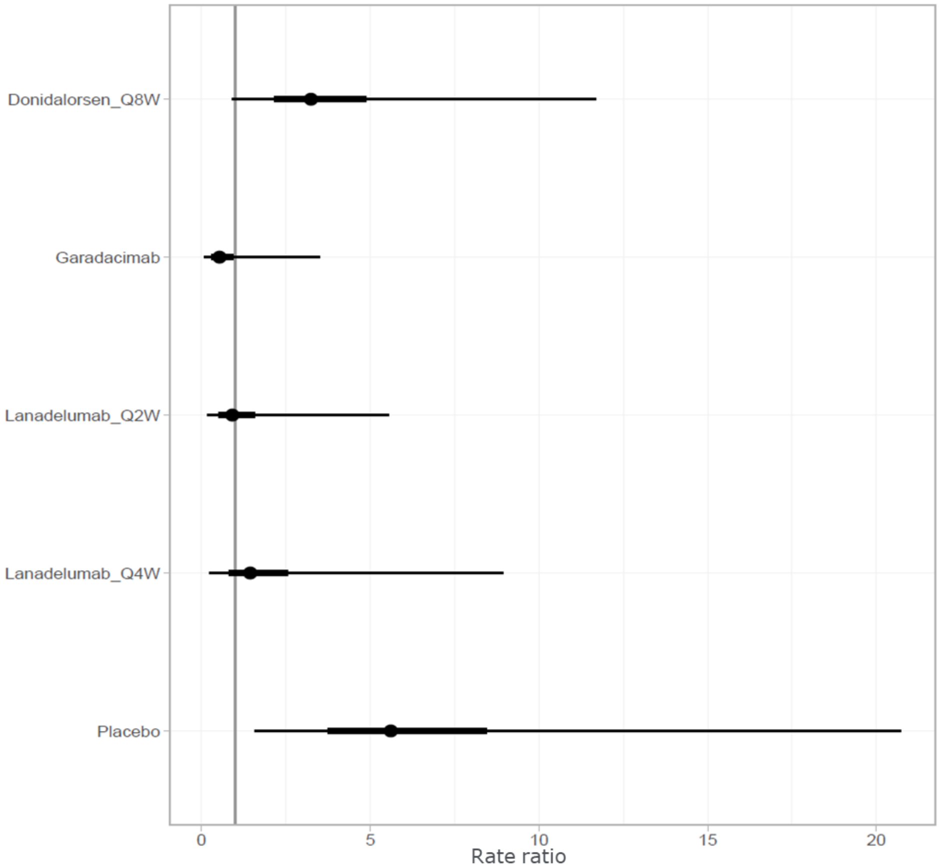
Rate ratios and 95% CrIs from the Random Effects model are shown in Table 28 and the forest plot in Figure 6. No statistically significant differences were observed between donidalorsen Q4W and donidalorsen Q8W, garadacimab, or both lanadelumab regimens for the mean number of moderate or severe attacks per month; the corresponding 95% credible intervals for the median rate ratios all included 1. Donidalorsen Q4W was associated with a numerically lower median rate ratio for the mean number of moderate or severe attacks per month compared with donidalorsen Q8W, and lanadelumab Q4W; donidalorsen Q4W was associated with a numerically higher median rate ratio for the mean number of moderate or severe attacks per month compared with garadacimab and lanadelumab Q2W. Donidalorsen Q4W was associated with a statistically lower median rate ratio for the mean number of moderate or severe attacks per month compared with placebo, as the 95% credible interval for the rate ratio lay entirely above 1.

Table 28 Median rate ratios and 95% CrIs for mean number of moderate or severe HAE attacks per month

Treatment	Median rate ratio (95% CrI)
Donidalorsen_Q8W	3.24 (0.90, 11.69)
Garadacimab	0.53 (0.09, 3.51)
Lanadelumab_Q2W	0.91 (0.16, 5.54)
Lanadelumab_Q4W	1.44 (0.24, 8.93)
Placebo	5.61 (1.59, 20.73)*

*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 6 Forest plot – median rate ratios and 95% CrIs – endpoint: mean number of moderate or severe HAE attacks per month treatment effects



Abbreviations: CrI – Credible interval; HAE = hereditary angioedema; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks.

5.2.6.4 Mean change from baseline in AE-QoL score

Mean differences and 95% CrIs from the Random Effects model are shown in Table 29 and the forest plot in Figure 7. No statistically significant differences were observed between donidalorsen Q4W and donidalorsen Q8W, or both lanadelumab regimens for the mean difference from baseline in AE-QoL score; the corresponding 95% credible interval for the mean difference included 0. Donidalorsen Q4W was associated with a numerically larger mean difference from baseline in AE-QoL score compared with donidalorsen Q8W and both lanadelumab regimens.

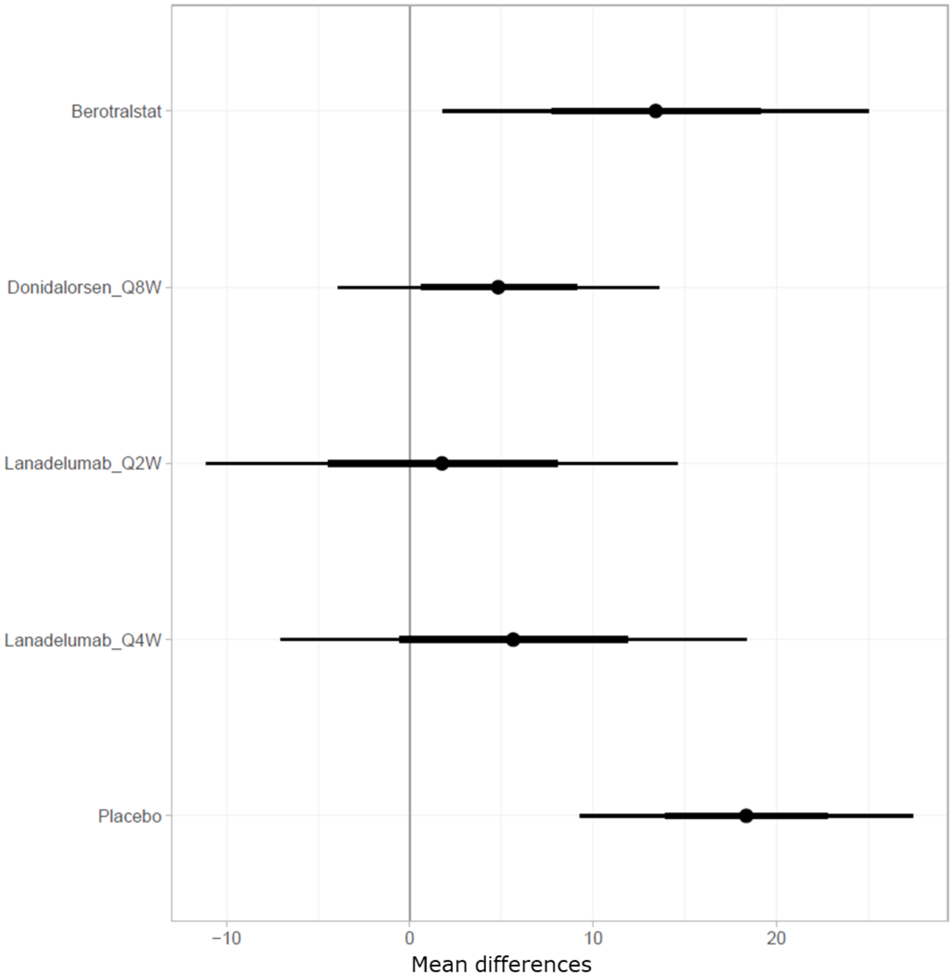
Donidalorsen Q4W was associated with a statistically significant larger mean difference from baseline in AE-QoL score compared with berotralstat and placebo, as the 95% CrIs for the mean differences lay entirely above 0.

Table 29 Mean difference and 95% CrIs from baseline in AE-QoL score

Treatment	Mean difference (95% CrI)
Berotralstat	13.41 (1.81, 24.99)*
Donidalorsen_Q8W	4.82 (-3.91, 13.57)
Lanadelumab_Q2W	1.75 (-11.08, 4.56)
Lanadelumab_Q4W	5.64 (-7.02, 18.36)
Placebo	18.35 (9.27, 27.42)*

*95% CrI does not include 1 and is therefore considered statistically significant
Abbreviations: AE-QoL - Angioedema Quality of Life Questionnaire; CrI – Credible interval; HAE – Hereditary angioedema; Q2W – every 2 weeks; Q4W – every 4 weeks; Q8W – every 8 weeks.

Figure 7 Forest plot – Median differences and 95% CrIs – endpoint: Mean difference from base-line in AE-QoL score treatment effects



Abbreviations: AE-QoL = Angioedema Quality of Life; CrI – Credible interval; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks.

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Appendix A. Main characteristics of studies included

Table 30 Main characteristic of studies included: OASIS-HAE

Trial name: OASIS-HAE		**NCT number: NCT05139810**
Objective	The purpose of this study was to evaluate the safety and efficacy of donidalorsen in participants with HAE and effect of donidalorsen on the quality and pattern of HAE attacks and their impact on QoL.	
Publications – title, author, journal, year	Efficacy and Safety of Donidalorsen for Hereditary Angioedema. Riedl MA, Tachdjian R, Lumry WR, Craig T, Karakaya G, Gelincik A, Stobiecki M, Jacobs JS, Gokmen NM, Reshef A, Gompels MM, Manning ME, Bordone L, Newman KB, Treadwell S, Wang S, Yarlas A, Cohn DM; OASIS-HAE Team. N Engl J Med. 2024 . Patient-Reported Outcomes in the Phase III OASIS-HAE Study of Donidalorsen for Hereditary Angioedema. Riedl MA, Yarlas A, Bordone L, Treadwell S, Wang S, Newman KB, Cohn DM. Allergy. 2025 (27). Novel Long-Term Prophylactic and On-Demand Therapies for Hereditary Angioedema. Wu AY, Banerji A. J Allergy Clin Immunol Pract. 2025 (24).	
Study type and design	Double-blinded randomised placebo-controlled phase 3 study. 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 via the Interactive Response Technology. Data from patients receiving placebo in both Cohort A and Cohort B were pooled for analyses; this pooled placebo group is referred to as the placebo group. No crossover was allowed. The participants, care providers, investigators, and outcomes assessors were masked throughout the study until all patients had completed the study and the database had been locked. The study is completed.	
Sample size (n)	91 patients	
Main inclusion criteria	1. Participants, or their legally appointed and authorised representatives, must provide written and signed informed consent form/assent 2. Participants must be aged ≥ 12 years at the time of informed consent and, as applicable, assent 3. Participants must have a documented diagnosis of HAE-C1INH-Type1/HAE-C1INH-Type2 4. Participants must:	

Trial name: OASIS-HAE	NCT number: NCT05139810
	1. Experience a minimum of 2 HAE attacks (confirmed by the Investigator) during the Screening Period 2. Be willing to complete the participant reported out-comes assessments throughout the study 5. Participants must have access to, and the ability to use acute medication(s) to treat angioedema attacks
Main exclusion criteria	1. Concurrent diagnosis of any other type of recurrent angi-oedema, including acquired, idiopathic angioedema or HAE with normal C1-INH (also known as HAE Type III) 2. Any clinically-significant abnormalities in screening laboratory values that would render a participant unsuitable for inclusion in the study 3. Treatment with another investigational drug or biological agent within 1 month or 5 half-lives, whichever is longer, of Screening 4. Participated in a prior ISIS 721744 study (NCT04030598) 5. Exposure to any of the following medications: 1. Angiotensin-converting enzyme (ACE) inhibitors or any oestrogen containing medications with systemic absorption within 4 weeks prior to Screening 2. Chronic prophylaxis with Takhzyro, Haegarda, Cin-ryze and Ruconest or Orladeyo within 5 half-lives prior to Screening 3. Oligonucleotides (including small interfering ribonu-cleic acid) within 4 months of Screening if single dose received, or within 12 months of Screening if multi-ple doses received. This exclusion does not apply to vaccines 6. Recent history (3 years) of, or current drug or alcohol abuse
Intervention	Donidalorsen 80 mg administered SC Q4W at Weeks 1, 5, 9, 13, 17, and 21. 46 patients were randomly assigned to this group. Donidalorsen 80 mg administered SC Q8W at Weeks 1, 9, and 17. 23 pa-tients were randomly assigned to this group.
Comparator(s)	Placebo 80 mg administered SC Q4W or placebo 80 mg administered SC Q8W. Data from patients receiving placebo were pooled for analysis to form the placebo group, which included 22 patients randomly assigned to it.
Follow-up time	The median duration of active study drug (donidalorsen) exposure was 168.01 days (25th percentile, 75th percentile: 167.00 to 169.07) in the

Trial name: OASIS-HAE	NCT number: NCT05139810
	Q4W group and 167.96 days (25th percentile, 75th percentile: 166.81 to 170.01) in the Q8W group. >50% of patients in every treatment arm completed the study treatment. Therefore, the median follow-up was at least 24 weeks.
Primary, secondary and exploratory endpoints	**Endpoints included in this application** Primary and secondary endpoints included are Percentage of Investigator-confirmed HAE attack-free patients from Week 5 to Week 25, Percentage of patients with Attack Rate (per 4 weeks) Reduction of ≥ 90% from baseline between Week 5 and 25, Time-normalised number of Investigator-confirmed HAE attacks (per 4 weeks) from Week 1 to Week 25, Time-normalised number of moderate or severe Investigator-confirmed HAE attacks (per 4 weeks) from Week 5 to Week 25, and Change from Baseline in AE-QoL questionnaire total score at Week 25. Specifically, the primary endpoint was Time-normalised number of Investigator-confirmed HAE attacks (per 4 weeks) from Week 1 to Week 25 compared to placebo for the Q4W group, while Time-normalised number of Investigator-confirmed HAE attacks (per 4 weeks) from Week 1 to Week 25 compared to placebo for the Q8W group was a secondary outcome. All other endpoints listed above were secondary endpoints. The exploratory endpoint "Percentage of patients with an AE-QoL improvement of at least 6 points from Baseline" and the safety endpoint "Percentage of patients who discontinued treatment permanently due to AEs" are included as well. Additionally, a qualitative review of the safety profile of donidalorsen is included. **Other endpoints** Secondary endpoints not included in this application are Time-normalised number of Investigator-confirmed HAE attacks (per 4 weeks) from Week 5 to Week 25, Number of patients with a clinical response defined as a ≥ 50% or ≥ 70% reduction from Baseline (i.e., screening rate) in Investigator-confirmed HAE attack rate between Week 5 to Week 25, Percent patients who are well controlled on the AECT at Week 25, and Number of Investigator-confirmed HAE attacks requiring acute HAE therapy from Week 5 to Week 25. Exploratory endpoints not included in this application are change or percent change from Baseline in the following: PKK level in plasma; Generalized Anxiety Disorder 7 (GAD-7) questionnaire score; EuroQoL-5-Dimensions questionnaire (EQ-5D-5L) health index and visual analogue scale (VAS); Patient Global Impression of Severity (PGIS); WPAI score; Change in each AE-QoL questionnaire domain score; Time-normalised number of Investigator-confirmed HAE attacks (per 4 week) from Week 17 to Week 25; Incidence of all cause and HAE attack-related emergency room visits, hospitalizations, and total inpatient days; Patient Global Impression of Change (PGIC); and Pharmacokinetics (potential exposure-response analysis using relevant exposure parameters (such as donidalorsen plasma C_{trough}) and biomarkers (plasma PKK) and/or clinical endpoints, as appropriate).

Trial name: OASIS-HAE	NCT number: NCT05139810
Method of analysis	Different methods were used to analyse each endpoint. Please see section 5.2.1.1-5.2.1.6 as well as Appendix B. The results are presented for the Full Analysis Set (n = 90), which includes all randomised patients who received at least one dose of study drug (donidalorsen or placebo).
Subgroup analyses	Pre-specified exploratory subgroup analyses were performed on the primary efficacy endpoint for age, sex, race, regions, and if the patient had taken any predefined prophylactic therapy. The subgroups include the following: • Age Category (12 to 17, 18 to 39, 40–64, ≥ 65) • Sex (Male, Female) • Race (Caucasian, Other/multiple) • Regions (North America, Europe, Middle East) • Taken any predefined prophylactic therapy, including lanadelumab, berotralstat, C1-INH? (Yes, No) In addition, pre-specified exploratory subgroup analyses were to be conducted on the primary endpoint and other preselected efficacy endpoints if any patient was considered to have a clinical history and/or screening period/Baseline HAE attack rate that is atypical for patients with HAE-C1INH-Type1 or HAE-C1INH-Type2, which may compromise the interpretation of the efficacy data (“atypical patients”); “atypical patients” were determined by the Medical Monitor and/or Investigators. Any “atypical patients” were identified prior to unblinding the data. The exploratory subgroup analyses would be based on “typical patients” (i.e., excluding “atypical patients”). These subgroup analyses are provided as change and percent change from Baseline for time-normalised Investigator-confirmed HAE attack rate from Week 1 to Week 25.
Other relevant information	N/A

Abbreviations: ACE = angiotensin-converting enzyme; AE = Adverse event; AECT = Angioedema Control Test; AE-QoL = Angioedema Quality of Life; C1-INH = C1-esterase inhibitor; EQ-5D-5L = EuroQoL-5-Dimensions questionnaire; GAD-7 = Generalized Anxiety Disorder 7; HAE = Hereditary angioedema; HAE-C1 inhibitor-Type 1 = HAE-C1INH-Type1; HAE-C1 inhibitor-Type 2 = HAE-C1INH-Type2; N/A = Not applicable; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PKK = Prekallikrein; QoL = Quality of life; Q4W = every 4 weeks; Q8W = every 8 weeks; VAS = visual analogue scale; WPAI = Work Productivity and Activity Impairment.
Source: ClinicalTrials.gov, 2021 (29); Ionis Pharmaceuticals, Inc., 2024 (23).

Table 31 Main characteristic of studies included: HELP

Trial name: HELP	**NCT number: NCT02586805**
Objective	To evaluate the efficacy and safety of lanadelumab in preventing acute angioedema attacks in patients with Type I and Type II HAE.
Publications – title, author, journal, year	Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. Banerji A, Riedl MA, Bernstein JA, Cicardi M, Longhurst HJ, Zuraw BL, Busse PJ, Anderson J, Magerl M, Martinez-Saguer I, Davis-Lorton M, Zanichelli A, Li HH, Craig T, Jacobs J, Johnston DT, Shapiro R, Yang WH, Lumry WR, Manning ME, Schwartz LB, Shennak M, Soteres D, Zaragoza-Urdaz RH, Gierer S, Smith AM, Tachdjian R, Wedner HJ, Hebert J, Rehman SM, Staubach P, Schranz J, Baptista J, Nothaft W, Maurer M; HELP Investigators. JAMA. 2018 (3). Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study. Lumry WR, Weller K, Magerl M, Banerji A, Longhurst HJ, Riedl MA, et al. Allergy. 2021 (25). Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema attacks. Riedl MA, Maurer M, Bernstein JA, Banerji A, Longhurst HJ, Li HH, et al. Allergy. 2020 (26).
Study type and design	Double-blinded randomised placebo-controlled phase 3 study. Randomisation was 2:1 lanadelumab to placebo; patients assigned to lanadelumab were further randomised 1:1:1 to one of the three dose regimens. Patients were enrolled and assigned to interventions using an interactive web-based randomisation system (Rho Inc) by blinded study staff in the order of enrolment. Randomisation was stratified by normalised number of attacks during the run-in period: 1 to less than 2, 2 to less than 3, or 3 or more attacks within 4 weeks using a within-stratum block size of 9. Attack rates were normalised to the number of attacks over 4 weeks (28 days). No crossover was allowed. The patients, care providers, investigators, and outcomes assessors were masked. The study is completed.
Sample size (n)	125
Main inclusion criteria	Inclusion Criteria: • Males and females 12 years of age or older at time of screening • Documented diagnosis of HAE, Type I or II • Baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks • Adult subjects and caregivers of subjects under the age of 18 are willing and able to read, understand, and sign an informed consent form. Subjects aged 12 to 17, whose caregiver

Trial name: HELP	NCT number: NCT02586805
	provides informed consent, are willing and able to read, understand and sign an assent form. • Males and females who are fertile and sexually active must adhere to contraception requirements.
Main exclusion criteria	Exclusion Criteria: • Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema, idiopathic angioedema, or recurrent angioedema associated with urticaria. • Participation in a prior DX-2930 study • Treatment with any other investigational drug or exposure to an investigational device within 4 weeks prior screening • Exposure to ACE inhibitors or any oestrogen-containing medications within 4 weeks prior to screening. • Exposure to androgens within 2 weeks prior to entering the run-in period. • Use of long-term prophylactic therapy for HAE within 2 weeks prior to entering the run-in period. • Use of short-term prophylaxis for HAE within 7 days prior to entering the run-in period. • Any of the following liver function test abnormalities: alanine aminotransferase > 3x upper limit of normal, or aspartate aminotransferase > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome). • Pregnancy or breastfeeding.
Intervention	Landelumab 150 mg Q4W (N = 28)[Ωπ], lanadelumab 300 mg Q4W[Ω] (N = 29), or lanadelumab 300 mg Q2W (N = 27).
Comparator(s)	Placebo Q2W (N = 41)
Follow-up time	>50% of patients in every treatment arm completed the study treatment. Therefore, the median follow-up was at least 26 weeks.
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary and secondary endpoints included in this application constitute: Rate of investigator confirmed HAE attacks during treatment period and Rate of Moderate or Severe Investigator Confirmed HAE Attacks. Exploratory endpoints included in this application constitute: Percentage of patients with ≥90% reduction in attack-rate, Mean change from

Trial name: HELP	NCT number: NCT02586805
	baseline in AE-QoL score, and Proportion of patients with at least a 6-point improvement from baseline in AE-QoL score. The safety endpoint "Percentage of patients who discontinued treatment due to AEs" is included as well. Additionally, a qualitative review of the safety profile of lanadelumab is included. **Other endpoints** The secondary endpoints Rate of Investigator Confirmed HAE Attack Requiring Acute Treatment and Rate of Investigator Confirmed Hereditary Angioedema Attacks During Day 14 Through Day 182 are not included in this application. Exploratory endpoints not included in this application are Time to first HAE attack after Day 14; Number of high-morbidity attacks (a high-morbidity attack was defined as any attack that was severe, laryngeal, hemodynamically significant, or resulted in hospitalisation); Characteristics of investigator-confirmed HAE attacks, including attack duration, severity, location, and medication use; Percentage of patients with ≥50% or ≥70% reduction in attack-rate relative to baseline; and Percentage of attack-free days. Other endpoints not included in this application are the plasma concentration of DX-2930, pharmacodynamic biomarker assays, anti-drug antibodies, and QoL data as collected with the EuroQoL Group 5-Dimension Questionnaire.
Method of analysis	Different methods were used to analyse each endpoint. Please see section 5.2.2.1-5.2.2.6 as well as Appendix B. The results are presented for the ITT population.
Subgroup analyses	Subgroup analyses include: • By LTP use before study entry (Yes, No) • By run-in period attack rate group (1 to <2 attacks/month, 2 to <3 attacks/month, ≥3 attacks/month) • By sex (Female, Male) • By BMI group (18.5 to <25 kg/m^2, 25 to <30 kg/m^2, ≥30 kg/m^2) Additionally, the impact of region on the primary efficacy endpoint was assessed by including a binary covariate (United States vs non-United States) in the primary analysis model. Moreover, one study has analyses outcomes by race (White, Black/African American, Asian, and other) and by ethnicity (Hispanic/Latino and non-Hispanic/non-Latino) (45).
Other relevant information	N/A

Abbreviations: ACE = angiotensin-converting enzyme; AE = Adverse event; AE-QoL = Angioedema Quality of Life; BMI = body mass index; HAE = hereditary angioedema; ITT = intention-to-treat; LTP = long-term prophylaxis; N/A = Not applicable; QoL = quality of life; Q2W = every 2 weeks; Q4W = every 4 weeks.
Notes: [Ω] To maintain the study blind, subjects were given placebo injections every other 2 weeks when they were not receiving drug. [π] The 150 mg Q4W treatment arm is not included in this application, as this dosage is intended for patients under 40 kg, which is assumed to not be applicable to most adults or adolescents over 12 years old.
Source: ClinicalTrials.gov, 2016 (30); Banerji et al. 2018 (3); Craig et al. 2022 (45).

Appendix B. Efficacy results per study

Results per study

Table 32 Results per study: OASIS-HAE

Results of OASIS-HAE (NCT05139810)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
HAE attack-free patients, Week 5 to Week 25	Placebo	22	n=2 (9.1%)	N/A	N/A	N/A	Reference			The percentages were based on the observed patients in the specific category. [a] The OR, its 95% CIs, 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 a covariate.	Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2).
	Donidalorsen 80 mg Q4W	45	n=24 (53.3)	N/A	N/A	N/A	OR[a]: 11.79	2.34, 59.36	0.003		
	Donidalorsen 80 mg Q8W	23	n=8 (34.8)	N/A	N/A	N/A	OR[a]: 3.23	0.46, 22.85	0.240		
≥90% reduction in HAE attack rate, from baseline between Week 5 to Week 25[a,b]	Placebo	22	n=2 (9.1%)	N/A	N/A	N/A	Reference			[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	Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2).
	Donidalorsen 80 mg Q4W	45	n=28 (62.2%)	N/A	N/A	N/A	OR[c]: 17.04	3.36, 86.42	< 0.001		
	Donidalorsen 80 mg Q8W	23	n=11 (47.8%)	N/A	N/A	N/A	OR[c]: 8.70	1.56, 48.52	0.014		

Results of OASIS-HAE (NCT05139810)											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										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 OR, its 95% CI, 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.	
HAE attack rate, Week 1-25	Placebo	22	Mean: 2.29 (SD: 1.807, SEM: 0.385)[a]	N/A	N/A	N/A	Reference			[a] The 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. [b] 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 per	Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2).
	Donidalorsen 80 mg Q4W	45	Mean: 0.89 (SD: 1.851, SEM: 0.276)[a]	N/A	N/A	N/A	Mean RR[b]: 0.19	0.107, 0.351	< 0.001		
	Donidalorsen 80 mg Q8W	23	Mean: 1.19 (SD: 1.629, SEM: 0.340)[a]	N/A	N/A	N/A	Mean RR[b]: 0.45	0.261, 0.777	0.004		

Results of OASIS-HAE (NCT05139810)										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										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. The mean RR is based on the LSM rate (not shown here, please see Table 9).	
Moderate or severe HAE attack rate. Week 5-25	Placebo	22	Mean: 1.35 (SD: 1.707, SEM: 0.364)[a]	N/A	N/A	N/A	Reference			[a] The time-normalised HAE attack rate was calculated as number of Investigator-confirmed HAE attacks occurring from Week 5 to Week 25, divided by the number of days the patient contributed to the period multiplied by 28. [b] 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 per 4 weeks that each patient was observed from Week 5 to Week	Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2).
	Donidalorsen 80 mg Q4W	45	Mean: 0.37 (SD: 1.026, SEM: 0.153)[a]	N/A	N/A	N/A	Mean RR[b]: 0.11	0.035, 0.339	< 0.001		
	Donidalorsen 80 mg Q8W	23	Mean: 0.90 (SD: 1.617, SEM: 0.337)[a]	N/A	N/A	N/A	Mean RR[b]: 0.59	0.276, 1.260	0.173		

Results of OASIS-HAE (NCT05139810)											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										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. The mean RR is based on the LSM rate (not shown here, please see Table 10).	
Change from Baseline to Week 25 in AE-QoL questionnaire total score	Placebo	18	Mean: -8.09 (SD: 18.083, SEM: 4.262)	N/A	N/A	N/A	Reference			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. The difference in LSM is based on LSMs shown in Table 11. The LSMs are based on a mixed effect model with repeated measures with fixed effects of treatment (donidalorsen or placebo), time (categorical), treatment-by-	Ionis Pharmaceuticals, Inc., 2024 (23); Riedl et al., 2024 (2).
	Donidalorsen 80 mg Q4W	42	Mean: -24.69 (SD: 15.895, SEM: 2.453)	N/A	N/A	N/A	Difference in LSM: -18.56	-27.673, -9.454	< 0.001		
	Donidalorsen 80 mg Q8W	22	Mean: -21.29 (SD: 22.719, SEM: 4.844)	N/A	N/A	N/A	Difference in LSM: -13.65	-24.024, -3.286	0.010		

Results of OASIS-HAE (NCT05139810)											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										time interaction, Baseline, and Treatment-by-Baseline interaction.	
Responders, Week 25	Placebo	20	n=9 (45.0%)	N/A	N/A	N/A	Reference			[a] Patients with at least 6-point improvement (reduction) from Baseline in AE-QoL total score at Week 25 are considered as responders. Patients who early discontinued Treatment period due to reasons of AEs or lack of efficacy are considered as non-responders; due to other reasons, patients are considered as missing. [B] The OR, its 95% CI, and p-value are calculated on a logistic regression with the Baseline and the Treatment-by-Baseline interaction as covariate.	Ionis Pharmaceuticals, Inc., 2024 (23).
	Donidalorsen 80 mg Q4W	42	n=37 (88.1%)[a]	N/A	N/A	N/A	OR[b]: 12.22	2.75, 54.27	<0.001		
	Donidalorsen 80 mg Q8W	21	n=15 (71.4%)[a]	N/A	N/A	N/A	OR[b]: 3.45	0.83, 14.29	0.087		

Abbreviations: AE = adverse event; AE-QoL = Angioedema Quality of Life; CI = confidence interval; HAE = Hereditary angioedema; LSM = least square mean; N/A = not applicable; OR = odds ratio; Q4W = every 4 weeks; Q8W = every 8 weeks; RR = rate ratio; SD = standard deviation; SEM = standard error of mean.

Table 33 Results per study: HELP

Results of HELP (NCT02586805)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
≥90% reduction in rate of HAE attacks[a, b], 26-week treatment period	Placebo	41	n=2 (4.9%)	Reference			N/A	N/A	N/A	[a] P-values shown for exploratory endpoints were not adjusted for multiplicity. All patients received injections Q2W, with those in the Q4W groups receiving placebo in between active treatments. [n] Achievement of a prespecified reduction from the run-in period in the HAE attack rate. The percentage reduction was calculated as the run-in period attack rate minus the treatment period attack rate divided by the run-in period attack rate, multiplied by 100. [c] The difference vs placebo was analysed using Fisher exact test.	Banerji et al. 2018 (3).
	Lanadelumab 300 mg Q2W	27	n=18 (66.7%)	61.8	39.5, 78.8	<0.001[c]	N/A	N/A	N/A		
	Lanadelumab 300 mg Q4W	29	n=16 (55.2%)	50.3	27.7, 68.8	<0.001[c]	N/A	N/A	N/A		
HAE attack rate[a], Day 0-182	Placebo	41	Mean (95% CI)[b, c]: 1.97 (1.64, 2.36)	Reference			Reference			[a] All patients received injections Q2W, with those in the Q4W groups receiving placebo in between active treatments. [b] Attack rates are model-based mean attacks per month, defined as 4	Banerji et al. 2018 (3).
	Lanadelumab 300 mg Q2W	27	Mean (95% CI)[b, c]: 0.26 (0.14, 0.46)	-1.71[d]	-2.09, -1.33	<0.001	RR[c]: 0.13	0.07, 0.24	<0.001[e]		

Results of HELP (NCT02586805)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	Lanade-lumab 300 mg Q4W	29	Mean (95% CI)[b, c]: 0.53 (0.36, 0.77)	-1.44[d]	-1.84, -1.04	<0.001	RR[c]: 0.27	0.18, 0.41	<0.001[e]	weeks. [c] Results are from a Poisson regression model accounting for overdispersion; treatment group and normalised baseline attack rate were fixed effects. The logarithm of time (days) each patient was observed during the treatment period was an offset variable. All p-values (Wald test) reported vs placebo. [d] Estimated from a nonlinear function of the model parameters. All p-values (Wald test) reported vs placebo. [e] P-value adjusted for multiple testing.	
Moderate or severe HAE attack rate[a], Day 0-182	Placebo	41	Mean (95% CI)[b, c]: 1.22 (0.97, 1.52)	Reference			Reference			[a] All patients received injections Q2W, with those in the Q4W groups receiving placebo in between active treatments. [b] Attack rates are model-based mean attacks per month, defined as 4 weeks. [c] Results are from a Poisson regression model accounting for overdispersion; treatment group and normalised baseline attack rate were fixed effects. The logarithm of	Banerji et al. 2018 (3).
	Lanade-lumab 300 mg Q2W	27	Mean (95% CI)[b, c]: 0.20 (0.11, 0.39)	-1.01[d]	-1.32, -0.71	<0.001	RR[c]: 0.17	0.08, 0.33	<0.001[e]		
	Lanade-lumab 300 mg Q4W	29	Mean (95% CI)[b, c]: 0.32 (0.20, 0.53)	-0.89[d]	-1.20, -0.58	<0.001	RR[c]: 0.27	0.16, 0.46	<0.001[e]		

Results of HELP (NCT02586805)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										time (days) each patient was observed during the treatment period was an offset variable. All p-values (Wald test) reported vs placebo. [d] Estimated from a nonlinear function of the model parameters. All p-values (Wald test) reported vs placebo. [e] P-value adjusted for multiple testing.	
Change ins AE-QoL total score[a], Day 0-182	Placebo	38	LSM (95% CI)[b]: -4.72 (-10.46, 1.02)	Reference			N/A	N/A	N/A	[a] All patients received injections Q2W, with those in the Q4W groups receiving placebo in between active treatments. [b] Change in AE-QoL scores is controlled for baseline scores and are LSMs. [c] Analysis of covariance post hoc pairwise comparison (Tukey-Kramer) vs placebo.	Banerji et al. 2018 (3).
	Lanadelumab 300 mg Q2W	26	LSM (95% CI)[b]: -21.29 (-28.21, -14.37)	Mean: -16.57	-28.53, -4.62	0.003[c]	N/A	N/A	N/A		
	Lanadelumab 300 mg Q4W	27	LSM (95% CI)[b]: -17.38 (-24.17, -10.58)	Mean: -12.66	-24.51, -0.80	0.03[c]	N/A	N/A	N/A		
Responders[a], Day 182	Placebo	38	36.84%[b]	Reference			Reference			[a] All patients received injections Q2W, with those in the Q4W groups receiving placebo in between active treatments. [b] Patients who were	Banerji et al. 2018 (3).
	Lanadelumab 300 mg Q2W	26	80.77%[b]	N/A	N/A	0.001	OR: 7.20	2.22, 23.37	0.001		

Results of HELP (NCT02586805)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	Lanade-lumab 300 mg Q4W	27	62.96%[b]	N/A	N/A	0.07	OR: 2.91	1.05, 8.10	0.04	considered to have re-sponded (responders) to the therapy were defined as achieving an improvement greater than or equal to the minimal clinically important difference of –6 for total scores from days 0 through 182. The questionnaire con-sisted of four domains (func-tioning, fatigue and mood, fears and shame, and nutri-tion) and 17 questions that were taken together for a to-tal score. Total raw scores were transformed to a linear scale of 0 to 100, with lower scores indicating lower im-pairment or higher health–re-lated QoL. ORs represent times the odds (vs not) to achieve a responder defini-tion compared with placebo.	

Abbreviations: AE-QoL = Angioedema Quality of Life; CI = confidence interval; HAE = Hereditary angioedema; LSM = least square mean; N/A = not applicable; OR = odds ratio; Q2W = every 2 weeks; Q4W = every 4 weeks; RR = rate ratio.

Appendix C. Comparative analysis of efficacy

Methodology

Current treatment landscape

There are no head-to-head studies comparing donidalorsen with other LTPs; therefore, an indirect comparison was necessary, and an NMA was selected as the most appropriate method given the availability of multiple licensed treatments and therapies seeking regulatory approval across European markets. For the purpose of the NMA, the following LTP treatments, and associated trials presented in Table 34, have been identified as comparators.

Table 34 NMA treatment comparators

Trial	Intervention	Dose	Dosing frequency	Route of administration	Source
OASIS-HAE	**Donidalorsen**	**80 mg**	**Q4W** **Q8W**	**SC**	**Riedl et al. 2024 (2)**
VANGUARD	Garadacimab	200 mg	Every month	SC	Craig et al. 2023 (42)
HELP	**Lanadelumab**	**300 mg**	**Q2W** **Q4W**	**SC**	**Banerji et al. 2018 (3)**
APeX-2	Berotralstat	150 mg	Everyday	Oral	Zuraw et al. 2021 (43)
COMPACT	C1-INH (Haegarda*)	60 international unit (IU)/kg	Q2W	SC	Longhurst et al. 2017 (46)
SAHARA	Plasma derived C1-INH	2,000 IU	Q2W	SC	Lumry et al. 2019 (39)
CHANGE	C1-INH nanofiltered (Cinryze)	1,000 units	Q2W	Intravenous	Zuraw et al. 2010 (38)

Abbreviations: C1-INH = C1-esterase inhibitor; IU = international unit; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Notes: *Marketed as Berinert in the United Kingdom

These comparators reflect the licensed LTP treatments across different European markets. The NMA will estimate the relative efficacy and patient QoL of donidalorsen compared with these established therapies in the absence of direct head-to-head studies. In this application, only the comparison of donidalorsen and lanadelumab is presented, as lanadelumab is the relevant comparator; therefore, donidalorsen and lanadelumab are mainly in focus in the following.

Objectives of the NMA

The primary objective of the NMA is to estimate the comparative efficacy and QoL of donidalorsen Q4W against donidalorsen Q8W, lanadelumab Q2W, and lanadelumab Q4W. This analysis aims to:

- Quantify treatment effects on key clinical outcomes, including:
  - Mean number of HAE attacks per month
  - Mean number of moderate or severe HAE attacks per month
  - Proportion of patients achieving ≥90% reduction in attacks from baseline
  - Mean change from baseline in the AE-QoL score
- Support heath technology assessments (HTAs) by generating robust comparative evidence in the absence of head-to-head trials
- Provide insights into the relative ranking of treatments across clinically meaningful endpoints to inform decision-making in European markets

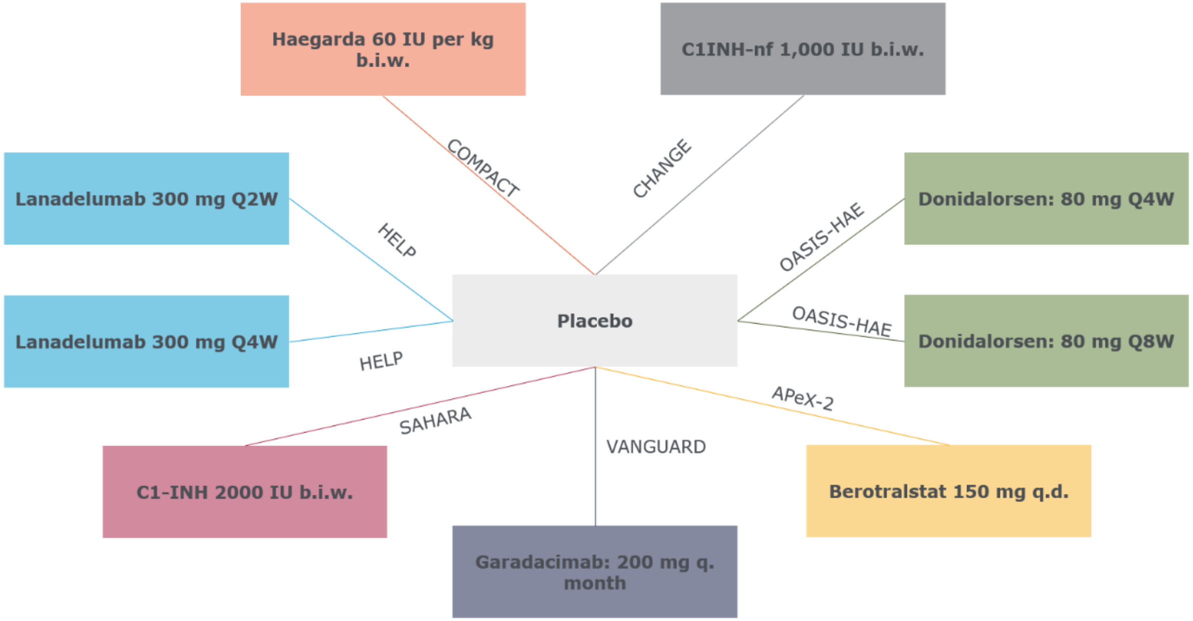
Network of evidence

A clinical SLR was undertaken on the 22nd of April 2025 (NMA was based on the original SLR with cut-off date 6th of June 2024, but no additional relevant publications were identified in SLR update with cut-off date 22nd of April 2025) to identify all relevant efficacy and safety data in studies conducted with HAE types I and II, for patients aged 12 years or older (please see Appendix D). The identified studies provided a connected network of evidence such that donidalorsen is indirectly connected to the original comparators of interest (Table 34), as presented in

Figure 8. In total, five studies met the inclusion criteria for the feasibility assessment, alongside OASIS-HAE; COMPACT, SAHARA, APeX-2, VANGUARD, and HELP. Additionally, the feasibility assessment includes the CHANGE study to incorporate Cinryze as a comparator; this study was not captured in the SLR as it encompasses a broader population aged ≥6 years, beyond the standard ≥12 years inclusion criteria of the SLR. The selection of these studies, including CHANGE, was validated by two HAE clinical experts, who also confirmed that no relevant studies were omitted (40,41). All studies from the original NMA are presented here (

Figure 8), as they contributed with placebo data, which will be presented in this application.

Figure 8 Connected evidence network



Abbreviations: b.i.w. = twice a week; C1-INH = C1-esterase inhibitor; C1INH-nf = nano filtered C1 inhibitor; IU = international units; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 4 weeks; q.d. = every day; q. month = every month.

Feasibility assessment

A feasibility assessment was conducted to inform whether an NMA between the RCTs is feasible. Conventional NMAs require a connected network to exist, with a connection between all interventions of interest; a level of homogeneity between-study and baseline characteristics of included studies to ensure a reliable comparison; and sufficient data must be available in an analysable form (47). The feasibility assessment investigated each of these requirements. The assessment followed standard guidelines, including those by NICE DSU and the Cochrane Handbook, to estimate the relative effect of two or more interventions when there are no direct head-to-head studies comparing the treatments directly (37). A detailed comparison of the OASIS-HAE and HELP studies is provided in section 5.1.2. In the following, key findings of the feasibility assessment are provided, as studies in the network (

Figure 8) contribute to the placebo arm:

- Study design: All included studies were Phase 3, randomised, double-blind, and placebo-controlled. Variations in study duration (12–26 weeks) and crossover designs were identified but did not preclude inclusion. The CHANGE and SAHARA studies were excluded from the network due to the lack of a washout period, which may introduce bias.
- Patient population: The eligibility criteria were broadly consistent across trials, with minor differences in age thresholds, diagnostic criteria, and baseline attack rates. These variations were not considered significant enough to bias the NMA results.
- Treatment arms: The licensed doses and administration regimens were largely consistent across the studies. Minor differences were observed but aligned with regulatory guidelines and product labels.
- Outcome measures: Key outcomes, such as mean monthly attack rates, percentage of patients who achieved a specified proportional reduction in attacks from baseline, mean monthly moderate or severe attack rate, and QoL scores, were sufficiently reported. However, heterogeneity in definitions and reporting periods was noted as a limitation.

It was concluded that it is feasible to conduct NMAs for some of the outcomes of interest: the mean monthly attack rate, percentage of patients who achieved a specified proportional reduction in attacks from baseline, mean monthly moderate or severe attack rate, and change in total AE-QoL scores. The feasibility of the outcomes of interest were validated by two HAE clinical experts (40,41).

For the mean number of attacks per month, all the studies, with the exception of CHANGE and SAHARA, are included in the network. To compare the proportion of patients achieving defined reductions in HAE attacks from baseline, a network was formed with the OASIS-HAE, VANGUARD, HELP, and APeX-2 studies. A smaller network including the OASIS-HAE, VANGUARD, and HELP studies was feasible to compare the mean number of moderate or severe HAE attacks. For the change in total AE-QoL score from baseline, a network was established with the OASIS-HAE, VANGUARD, HELP, and APeX-2 studies.

Analyses

In the analyses, data for all studies included in the network per outcome was included, with CHANGE and SAHARA being exceptions from the main network of evidence.

Random effects models were run for each outcome, as a preference is given to the random effects model as recommended by the Multi-parameter Evidence Synthesis Research Group, for the reasons highlighted in the description of 'Model selection' below (44).

The outcomes that were analysed in the ITT population, included in the DMC's protocol, and previously assessed by the DMC are as follows:

- Mean number of HAE attacks per month
- Mean number of moderate or severe HAE attacks per month
- Proportion of patients who experienced ≥ 90% reduction in attacks compared with baseline

- Change in the total AE-QoL score from baseline

Model specifications

The NMA was conducted to allow simultaneous synthesis and inference regarding the comparative effectiveness of donidalorsen versus lanadelumab. The analysis included three endpoints: count, binary, and continuous outcomes. Donidalorsen Q4W was used as the reference treatment for these analyses. A summary of the analyses is detailed below.

For count data endpoints, namely mean number of HAE attacks per month and mean number of moderate or severe HAE attacks per month, reported data on numbers of attacks, were analysed to synthesise RRs and CrIs, assuming a Poisson distribution for the total number of attacks reported within each study.

The binary outcome, namely proportion of patients experiencing ≥90% reduction in attacks from baseline, was analysed to synthesise ORs, assuming a binomial distribution for the numbers of patients achieving the ≥90% reduction reported within each study.

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

Prior distributions

Non-informative priors

Due to the sparsity of the networks specified in the current analyses, it was concluded that there were insufficient sample data to inform the between-study heterogeneity of treatment effects. As such, non-informative priors were only considered for mean of treatment effects and trial-specific baseline treatment effect.

Informative priors

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

The informative priors, developed by Turner et al., were based on a study of nearly 15,000 meta-analyses (48). As such, priors for between-study variance identified by Turner et al. were used throughout. The prior was specified individually for pharmacological versus placebo/control and pharmacological versus pharmacological studies; since all studies being considered were pharmacological versus placebo, the prior for this comparison was used.

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:

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

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. A summary of the assumptions and calculations are highlighted in Table 35.

Table 35 Meta-analysed data for the mean number of HAE attacks per month

Study	Publication	Treatment	n	Total number of attacks	Total exposure time (days)	Calculations/ assumptions
OASIS-HAE	Riedl et al. 2024 (2)	Donidalorsen 80 mg Q4W	45	123*	7,875*	Exposure time calculated by multiplying n by follow-up time in months. This was then converted to days upon multiplying the exposure time in months by the number of days in a month as per each study. Number of attacks calculated by multiplying exposure time by the LSM.
		Donidalorsen 80 mg Q8W	23	146*	4,025*	
		Placebo	22	311*	3,850*	
HELP	Banerji et al. 2018 (3)	Lanadelumab 300 mg Q2W	27	46†	4,954*	Exposure time calculated by dividing total number of attacks by the arithmetic mean attack rate per month. This was then converted to days upon multiplying the exposure time in months by the number of days in a month as per each study.
		Lanadelumab 300 mg Q4W	29	105†	5,547*	
		Placebo	41	572†	8,130*	

Abbreviations: HAE = Hereditary angioedema; IU = international unit; LSM = Least square mean; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks.
Notes: * In the absence of published data, the person-days have been estimated. † Data reported in the relevant publication.

Model assessment

Convergence to the target posterior distributions were assessed using the Gelman-Rubin statistic and various diagnostic plots including density and trace plots for each parameter, and autocorrelation plots. A suitable burn-in and number of iterations of the Markov chains to estimate parameters were selected, allowing for thinning if required. The burn-in, number of iterations and thinning used for each outcome are reported, aligning with NICE DSU guidelines (49).

Model selection

A random effects 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.

Random effects models account for heterogeneity between studies whilst fixed effects models do not and therefore may be considered less relevant and can lead to artificially narrow CrIs. Therefore, the random effects model is considered as the most relevant model in this analysis as recommended by the Multi-parameter Evidence Synthesis Research Group (44).

Software

The 'multinma' R package, amongst others, and R version 4.2.1 or above via RStudio was used to perform the analyses (50,51).

Key opinion leader validation

A call was held with two HAE clinical experts, separately, to validate the feasibility of the NMA. During the calls, the two HAE clinical experts validated the prognostic factors and treatment effect modifiers (TEMs) identified as part of the feasibility assessment, the treatments and their respective clinical studies, as well as the generalisability of the clinical studies to be considered for inclusion in the NMA.

Based on a patient-reported burden of disease study (52), and a published NMA for lanadelumab and berotralstat (53), the following prognostic factors were included in the NMA: age, sex, race, HAE phenotype, presence of family history, BMI, age at symptom onset, frequency of HAE attacks, and types of HAE attacks experienced. Though the clinicians believed some factors were more significant than others, the clinicians agreed with the prognostic factors identified and did not recommend any additional factors to be considered.

Treatment effect modifiers refer to variables or factors that can influence the magnitude or direction of the treatment effects being compared and can therefore introduce bias. In the NMA, the following TEMs were included: prior treatments, concomitant treatments, and the baseline attack rate. The clinical experts agreed with the TEMs but commented that a higher baseline attack may predict a larger absolute reduction in attack rate in the trial, although the proportional reduction from baseline is not expected to change; however LSM is used to account for this and this has been used for the majority of attack rate-related inputs in the NMA, with the exception of inputs from HELP and COMPACT which did not report LSM values, rather only the arithmetic mean values.

The comparator treatments and related trials included in the NMA are listed in Table 34 and reflect the licensed LTP treatments for HAE in Europe. These comparators were identified during the SLR described in Appendix D.

Limitations of the NMA

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. All results are presented with a 95% CrI, 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 variation in how data was presented. Although, the raw number of attacks per month was available from OASIS-HAE, these data were not used in the analysis to ensure consistency with other trials used to inform the analysis. The LSM attack rates, derived using a Poisson regression, were used to inform the mean attack rates from OASIS-HAE, and a back-calculation method was employed to derive the necessary inputs to facilitate comparison with other trials. Whilst the arithmetic mean rate is often considered appropriate for such calculations where the raw data are available, the LSM was considered more appropriate as the Poisson regression model included treatment groups and baseline attack rate as fixed effect, and the LSM was reported in comparator trials. This decision was made to maintain consistency across all comparators and to avoid introducing a negative bias towards donidalorsen.

The absence of a washout period in the CHANGE and SAHARA trials precluded their inclusion in the analyses, as this may have introduced bias to the analyses.

Some treatments in this analysis have a ‘steady state period’ during which the treatment effect is considered optimal, typically occurring several weeks after treatment initiation. Since the original analysis uses data from day one of each clinical trial apart from OASIS-HAE, additional analyses was required to evaluate the treatment effects during the ‘steady state period’, which commenced in Q2 2025. Across all outcomes, results were broadly consistent with those observed in the original NMA. More detailed results can be provided upon request.

Results

Table 36 Results from the comparative analysis of donidalorsen vs. lanadelumab for adults and adolescents patient aged 12 years and older with HAE

Outcome measure	Donidalorsen 80 mg Q8W	Lanadelumab 300 mg Q2W	Lanadelumab 300 mg Q4W	Placebo
Median OR for proportion of patients achieving a ≥90% reduction in HAE attacks from baseline (95% CrI)	0.66 (0.14, 3.13)	7.26 (0.45, 132.76)	4.34 (0.30, 80.14)	0.15 (0.02, 0.81)*
Median RRs for mean number of HAE attacks per month (95% CrI)	2.32 (0.67, 8.28)	0.67 (0.11, 4.02)	1.38 (0.23, 8.93)	5.15 (1.48, 18.06)*
Median RRs for mean number of moderate or severe HAE attacks per month (95% CrI)	3.24 (0.90, 11.69)	0.91 (0.16, 5.54)	1.44 (0.24, 8.93)	5.61 (1.59, 20.73)*
Median mean difference from baseline in AE-QoL score (95% CrI)	4.82 (-3.91, 13.57)	1.75 (-11.08, 4.56)	5.64 (-7.02, 18.36)	18.35 (9.27, 27.42)*

Abbreviations: AE-QoL = Angioedema Quality of Life; CrI = credible interval; HAE = hereditary angioedema; OR = odds ratio; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; RR = rate ratio.
Notes: *95% CrI does not include 1 and is therefore considered statistically significant.

Appendix D. Literature searches for the clinical assessment

D.1 Efficacy and safety of the intervention and comparator(s)

The objective of the global SLR was to identify existing clinical, cost-effectiveness, HRQoL, cost and resource use, and burden of disease studies conducted in HAE. The SLR was conducted in line with HTA requirements across Europe and thus will support subsequent HTA submissions for donidalorsen for the treatment of patients 12 years and older with HAE.

A global single integrated SLR was conducted to answer the following research questions, which follow the PICOS (population, interventions, comparators, outcomes and study type) principle (54):

1. What is the efficacy and safety reported in clinical studies (RCT and non-RCTs) of therapies for HAE?
2. What economic evidence is available for current therapies for HAE?
3. What utilities and disutilities are associated with patients with HAE and their caregivers?
4. What are the costs and resource use associated with HAE?
5. What are the associated disease burdens from a patient's perspective with current therapies?

This locally adapted SLR focuses on the first research question in the latest updated global SLR. Accordingly, information specific to this research question is presented where available, whereas general elements from the global SLR (e.g., the combined search strategy) are reported when information is not available at the individual question level. Moreover, search strings from the original global SLR (from the 6th of June 2024) are presented in addition to search strings from the latest updated SLR (22nd of April 2025).

Searches to identify evidence for the first research question were conducted in the databases presented in Table 37.

Table 37 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase*	EMBASE interface	1974 to 22.04.2025	Original: 06.06.2024 Updated: 22.04.2025
Medline*	EMBASE interface	1966 to 22.04.2025	Original: 06.06.2024 Updated: 22.04.2025

Database	Platform/source	Relevant period for the search	Date of search completion
Medline In-Process*	EMBASE interface	1966 to 22.04.2025	Original: 06.06.2024 Updated: 22.04.2025
CENTRAL	Cochrane Library	N/A$^{\Omega}$	Original: 06.06.2024 Updated: 22.04.2025
Cochrane Clinical Answers	Cochrane Library	N/A$^{\pi}$	Original: 06.06.2024 Updated: 22.04.2025

Abbreviations: N/A = not applicable.
Notes: * These databases were used to identify evidence for all five research questions. $^{\Omega}$ CENTRAL first began publication in 1996, but its composite nature means that it does not have a start date, like some biomedical databases do (55). $^{\pi}$ Cochrane Clinical Answers as developed in partnership between Cochrane and Wiley and in 2018 became part of the suite of databases available to all Cochrane Library subscribers (56).

Supplementary searches of "grey" literature were performed in Google Scholar and through websites. The websites are presented in Table 38.

Table 38 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
National Institute for Health and Care Excellence	https://www.nice.org.uk/	Manual search	Original: 06.06.2024 Updated: 22.04.2025
Scottish Medicines Consortium	https://scottishmedicines.org.uk/	Manual search	Original: 06.06.2024 Updated: 22.04.2025
Italian Agency for Pharmaceuticals	https://www.aifa.gov.it/	Manual search	Original: 06.06.2024 Updated: 22.04.2025
Spanish Agency of Medicines and Medical Devices	https://www.aemps.gob.es/	Manual search	Original: 06.06.2024 Updated: 22.04.2025
Swedish Dental and Pharmaceutical Benefits Agency	https://www.tlv.se/	Manual search	Original: 06.06.2024 Updated: 22.04.2025
Institute for Quality and Efficiency in Healthcare	https://www.iqwig.de/	Manual search	Original: 06.06.2024 Updated: 22.04.2025
National Institute for Sickness Insurance	https://www.inami.fgov.be/	Manual search	Original: 06.06.2024 Updated: 22.04.2025

Source name	Location/source	Search strategy	Date of search
and Universal Health Coverage			
Netherlands Authority for Healthcare Insurance and Youth Care	https://www.zorginstituutnederland.nl/	Manual search	Original: 06.06.2024 Updated: 22.04.2025

Furthermore, searches included clinicaltrials.gov, International Clinical Trials Registry Platform Search Portal, bibliographic searching of any SLRs identified during screening, and relevant congresses over the last two years. The relevant congresses are shown in Table 39.

Table 39 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
European Academy of Allergy and Clinical Immunology Annual Congress	https://eaaci.org/events/annual-congress/	Manual search	Not reported	Original: 06.06.2024 Updated: 22.04.2025
HAE International global conference, regional conferences and workshops	N/A	Manual search	Not reported	Original: 06.06.2024 Updated: 22.04.2025
American Academy of Allergy, Asthma and Immunology Annual Meeting	https://annualmeeting.aaaai.org/	Manual search	Not reported	Original: 06.06.2024 Updated: 22.04.2025
American College of Allergy, Asthma & Immunology Annual Meeting	https://annualmeeting.acaai.org/	Manual search	Not reported	Original: 06.06.2024 Updated: 22.04.2025
Bradykinin Symposium	https://bradykinin-symposium.de/	Manual search	Not reported	Original: 06.06.2024 Updated: 22.04.2025

Abbreviations: HAE = hereditary angioedema.

D.1.2 Search strategies

The systematic literature searches were performed using a pre-defined search strategy to identify eligible studies. Search strategies were developed to include the relevant population, interventions, comparators, study types, and date restriction. The search strategies from both the original and the updated SLRs are presented below (Table 40, Table 4141, Table 4242, and Table 43), even though the updated SLR is in focus in this application. The brand name of donidalorsen (DAWNZERA) was not included in the search strings, as it was not public knowledge at the time of the searches. Therefore, no additional studies would have been identified by adding DAWNZERA to the search strings.

Table 40 of search strategy table for EMBASE, MEDLINE and MEDLINE In-Process (EMBASE interface) (6 June 2024)

No.	Description	Query	Results
		Clinical strategy	
#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 ‘stanozolol’/syn OR ‘winstrol’/syn OR ‘tranexamic acid’/syn OR ‘epsilon aminocaproic acid’/syn OR ‘long term prophyaxis’/syn OR ‘long-term prophylaxis’/syn OR ‘ltp’/syn	67,969
#3	Study types: RCT Filter (57)	('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	4,863,885

		('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 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		
#8	Economic Filter (57)	'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 (58)	‘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 qwb):ab,ti OR (multiattribute* OR multi attribute*):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 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 sfeight):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-	1,329,144

		qol’:ab,ti OR (angioedema NEXT/2 quality of life) OR (angioedema NEXT/2 qol) OR ‘pedsql’: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
#13	Combine terms	#7 OR #12	5,906

Table 41 of search strategy table for EMBASE, MEDLINE and MEDLINE In-Process (EMBASE interface) (22 April 2025)

No.	Description	Query	Results
		Clinical strategy	
#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	31,906
#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 ‘stanozolol’/syn OR ‘winstrol’/syn OR ‘tranexamic acid’/syn OR ‘epsilon	71,082

		aminocaproic acid'/syn OR 'long-term prophyaxis'/syn OR 'long-term prophylaxis'/syn OR 'ltp'/syn	
#3	Study types: RCT Filter (57)	('clinical trial'/de OR 'randomised 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)	3,076,718
#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	2,930,359
#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 'randomised controlled trial'/de) OR 'cohort analysis'/de OR (cohort NEXT/1 (study OR studies)) OR (('case control' NEXT/1 (study OR 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)	5,226,113
#6	Combine filters	#3 OR #4 OR #5	8,458,572
#7	Combine filters	#1 AND #2 AND #6 AND [humans]/lim	1,650
	Cost-effectiveness, HRQoL, and cost and resource use studies search strategy		
#8	Economic Filter (57)	'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*	1,287,637
#9	Quality of life filter (58)	'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	1,419,464

		OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwb):ab,ti OR (multiattribute* OR multi attribute*):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 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 sfeight):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 ‘pedsql’: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 'hospitalisation'/de OR hospitalisation*: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 re-admitted: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)	2,562,101
#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')	28,959

#12	Combine terms	#1 AND (#8 OR #9 OR #10 OR #11) AND [humans]/lim	5,067
#13	Combine terms	#7 OR #12	6,333
#14	Date restriction	#13 AND [06-06-2024]/sd NOT [23-04-2025]/sd	411

Table 42 of search strategy table for CENTRAL (Cochrane Library interface) (6 June 2024)

No.	Description	Query	Results
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 43 of search strategy table for CENTRAL (Cochrane Library interface) (22 April 2025)

No.	Description	Query	Results
1	Terms for population	MeSH descriptor: [Angioedemas, Hereditary] explode all trees	172
2	Terms for population	(hereditary angioedema):ab,ti OR (hae):ab,ti	580
3	Combine terms	#1 or #2	156
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	6103

5	Combine terms	#3 and #4	56
6	Date re-striction	#5, restricted to “with Publication Year from 2024 to 2025, with Cochrane Library publication date from Jun 2024 to Apr 2025, in Trials	3

D.1.3 Systematic selection of studies

Global selection criteria

The selection criteria specified in Table 44and Table 4545 were used to inform the inclusion and exclusion of studies at first and second pass stages of the reviews (see description below the tables). Only papers published in English were accepted. Studies published as abstracts, conference presentations, or press releases were eligible if adequate data were provided in line with the inclusion criteria.

Local selection criteria

Most of the selection criteria presented in Table 44 apply in the locally adapted SLR with some moderations. Donidalorsen and lanadelumab are the interventions of interest. Only endpoints included in the DMC’s protocol for development of the treatment guideline (4) and evidence review (5) are of interest (Number and/or percentage reduction of HAE attacks, Number and/or percentage reduction of attacks by severity, Number and/or percentage reduction of patients attack-free, All AEs and SAEs, Discontinuation due to AEs, and Utility scores measured using the AE-QoL tools). Finally, phase 3 RCTs are the study type of interest, and publications available only as abstracts and conference abstracts (including posters) will be excluded. Likewise, HTA submission documents will be excluded as well.

The selection criteria presented in Table 45 do not apply in this locally adapted SLR, as they only concern non-RCTs. In this application, only RCTs are of interest, as the purpose of the SLR is to identify literature relevant for the NMA. The NMA includes only phase 3 RCTs, as these are considered the gold standard for demonstrating the efficacy and safety of interventions. For each trial, only the randomised treatment period is assessed in order to minimise bias, ensure comparability between treatment groups, increase internal validity, and identify potential confounding variables and TEMs (59). Furthermore, the DMC’s protocol for the development of the treatment guideline for HAE explicitly states that only systematic meta-analyses and RCTs will be included (4).

Table 44 Inclusion and exclusion criteria used for assessment of studies (RCTs)$^{\Omega}$

Clinical effectiveness	Inclusion criteria	Exclusion criteria
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
Interventions	• Donidalorsen • Garadacimab (CSL312) • Sebetralstat • pdC1-INH (Cinryze®) • pdC1-INH (Berinert®) • pdC1-INH (Haegarda®) • Lanadelumab (Takhzyro®) • Berotralstat (Orladeyo®) • Danazol (Danocrine®) • Stanozolol (Winstrol®) • Androgens • Tranexamic acid • Epsilon aminocaproic acid	• Interventions not listed in inclusion criteria • Relevant intervention, but not investigated for HAE treatment

	• Other LTP treatment	
Comparators	• Placebo • Standard of care • Active comparator	• Comparators not listed in inclusion criteria
Outcomes	Efficacy: • Number and/or percentage reduction of HAE attacks (within various timeframes e.g., per month) • Number and/or percentage reduction of attacks by severity • Mild: transient or mild discomfort • Moderate: mild to moderate limitation in activity, some assistance needed • Severe: marked limitation in activity, assistance required • Other definitions of severity will be captured • Number and/or percentage reduction of attacks leading to on-demand therapy use • Number and/or percentage reduction of patients attack-free • Location of attacks • Peripheral angioedema: cutaneous swelling involving an extremity, face, neck, torso, and/or genitourinary region	• No reported outcomes of interest (i.e. only reported pharmacodynamics, pharmacokinetics)

	• Abdominal angioedema: abdominal pain, with or without abdominal distension, nausea, vomiting, or diarrhoea • Laryngeal angioedema: stridor, dyspnoea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx • Time to first attack • Duration of attacks • Need for acute treatment • Mortality data • Attack-free days Safety and tolerability: • All AEs and SAEs • Discontinuation due to AEs • Incidence of emergency room visits HRQoL • Utility scores measured using either specific (e.g. AE-QoL, AECT) or generic tools (e.g. EuroQoL 5-Dimension, Health Utilities Index, Short Form 6-Dimension, Child Health Utility 9-Dimension), or directly elicited (e.g. Time trade-off)	
Study type	• RCTs	• Non-randomised studies, observational studies, cohorts, and case series (including patient registries)

		• Narrative reviews • Systematic reviews and meta-analyses** • Preclinical studies (Animal studies and *in vitro/ex vivo* studies) • Prognostic studies • Case reports • Commentaries, editorials and letters • Consensus reports
Publication type	• Article • Conference abstract • Conference paper • Article in press	• Short survey • Reviews • Letters • Comment articles
Language restrictions	• English	• Non-English

Abbreviations: AE = adverse event; AECT = Angioedema Control Test; AE-QoL = Angioedema Quality of Life; HAE = hereditary angioedema; HRQoL = health-related quality of life; RCT = randomised controlled trial; SAE = serious adverse event; SLR = systematic literature review.
Notes: [Ω] These criteria apply to the global SLR. The criteria for the locally adapted SLR are described above this table. *Unless results from HAE patients only are included separately; **SLRs will be checked for any additional relevant studies.

Table 45 Inclusion and exclusion criteria used for assessment of studies (non-RCTs)[Ω]

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Patients with HAE aged 12 years old or above	• Studies that include any other patients/popula-tions* • Studies of patients with HAE-nC1INH (Type III) only
Interventions	• Donidalorsen • Garadacimab (CSL312) • Sebetralstat • pdC1-INH (Cinryze®) • pdC1-INH (Berinert®) • pdC1-INH (Haegarda®) • Lanadelumab (Takhzyro®) • Berotralstat (Orladeyo®) • Androgens • Danazol (Danocrine®) • Stanozolol (Winstrol®) • Tranexamic acid • Epsilon aminocaproic acid	• Interventions not listed in inclusion criteria • Relevant intervention, but not investigated for HAE treatment

	• Other LTP treatment	
Comparators	• Placebo • Standard of care • Active comparator	• Comparators not listed in inclusion criteria
Outcomes	Efficacy: • Number and/or percentage reduction of HAE attacks (within various timeframes e.g., per month) • Number and/or percentage reduction of attacks by severity • Mild: transient or mild discomfort • Moderate: mild to moderate limitation in activity, some assistance needed • Severe: marked limitation in activity, assistance required • Other definitions of severity will be captured • Number and/or percentage reduction of attacks leading to on-demand therapy use • Number and/or percentage reduction of patients attack-free • Location of attacks • Peripheral angioedema: cutaneous swelling involving an extremity, face, neck, torso, and/or genitourinary region	• No reported outcomes of interest

	• Abdominal angioedema: abdominal pain, with or without abdominal distension, nausea, vomiting, or diarrhoea • Laryngeal angioedema: stridor, dyspnoea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx • Time to first attack • Duration of attacks • Need for acute treatment • Mortality data • Attack-free days Safety and tolerability: • All AEs and SAEs • Discontinuation due to AEs • Incidence of emergency room visits HRQoL • Utility scores measured using either specific (e.g. AE-QoL, AECT) or generic tools (e.g. EuroQoL 5-Dimension, Health Utilities Index, Short Form 6-Dimension, Child Health Utility 9-Dimension), or directly elicited (e.g. Time tradeoff)	
Study type	• Non-randomised studies	• Narrative reviews

	• Observational studies (including patient registries) • Retrospective analyses	• Systematic reviews and meta-analyses** • Preclinical studies (Animal studies and *in vitro/ex vivo* studies) • Prognostic studies • Case reports and case series fewer than five patients • Commentaries, editorials and letters • Consensus reports
Publication type	• Article • Conference abstract • Conference paper • Article in press	• Short survey • Reviews • Letters • Comment articles
Language restrictions	• English	• Non-English

Abbreviations: AE = adverse event; AECT = Angioedema Control Test; AE-QoL = Angioedema Quality of Life; HAE = hereditary angioedema; HRQoL = health-related quality of life; RCT = randomised controlled trial; SAE = serious adverse event; SLR = systematic literature review.
Notes: $^{\Omega}$ These criteria apply to the global SLR, as only RCTs are relevant in the locally adapted SLR. *Unless results from HAE patients only are included separately; **SLRs will be checked for any additional relevant studies.

Selection process

Following the removal of duplicate records across the databases searched, two independent reviewers assessed the relevance of identified studies based on title and abstract (first pass) for inclusion using the review question and selection criteria. A discussion was held between the two reviewers after 20% of the studies had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required.

Following completion of first pass screening, full-text copies of all potentially relevant records were obtained and evaluated in more detail (second pass) against the pre-defined selection criteria. A discussion was held between the two reviewers after 20% of the studies had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required.

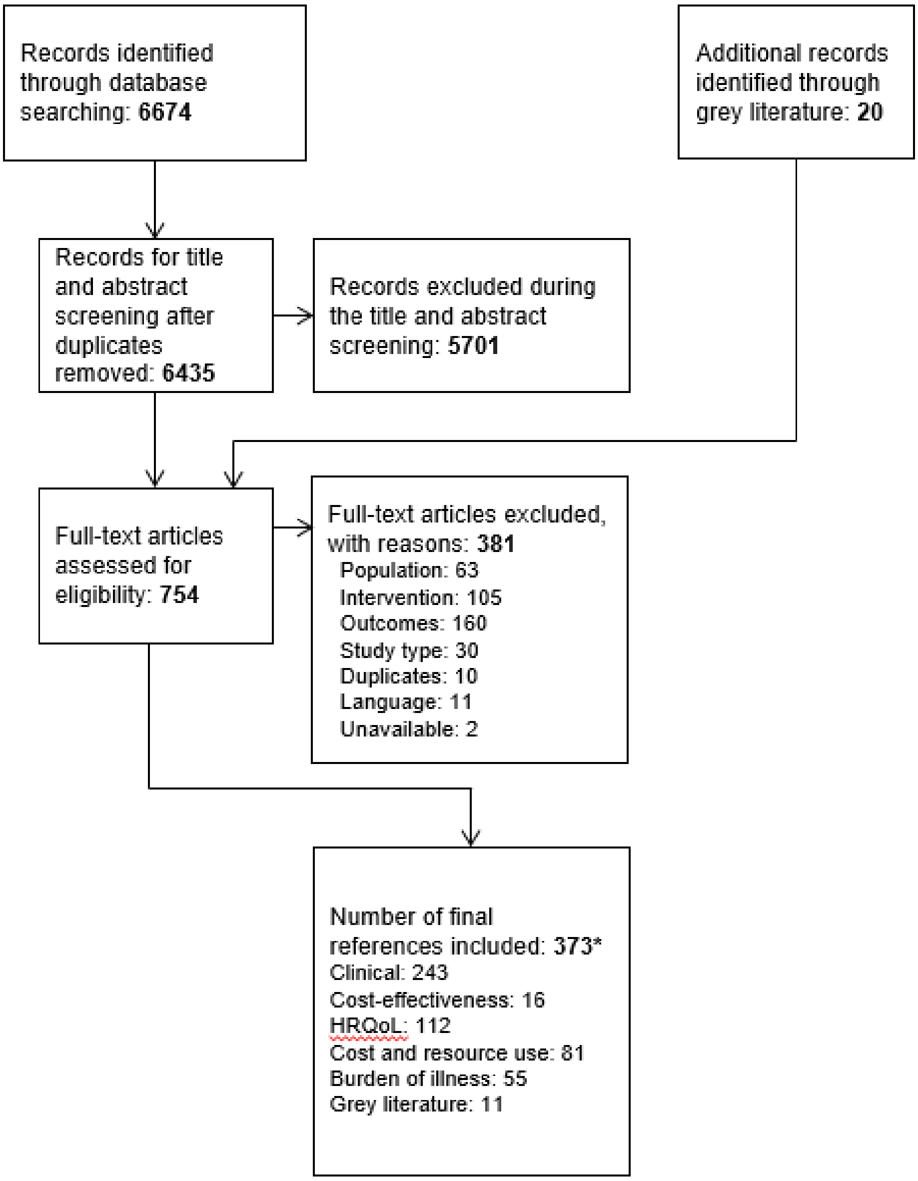
Data was extracted by one reviewer and checked for accuracy by a second reviewer. Discrepancies were resolved through discussion. For each publication, data was extracted into a data collection form (Excel-based with tables).

Results

Searches were conducted in June 2024 and refreshed on 22nd April 2025 using the same search strategies and methodology. Duplicate references were removed following the merger of the 2025 and 2024 search results. The results presented in this report reflect the combined 2024 and 2025 SLR search findings.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram illustrated in Figure 9 demonstrates how references were reviewed and extracted across all research questions. The database searches retrieved 6,674 references, of which 239 were duplicates, leaving 6,435 unique references for first pass screening. Additionally, 20 papers were found through grey literature searches. Of these, 754 references (including the grey literature searches) were assessed at second pass and 373 were included and considered for extraction. Of the 754 references assessed, 381 were excluded at secondary screening; 160 did not meet the outcome criteria, 105 did not meet the intervention/comparator criteria, 63 did not meet the population criteria, 30 did not meet the study type criteria, 11 were not in English, ten were duplicates, two were unavailable (not available online). Of the 373 unique references included, 119 were full-text papers and extracted; the remaining references were abstracts or posters (n = 254).

Figure 9 PRISMA Diagram (global)

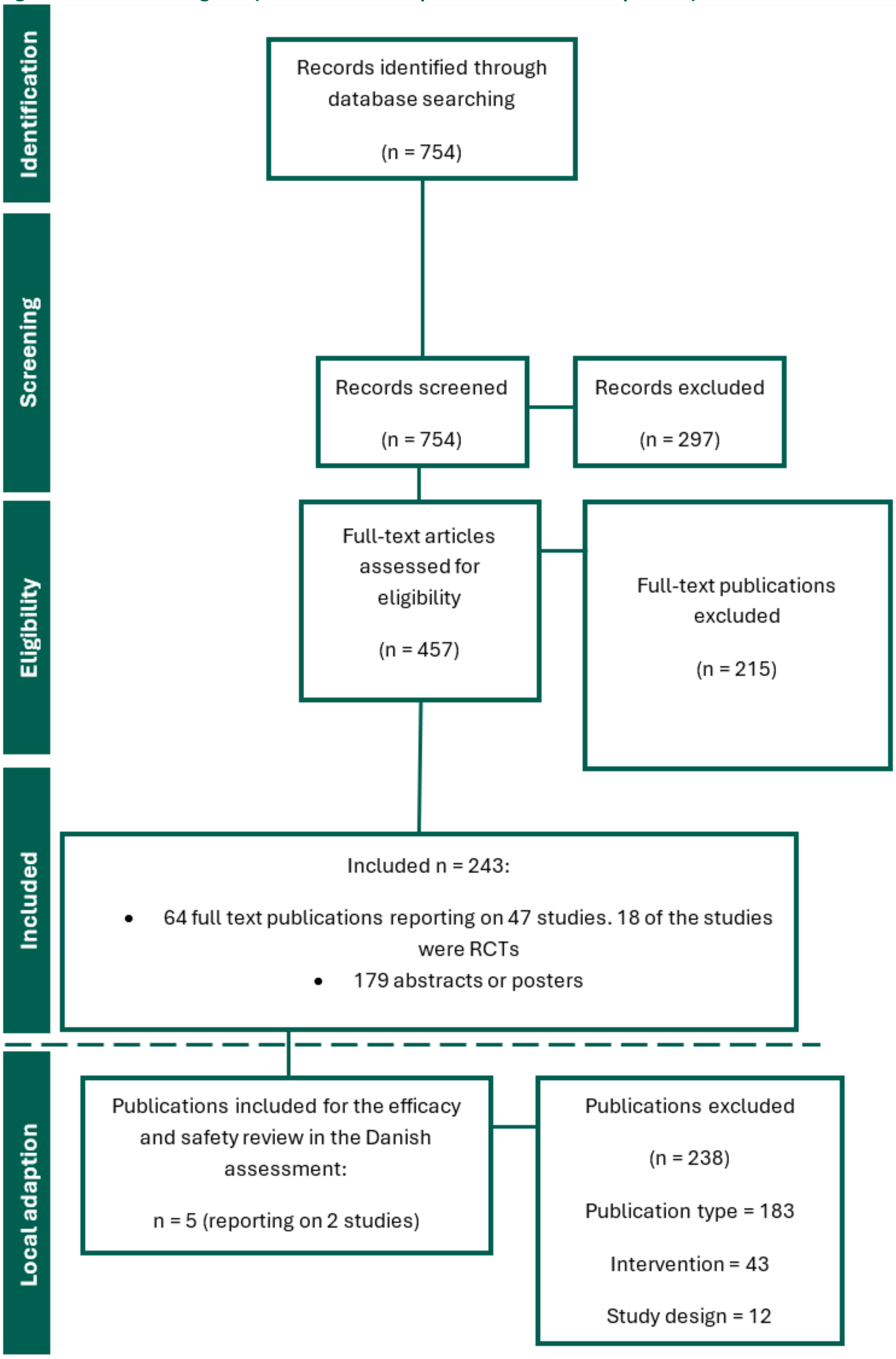


Abbreviations: HRQoL = health-related quality of life; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
Notes: *Of which n=119 were full texts and n=254 were abstracts or posters. This is the total number of unique references, as some references are included in multiple research questions.

In the following, the PRISMA flow for the first research question is described. After first pass screening 457 references (of the 754 total) were considered for secondary screening for review question one after which a total of 215 references were excluded because they did not meet the selection criteria. Of the total 243 references included, 64 full texts were extracted and these form the focus of this report; 179 were abstracts or posters. In the locally adapted SLR, abstracts and posters were not included in the final evidence base, as they generally lack sufficient details on methodology and results to allow for quality assessment and do not provide the level of detail required for this application.

In total 47 full-text studies (reported in 64 publications) were extracted, of which 18 studies were RCTs, 25 studies were non-RCTs, and four were HTA submissions included as part of the grey literature search. Only two RCTs (OASIS-HAE and HELP) reported in five publications were included in locally adapted SLR, as these two studies included the interventions of interest (donidalorsen and lanadelumab) and were phase 3 RCTs. A summary of these extracted studies is presented in Table 46. No studies were excluded due to quality issues identified during quality assessment. The PRSIMA flow chart for the first research questions and the locally adapted SLR is presented in Figure 10. Table 47 presents the full-text references that were included in the global SLR but excluded from the locally adapted SLR. The 179 abstracts or posters excluded are not presented in Table 47.

Figure 10 PRISMA Diagram (clinical research question and local adaptation)



Abbreviations: PRSIMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomised controlled trial.
Notes: 179 of the references excluded based on publication type were abstracts or posters, while four were HTA submission documents.

Table 46 Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
OASIS-HAE Riedl et al. 2024 (2) Wu & Banerji 2025 (24)	Evaluate the safety and efficacy of donidalorsen in participants with HAE and effect of donidalorsen on the quality and pattern of HAE attacks and their impact on QoL.	Phase 3, multicentre, double-blind, randomised, placebo-controlled study	Patients aged ≥12 years with a confirmed diagnosis of HAE-C1INH-Type1 or HAE-C1INH-Type2, and with at least two investigator-confirmed HAE attacks during the Run-in Period (56 days to one day before randomisation).	Donidalorsen: 80 mg Q4W Donidalorsen: 80 mg Q8W Placebo	Time-Normalised Investigator-Confirmed HAE Attack Rate (Per Month) From Week 1 to Week 25 [Time Frame: Week 1 to Week 25]	Time-Normalised Investigator-Confirmed HAE Attack Rate (Per Month) From Week 5 to Week 25 [Time Frame: Week 5 to Week 25] Percentage of Investigator-Confirmed HAE Attack-Free Participants From Week 5 to Week 25 [Time Frame: Week 5 to Week 25] Time-Normalised Moderate or Severe Investigator-Confirmed HAE Attack Rate (Per Month) From Week 5 to Week 25 [Time Frame: Week 5 to Week 25]

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						Number of Participants With a Clinical Response From Week 5 to Week 25 [Time Frame: Week 5 to Week 25] Investigator-Confirmed HAE Attack Rate Requiring Acute HAE Therapy From Week 5 to Week 25 [Time Frame: Week 5 to Week 25] Percentage of Participants Who Are Well Controlled on the AECT at Week 25 [Time Frame: Week 25] Change From Baseline in AE-QoL Questionnaire Total Score at

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						Week 25 [Time Frame: Week 25]
HELP Banerji et al. 2018 (3) Lumry et al. 2021 (25) Riedl et al. 2020 (26)	Evaluate the efficacy and safety of lanadelumab in preventing acute angioedema attacks in patients with Type I and Type II HAE.	Phase 3, randomised, double-blind, parallel-group, placebo-controlled trial	Patients aged ≥12 years with HAE type 1 or 2, and with at least one HAE attack during the 4-week run-in period.	Lanadelumab: 150 mg Q4W Lanadelumab: 300 mg Q4W Lanadelumab: 300 mg Q2W Placebo	Rate of Investigator Confirmed HAE Attacks During Treatment Period [Time Frame: From Day 0 to Day 182]	Rate of Investigator Confirmed HAE Attack Requiring Acute Treatment [Time Frame: From Day 0 to Day 182] Rate of Moderate or Severe Investigator Confirmed HAE Attacks [Time Frame: From Day 0 to Day 182] Rate of Investigator Confirmed HAE Attacks During Day 14 Through Day 182 [Time Frame: From Day 14 to Day 182]

Abbreviations: AECT = Angioedema Control Test; AE-QoL = Angioedema Quality of Life; HAE = hereditary angioedema; HAE-C1INH-Type1 = HAE-C1 inhibitor-Type 1; HAE-C1INH-Type2 = HAE-C1 inhibitor-Type 2; QoL = quality of life; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks.

Table 47 Full-text references excluded in the locally adapted SLR

Author (Study)	Reference	Reason for exclusion
Craig 2024 (HELP-OLE)	Craig et al. 2024 (60)	Study design
Craig 2024 (HELP-OLE)	Banerji et al. 2022 (61)	Study design
Craig 2024 (HELP-OLE)	Craig et al. 2022 (62)	Study design
Craig 2024 (HELP-OLE)	Lumry et al. 2023 (63)	Study design
Aygören-Pürsün 2018 (APeX-1)	Aygören-Pürsün et al. 2018 (64)	Intervention
Lumry 2019 (SAHARA)	Lumry et al. 2019 (39)	Intervention
Longhurst 2017 (COMPACT)	Longhurst et al. 2017 (46)	Intervention
Longhurst 2017 (COMPACT)	Bernstein et al 2020 (65)	Intervention
Longhurst 2017 (COMPACT)	Craig et al. 2019 (66)	Intervention
Longhurst 2017 (COMPACT)	Craig et al. 2019 (67)	Intervention
Longhurst 2017 (COMPACT)	Craig et al. 2017 (68)	Intervention
Longhurst 2017 (COMPACT)	Levy et al. 2020 (69)	Intervention

Longhurst 2017 (COMPACT)	Li et al. 2018 (70)	Intervention
Zuraw 2021 (APeX-2)	Zuraw et al. 2021 (43)	Intervention
Zuraw 2021 (APeX-2)	Wedner et al. 2021 (71)	Intervention
Zuraw 2021 (APeX-2)	Kiani-Alkhan et al. 2024 (72)	Intervention
Ohsawa 2021 (APeX-J)	Ohsawa et al. 2021 (73)	Intervention
Ohsawa 2021 (APeX-J)	Honda et al. 2024 (74)	Intervention
Riedl 2018 (OPuS-2)	Riedl et al. 2018 (75)	Intervention
Craig 2023 (VANGUARD)	Craig et al. 2023 (42)	Intervention
Lumry 2014 (NCT01005888)	Lumry et al. 2014 (76)	Intervention
Riedl 2017 (NCT02247739)	Riedl et al. 2017 (77)	Intervention
Banerji 2017 (NCT02093923)	Banerji et al. 2017 (78)	Study design
Craig 2022 (NCT03712228)	Craig et al. 2022 (79)	Intervention
Craig 2022 (NCT03712228)	Craig et al. 2024 (80)	Intervention
Fijen 2022 (NCT04030598)	Fijen et al. 2022 (81)	Study design

Fijen 2022 (NCT04030598)	Petersen et al. 2024 (82)	Study design
Riedl 2016 (NCT01756157)	Riedl et al. 2016 (83)	Intervention
Fukuda 2023 (EUdraCT 2019-003921-99)	Fukuda et al. 2023 (84)	Intervention
Szegedi 2008	Szegedi et al. 2008 (85)	Intervention
Castaldo 2021	Castaldo et al. 2021 (86)	Study design
Craig 2017	Craig et al. 2017 (87)	Intervention
Federici 2018	Federici et al. 2018 (88)	Intervention
Zuraw 2016	Zuraw et al. 2016 (89)	Intervention
Srinivasan 2024	Srinivasan et al. 2024 (90)	Intervention
Bork 2020	Bork et al. 2024 (91)	Intervention
Gelfand 1976	Gelfand et al. 1976 (92)	Intervention
Bork 2008	Bork et al. 2008 (93)	Intervention
Bernstein 2014	Bernstein et al. 2014 (94)	Intervention
Greve 2016	Greve et al. 2016 (95)	Intervention

Johnson 2021	Johnson et al. 2021 (96)	Intervention
Reshef 2013	Reshef et al. 2013 (97)	Intervention
Wintenberger 2014	Wintenberger et al. 2014 (98)	Intervention
Busse 2015	Busse et al. 2015 (99)	Intervention
Bygum 2014	Bygum et al. 2014 (100)	Study design
Waytes 1996	Waytes et al. 1996 (101)	Intervention
Lindsay 2022	Lindsay et al. 2022 (102)	Intervention
Frank 1972	Frank et al. 1972 (103)	Intervention
Yildiz 2021	Yildiz et al. 2021 (104)	Intervention
Baker 2013	Baker et al. 2013 (105)	Intervention
Johnson 2023	Johnson et al. 2023 (106)	Intervention
Yao 2025	Yao et al. 2025 (107)	Study design
Magerl 2025 (INTEGRATED)	Magerl et al. 2025 (108)	Study design
Entrala 2024	Entrala et al. 2024 (109)	Intervention

Piotrowicz 2021	Piotrowicz et al. 2021 (110)	Study design
NICE 2021	NICE TA738 (111)	Publication type
NICE 2019	NICE TA606 (112)	Publication type
SMC 2019	SMC 2206 (113)	Publication type
SMC 2022	SMC 2405 (114)	Publication type

D.1.4 Quality assessment

Each RCT identified in the clinical SLR underwent a comprehensive quality assessment using version 2 of the Cochrane risk of bias tool for randomised trials (115). In addition, non-RCTs were assessed according to Centre for Reviews and Dissemination's guidance.

No studies were excluded due to quality issues identified during quality assessment. Details of the quality assessments are not reported here, as the assessments were conducted separately for each publication; further information is available upon request.

D.1.5 Unpublished data

The clinical study report for OASIS-HAE (Ionis Pharmaceuticals, Inc., 2024 (23)) has been used in this application, as it provides additional details beyond those published in Riedl et al. 2024 (2). However, most of the results presented here are also available in Riedl et al. 2024 (2), as reflected by the fact that tables and figures referencing Ionis Pharmaceuticals, Inc., 2024 (23) typically also reference Riedl et al. 2024 (2) or ClinicalTrials.gov, 2021 (29). The unpublished data from the clinical study report for OASIS-HAE originate from an internal document describing the study methods and results in detail and are therefore considered to be of high quality. Additional publications are planned of OASIS-HAE long-term safety and efficacy of donidalorsen in patients from OASIS-HAE who subsequently enrolled in the open-label extension (OLE) cohort (NCT05392114) of the ongoing OASISplus study. Final results from the OASISplus OLE cohort (34) are not yet published; however, a publication of the results from the full OLE cohort is planned shortly after the open-label extension is closed early 2027. Additionally, a final publication on the OLE switch cohort, based on a longer cut-off, is also planned in 2027. Some of the unpublished data from the OASISplus study has been presented at the 2025 American Collage of Allergy, Asthma & Immunology (ACAAI) Annual Scientific Meeting on November 7th, 2025 (115).

Appendix E. Clinical comparison scheme

In Table 48 we present our suggestion for the placement of donidalorsen in the DMC's table of positioning of medicines for the prophylactic treatment of HAE (corresponding to Table 1 in Medicinrådet, 2025 (116)).

Table 48 Suggestion for the DMC's positioning of medicinal products for the preventive treatment of HAE

	Pharmaceutical
Use for at least 80 % of the population*	SC C1-inhibitor (Berinert[1] 2000 IU and 3000 IU)
	SC donidalorsen
	SC garadacimab
	SC lanadelumab
Consider	oral berotralstat
Only use in special cases	Intravenous C1-inhibitor (Cinryze[1])

Abbreviations: DMC = Danish Medicines Council; HAE = hereditary angioedema; IU = international units; SC = subcutaneous.
Notes: * The percentage describes the proportion of the patient population that, at a minimum, should initiate treatment with the medicinal product that is designated as the first choice in the recommendation. [1] Only the listed medicinal products and strengths are approved for routine preventive treatment.

In Table 49 we present our suggestion for the DMC's basis for calculating comparable doses for similar first choice medicines for long-term prophylactic treatment of HAE (corresponding to Table 2 in Medicinrådet, 2025 (116)). The comparable dose suggested by Otsuka is based on donidalorsen Summary of Product Characteristics (22) and the proportion of patients who were stable and attack-free for at least 3 months in the OASIS-HAE trial in a comparable way as to how the DMC has calculated the comparable dose and quantify for s.c. lanadelumab.

The Summary of Product Characteristics for lanadelumab specifies that the recommended starting dose is 300 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction to 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight. The DMC estimates that approximately 50% of patients treated with lanadelumab have their dose adjusted from treatment every 2 weeks to every 4 weeks over a 9-12 month period with gradual tapering in treatment frequency. Experience from Denmark, as well as long-term follow-up studies conducted in other European countries, show that this is also the case in clinical practice (NICE assessment of Andembry 2025).

The Summary of Product Characteristics for donidalorsen specifies that the recommended starting dose in adult and adolescent patients is 80 mg donidalorsen administered once monthly. In a similar way to lanadelumab, the dosing interval can be extended to 80 mg every two months if patients are well controlled (e.g., attack free). However, the approved posology includes the additional element that the time period for the observation is specified to at least three months while receiving donidalorsen. Data requested by the EMA from the OASIS-HAE phase 3 trial showed that >75% of patients starting on Q4W dosing were stable and attack-free for at least three consecutive months during the 25 week trial period (>80% in the European subgroup of patients). It is fair to assume that similar results are to be expected in Danish patients. Considering current Danish clinical practice, Otsuka believes that it is a conservative estimate to assume that 75% of patients will have their dose adjusted from every month to every other month over a similar time period as experienced for lanadelumab.

The comparable dose suggested by Otsuka is therefore based on the proportion of patients who were stable and attack-free for at least 3 months in the OASIS-HAE trial. The weighted average of monthly and bi-monthly dose intervals is suggested to be calculated as follows: 25% 80 mg once monthly (12 doses/year) and 75% 80 mg every two months (6 doses/year). With 1,84 units during 8 weeks being equivalent to once monthly dosing, as for garadacimab, the quantity for donidalorsen equates to 25%*1,84 units plus 75%*0,92 units which is equal to a weighted average of 1,15 units per 8 week period.

Table 49 Suggestion for the DMC's basis for comparable doses for long-term prophylactic treatment of HAE

Pharmaceutical	Comparable doses	Quantity
SC C1-inhibitor (Berinert[1] 2000 IU and 3000 IU)	60 IE/kg body weight, every 2-3 days	33,6 packs of 2000 IE or 22,4 packs of 3000 IE *Alt. 67.200 IE[2]*
SC garadacimab	200 mg once monthly (12 doses/year)	1,84 units 200 mg pen *Alt. 368 mg*
SC lanadelumab	50%: 300 mg every 2 weeks 50%: 300 mg every 4 weeks	3 units 300 mg pen *Alt. 900 mg*
SC donidalorsen	25%: 80 mg once monthly 75%: 80 mg every 2 months	1.15 units 80 mg pen *Alt. 92 mg*

[1]Only these forms/strengths are approved for routine prophylactic treatment. [2]Calculated based on an average body weight of 70 kg.

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