24 November 2025
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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Dawnzera (donidalorsen)
Treatment of hereditary angioedema
EU/3/24/2898

Sponsor: Otsuka Pharmaceutical Netherlands B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Donidalorsen
Other name(s)	-
International Non-Proprietary Name	Donidalorsen
Tradename	Dawnzera
Orphan condition	Treatment of hereditary angioedema
Sponsor's details:	Otsuka Pharmaceutical Netherlands B.V. Herikerbergweg 292 1101 CT Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Ionis Ireland Limited
COMP opinion	18 January 2024
EC decision	19 February 2024
EC registration number	EU/3/24/2898
Post-designation procedural history	
Transfer of sponsorship	Transfer from Ionis Ireland Limited to Otsuka Pharmaceutical Netherlands B.V. - EC decision of 16 August 2024
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Finbarr Leacy / Paolo Gasparini
Applicant	Otsuka Pharmaceutical Netherlands B.V.
Application submission	20 November 2024
Procedure start	27 December 2024
Procedure number	EMA/H/C/006554
Invented name	Dawnzera
Proposed therapeutic indication	Dawnzera is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older. Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Dawnzera
CHMP opinion	13 November 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Cécile Dop / Joao Rocha
Sponsor's report submission	25 April 2025
COMP discussion and adoption of list of questions	4-6 November 2025
Oral explanation	2 December 2025
Sponsor's removal request	20 November 2025

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal designation in 2024 was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing donidalorsen was considered justified based on preliminary clinical data showing a significant reduction in attacks in patients with the condition;
- the condition is life-threatening and chronically debilitating due to recurrent attacks of oedema in various parts of the body that may cause airway obstruction leading to asphyxia;
- the condition was estimated to be affecting less than 0.5 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing donidalorsen will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing a significant reduction in attacks in patients with the condition which compares favourably to authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing donidalorsen as an orphan medicinal product for the orphan condition: treatment of hereditary angioedema".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Hereditary angioedema (HAE) is a genetic, rare, chronic, debilitating and potentially life-threatening disorder characterised by recurrent, and often unpredictable, attacks of swelling in any subcutaneous or submucosal part of the body, without the presence of hives (Bernstein 2018). The type of swelling seen in HAE is bradykinin mediated rather than histaminergic and therefore is not responsive to the

use of steroids and/or antihistamines. HAE attacks often occur without a trigger; however, precipitating factors shown to contribute to the frequency of attacks include stress, trauma, infection, menstruation and pregnancy, as well as various medications (such as oestrogen-containing drugs and angiotensin-converting enzyme inhibitors) (Gower 2011).

HAE is an autosomal dominant genetic disorder caused by one of more than 450 different mutations in the serine protease inhibitor G1 (SERPING1) gene which leads to either a deficiency in the serine protease inhibitor, C1 inhibitor (C1INH); classified as Type I HAE, or a dysfunction of C1INH; classified as Type II HAE. Type I HAE is by far the most common, accounting for 85% of all HAE cases (Lumry 2013).

C1INH is a major regulator of the complement, contact and coagulation cascades through inhibition of several different proteases (including plasma kallikrein and coagulation factors XIa and XIIa). Given its role in regulating these systems, a deficiency of C1INH causes uncontrolled activation of these cascades, resulting in increased vascular permeability and the classic symptoms of HAE (Lumry 2013).

Diagnosis consists of careful consideration of clinical symptoms like recurrent abdominal pain or angioedema without urticaria, family history and genetic counselling. As 25% of patients with HAE present with a spontaneous C1INH mutation, an absence of family history is not sufficient to rule out a diagnosis of HAE. Confirmation of HAE requires laboratory testing by measurement of complement factor 4 (C4) and C1INH functional and quantitative levels. If both C4 and C1INH levels and C1INH functional activity are low, this is consistent with Type I HAE. However, if the C4 and C1INH levels are normal but the C1INH functional activity is low, then Type II HAE is considered likely (Bernstein 2018).

The approved therapeutic indication "Dawnzera is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older" falls within the scope of the designated orphan condition "treatment of hereditary angioedema".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

There have been no changes in the seriousness of the condition since the time of orphan designation. Hereditary angioedema (HAE) shows considerable variability in severity between individuals. Disease burden is determined not only by the frequency and severity of attacks, but also by the impact on daily activities and overall quality of life (QoL) (Bork et al., 2021). Even when attacks are generally mild, laryngeal involvement can be life-threatening, and more than half of patients experience at least one laryngeal attack during their lifetime (Bork et al., 2006). Psychological comorbidities are common; high rates of depression and anxiety have been reported in international surveys (Mendivil et al., 2021). Patients receiving injectable long-term prophylaxis (LTP) report burdensome dosing schedules, injection/infusion-site reactions, discomfort during administration, gastrointestinal side effects, and insufficient reduction of attack burden (Aygören-Pürsün et al., 2014; Banerji, 2013). Patients treated with non-androgen oral LTPs similarly report frequent side effects, gastrointestinal symptoms, suboptimal efficacy, and preference for alternative administration routes. HAE also affects personal, educational, and professional life decisions (Lumry & Settipane, 2020; Bork, Bygum & Hardt, 2008; Maurer et al., 2022).

Therapeutic options for HAE have expanded significantly over the past two decades. Early management relied on attenuated androgens and antifibrinolytics, though their long-term use is limited by safety

issues or insufficient efficacy (Fijen, Bork & Cohn, 2021; Bork et al., 2008). Plasma-derived C1 inhibitor (C1-INH) concentrates later became available, initially intravenously and subsequently as subcutaneous formulations (Anderson & Maina, 2022). More recently, treatments targeting components of the kallikrein–kinin pathway have been approved for both on-demand and prophylactic use (Fijen et al., 2023; Nordendorf et al., 2017).

The 2021 WAO/EAACI guidelines define treatment goals as achieving complete disease control and enabling patients to live normal lives (Maurer et al., 2022). Although current therapies reduce monthly attacks and associated symptoms (Anderson & Maina, 2022), a substantial proportion of patients still experience inadequate disease control and impaired QoL. A Dutch study of adults receiving HAE therapy (59% prophylactic, 28% on-demand, 13% untreated) found that 36% reported poor disease control and persistent reduced QoL (Fijen et al., 2023). Similar findings have been reported in studies from Europe, Australia, and Canada (Mendivil et al., 2021; Nordendorf et al., 2017).

For patients with HAE with normal C1-INH (HAE-nC1INH), available therapies are generally used off-label (Gompels et al., 2005; Lumry, 2013; Zuraw, 2008). Recent findings also indicate an increased prevalence of epilepsy (16.7%) among HAE-nC1INH patients (Kuwahara et al., 2020).

Together, these data support that HAE remains a potentially life-threatening and chronically debilitating condition.

Number of people affected or at risk

At the time of the initial orphan designation, the sponsor estimated that hereditary angioedema (HAE) affected fewer than 0.5 in 10,000 persons in the European Union. For the maintenance of the orphan designation, the sponsor now estimates a global prevalence of approximately 1 in 50,000 individuals, with reported ranges from 1:10,000 to 1:150,000, and notes that no meaningful differences in prevalence have been described across racial, ethnic, or sex groups (Lumry, 2013; Zuraw, 2008; Germenis & Speletas, 2016). Within this total population, HAE Type 1 is considered by the sponsor to represent 80%–85% of cases, and Type 2 to represent 15%–20% (Zuraw, 2008; Germenis & Speletas, 2016). The sponsor acknowledges that epidemiological evidence for HAE with normal C1 inhibitor (HAE-nC1INH; Type 3) remains limited.

According to the sponsor, genetically defined forms of HAE-nC1INH (e.g., HAE-FXII, HAE-PLG, HAE-ANGPT1, and HAE-KNG1) have thus far been identified primarily within European cohorts, including Germany, France, Spain, and Italy (Bork et al., 2020). Based on the sponsor's calculations, HAE-nC1INH represents approximately 1,230–1,331 cases out of an estimated 5,860–6,388 total HAE cases, corresponding to 19.2%–22.7% of all HAE (Riedl et al., 2023). An international analysis of Angioedema Centers of Reference and Excellence (published in 2025 and predominantly reflecting European experience) reported an average estimated HAE-nC1INH proportion of 24% (range 2%–44%). The sponsor notes that robust prevalence data for the United States remain limited. A population-based survey in Germany estimated the prevalence of HAE-FXII at approximately 1 in 400,000 individuals (Bork et al., 2015).

A recent systematic review and meta-analysis of 25 epidemiological studies (2000–2024) identified 11,245 HAE cases worldwide and estimated a pooled prevalence of 1.22 per 100,000 (95% CI: 0.91–1.53), with lower reported prevalence in Asia and Africa than in Europe and North America (Fisch et al., 2025). Another review estimated the prevalence of HAE-C1-INH in Europe at approximately 1 in 67,000 (1.5 diagnosed cases per 100,000) (Aygören-Pürsün et al., 2018).

Additional population-based studies report prevalence estimates consistent with these figures, including: Spain (1 in 91,162), Norway (1 in 66,597), Denmark (1 in 72,671), Sweden (1 in 64,028),

Italy (1 in 66,284), Greece (1 in 93,235), the United States (1 in 331,449), Austria (1 in 64,369), and Slovenia (1 in 105,000) (Schöffl et al., 2019; Rijavec et al., 2013).

A separate global epidemiological assessment incorporating 24 studies from 2000–2024 also identified 11,245 individuals with HAE and estimated a worldwide prevalence of 1–2 cases per 100,000 (Fisch et al., 2025). According to the sponsor, this newly published evidence - available after the 2024 orphan designation - reinforces earlier conclusions that HAE remains an orphan condition.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Current treatment strategies for hereditary angioedema (HAE) aim to prevent the frequency and severity of angioedema attacks and include: (i) on-demand (acute) treatment during an attack, (ii) short-term prophylaxis to prevent attacks associated with procedures known to trigger symptoms, and (iii) long-term prophylaxis.

The currently authorised medicinal products in the EU are included in Tables 1 and 2.

For the assessment of orphan maintenance, products authorised only for on-demand treatment (icatibant, conestat alfa, CINRYZE, BERINERT, EKTERLY) are not considered relevant comparators, as they do not share the same therapeutic objective as Dawnzera (donidalorsen), i.e. long-term prophylaxis.

Among prophylactic therapies, TAKHZYRO, ORLADEYO, BERINERT and ANDEMBRY are considered satisfactory methods. Each is authorised for the routine prevention of hereditary angioedema (HAE) attacks in a population that includes patients aged ≥12 years, without restrictions related to disease severity or prior treatment failure.

CINRYZE, although authorised for prophylaxis and indicated in patients aged ≥6 years, has more restrictive label wording: it is limited to patients with severe or recurrent disease who are intolerant to or insufficiently protected by oral prophylaxis or repeated on-demand therapy. Nevertheless, the sponsor considers CINRYZE to be a satisfactory method. Therefore, Cinryze is only partially comparable, as it applies only to a subset of the target population for Dawnzera.

In summary TAKHZYRO, ORLADEYO, BERINERT, ANDEMBRY, and Danazol represent satisfactory existing methods for the proposed indication, CINRYZE is partially comparable due to its restricted label wording, and products authorised only for on-demand treatment do not represent alternatives for long-term prophylaxis.

Table 1. Products authorised for the on-demand treatment of acute HAE attacks.

Commercial denomination (INN)	Route of administration	Therapeutic indication	Mechanism of action	Satisfactory method
FIRAZYR (icatibant) 30 mg solution for injection in pre-filled syringe	SC	symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged	bradykinin type 2 receptor antagonist	No

2008		2 years and older, with C1-esterase-inhibitor deficiency.		
RUCONEST conestat alfa 2100 Units powder for solution for injection. 2010	IV	treatment of acute angioedema attacks in adults, adolescents, and children (aged 2 years and above) with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency.	C1 inhibitor	No
CINRYZE (C1 inhibitor (human) produced from the plasma of human donors) 500 IU powder and solvent for solution for injection 2011	IV	Treatment and pre-procedure prevention of angioedema attacks in adults, adolescents and children (2 years old and above) with hereditary angioedema (HAE).	Plasma derived Human C1-esterase inhibitor	No
BERINERT (Plasma Human C1-esterase inhibitor) 500 IU powder and solvent for solution for injection/infusion2013	IV or slow infusion	Hereditary angioedema type I and II (HAE). Treatment and pre-procedure prevention of acute episodes. Children and adults	C1 inhibitor	No
Ekterly (sebetralstat) 300 mg film-coated tablets 2025	Oral	Symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.	inhibitor of plasma kallikrein	No

Table 2. Products authorised for the prophylaxis of acute HAE attacks.

Commercial denomination (INN)	**Route of administration**	**Therapeutic indication**	**Mechanism of action**	**Satisfactory method**
CINRYZE (C1-esterase inhibitor) 500 IU powder and solvent for solution for injection 2011	IV	Routine prevention of angioedema attacks in adults, adolescents and children (6 years old and above) with severe and recurrent attacks of hereditary angioedema (HAE), who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment	C1-esterase inhibitor	No

TAKHZYRO (lanadelumab) 150 or 300 mg solution for injection in pre-filled syringe 2018	SC	routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 2 years and older.	Inhibitor of plasma kallikrein	Yes
ORLADEYO (berotralstat) 150 mg hard capsules 2021	Oral	routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older	Inhibitor of plasma kallikrein	Yes
ANDEMBRY (garadacimab) 200 mg solution for injection 2025	SC	routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older	Activated factor XII inhibitor	Yes
Danazol	Oral	Routine prevention of recurrent HAE attacks	Synthetic attenuated androgen	Yes
BERINERT (Plasma Human C1-esterase inhibitor) 500 IU powder and solvent for solution for injection/infusion2013	IV or slow infusion	Hereditary angioedema type I and II (HAE). Treatment and pre-procedure prevention of acute episodes. Children and adults	C1 inhibitor	No

Significant benefit

HAE is characterised by recurrent, non-pruritic, non-pitting oedema affecting subcutaneous and submucosal tissues, driven by excess bradykinin due to uncontrolled activation of the kallikrein–kinin system. Bradykinin generation follows cleavage of cleaved high-molecular-weight kininogen (cHK) by active plasma kallikrein. Prekallikrein (PKK) is the upstream precursor of kallikrein and is therefore an early component within this pathway. Current prophylactic therapies act by C1-INH supplementation, direct plasma kallikrein inhibition (antibody or small molecule), or FXIIa inhibition. Donidalorsen is a ligand-conjugated antisense oligonucleotide that selectively reduces hepatic PKK mRNA, thereby lowering PKK protein, limiting conversion to active kallikrein and preventing bradykinin generation. The sponsor's premise is that this upstream, RNA-targeting mechanism can produce durable target suppression and supports an extended-interval dosing strategy, potentially addressing residual disease activity and quality-of-life (QoL) deficits that persist in a proportion of patients despite available prophylaxis.

Donidalorsen is intended for routine prevention of recurrent hereditary angioedema (HAE) attacks in adults and adolescents aged 12 years and older.

The sponsor's justification for maintaining orphan designation for donidalorsen is based on two main arguments intended to demonstrate that the product offers a significant benefit compared with existing satisfactory methods for long-term prophylaxis of HAE:

1. A clinically relevant advantage (CRA) on efficacy grounds.
2. A major contribution to patient care (MCPC) through improved treatment practicality and reduced burden.

Clinically Relevant Advantage (CRA) on efficacy grounds

The sponsor proposes that donidalorsen provides a clinically relevant advantage over currently available therapies for long-term prophylaxis of HAE. According to the sponsor, donidalorsen reduces or eliminates attacks for a substantial proportion of patients, achieves high attack-free rates, and leads to clinically meaningful improvements in patient-reported outcomes, suggesting near-complete disease control at the individual level. The evidence supporting this position is based on results from the Phase 2 and Phase 3 randomized controlled studies and their subsequent long-term open-label extensions.

In the Phase 2 trial (ISIS 721744-CS2), donidalorsen was associated with a marked reduction in attack frequency. During Weeks 5–17, patients receiving donidalorsen experienced a 97% reduction in mean monthly HAE attack rate compared with placebo. More than 90% of patients remained attack-free over the predefined evaluation period, and improvements were seen in angioedema-specific quality of life, exceeding the threshold for clinically meaningful benefit on the AE-QoL (≥6-point improvement).

The Phase 3 study (ISIS 721744-CS5) confirmed these findings in a larger patient population. Over Weeks 5–25, donidalorsen reduced the mean monthly attack rate by 87% compared with placebo. More than half of patients receiving donidalorsen remained attack-free (53.3% vs 9.1% with placebo). At Week 25, approximately 91% of patients treated every four weeks achieved well-controlled disease status on the AECT (score ≥10), compared with 40.9% on placebo. Donidalorsen also reduced moderate or severe attacks by approximately 89% and attacks requiring acute treatment by approximately 92% versus placebo. The sponsor interprets these findings as demonstrating a level of attack prevention that exceeds placebo-controlled expectations.

The sponsor states that the preventive effect is durable, based on outcomes from long-term open-label extension studies. In the Phase 2 extension, treatment effects were maintained for up to two years, with a 96% reduction in attack rate from baseline and no evidence of diminished effect over time. In patients from the Phase 3 study transitioning into the open-label extension (CS5→CS7), attack reductions of 93% (Q4W dosing) and 92% (Q8W dosing) were reported after approximately one year of treatment. Across these extensions, improvements in quality of life were maintained (AE-QoL improvements of +24 to +28 points), high proportions of patients continued to achieve AECT scores consistent with controlled disease, and similar levels of disease control were reported between the Q4W and Q8W dosing schedules.

To provide context, the sponsor compares this data with published efficacy results for existing prophylactic therapies (Table 3 and Table 4). Lanadelumab demonstrated an 87% reduction in attack rate versus placebo in a Phase 3 study, and garadacimab an 86.5% reduction versus placebo in a Phase 3 study. C1-INH concentrates (Berinert/Cinryze) have shown reductions of 88–95% in attack rates, although these therapies typically require twice-weekly intravenous administration. Based on this comparison, the sponsor argues that donidalorsen provides a clinically relevant advantage by delivering a high degree of attack prevention and sustained disease control with less frequent administration.

Table 3. Presentation of the Key Efficacy Data for Donidalorsen and Currently Approved Prophylaxis Therapies for HAE.

	Donidalorsen (Ionis)							**Andembry® Garadacimab (CSL Behring)**		**Takhzyro® Lanadelumab (Takeda)**		
ROA, Interval	*SC Q4W (80 mg)*				*SC Q8W (80 mg)*			*SC (200 mg), SC Q4W (200 mg)*		*SC Q2W (300mg)*	*SC Q4W (300mg)*	*SC Q2W (300mg)*
Trial	*Phase 2[a]*	*Phase 2 OLE[a]*	*Phase 3*	*Phase 3 (OLE)*	*Phase 2 OLE[a]*	*Phase 3*	*Phase 3 (OLE)[a]*	*Phase 3[b]*	*Phase 3 (OLE) (interim results)[c]*	*Phase 3[d]*		*Phase 3 (OLE[e]*
HAE Type	*Part A: HAE-1/HAE-2* *Part B: HAE-nC1-INH.*	*HAE-1/HAE-2*	*HAE-1/HAE-2*	*HAE-1/HAE-2*	*HAE-1/HAE-2*	*HAE-1/HAE-2*	*HAE-1/HAE-2*	*HAE-1/HAE-2*	*HAE-1/HAE-2* *HAE-nC1-INH*	*HAE-1/HAE-2*		*HAE-1/HAE-2*
Time-normalized number of HAE attacks (the rate of attacks)	Part A Week 1 - 17 Active: 0.22/month vs PBO: 2.29/month Week 5 - 17 Active: 0.06/month vs PBO: 2.13/month Part B Week 1 - 17 Active: 1.52/month vs. 4.23 run in period Week 5 - 17 Active: 1.78/month	Week 1 – to end of on treatment period Active 0.04 vs run in baseline 2.69	Week 1 - 25 Active: 0.44/month vs PBO: 2.26/month Week 5 - 25 Active: 0.30/month vs PBO: 2.25/month	-	Week 1 – to end of on treatment period Active 0.03 vs run in baseline 2.20	Week 1 - 25 Active: 1.02/month vs PBO: 2.26/month Week 5 - 25 Active: 0.90/month vs PBO: 2.25/month	-	26 Weeks Active: 0.27/month vs PBO: 2.01/month	13.8 months Active 0.16/month vs run in period 3.57/month	26 Weeks Active 0.26/month vs PBO 1.97/month	26 Weeks Active 0.53/month vs PBO 1.97/month	30 months Active 0.25/month vs baseline 3.05/month
Percentage of HAE Attack-Free Patients	Part A Week 1 - 17 Active 92.3% vs PBO 0 Part B 33.3%	-	Week 5 - 25 Active: 53.3% vs PBO: 9.1%	-	-	Week 5 - 25 Active: 34.8% vs PBO: 9.1%	-	Months 1-3 Active 28% vs PBO 2% 6 months Active 61.5% vs PBO 0	13.8 months 60%	26 Weeks Active 44% vs PBO 2%	26 Weeks Active 31% vs PBO 2%	37.3%

Time-Normalized Moderate or Severe HAE Attack Rate	Part A Week 5 - 17 Active: 0.05/month vs PBO: 1.20/month 96% reduction vs PBO Part B Week 1 - 17 Active: 0.76/month Week 5 - 17 Active: 0.89	Week 1 – end of on treatment period Active 0.02 /month vs run in baseline 1.86/month	Week 5 - 25 Active: 0.12/month vs PBO: 1.15/month 89% reduction vs PBO	-	Week 1 – end of on treatment period Active 0.17 /month vs run in baseline 1.62/month	Week 5 - 25 Active: 0.68/month vs PBO: 1.15/month 41% reduction vs PBO	-	6 months Active: 0.13 vs PBO: 1.35	13.8 months Active 0.11 vs run in period 2.59	26 Weeks Active 0.20/month vs PBO 1.22/month	26 Weeks Active 0.32/month vs PBO 1.22/month	30 Weeks Active 0.20/month vs PBO 2.03/month 93.4% reduction vs baseline 84.3% reduction vs baseline
HAE Attack Rate Requiring Acute HAE Therapy	Part A Week 5 - 17 Active: 0.06 vs PBO: 1.16 95% reduction vs PBO Part B Week 5 - 17 Active: 0.89	Week 1 – end of on treatment period Active 0.02 /month vs run in baseline 1.57/month	Week 5 - 25 Active: 0.15 vs PBO: 1.80 92% reduction vs PBO	-	Week 1 – end of on treatment period Active 0.29 /month vs run in baseline 1.27/month	Week 5 - 25 Active: 0.59 vs PBO: 1.80	-	6 months Active: 0.23/month vs PBO: 1.86/month	13.8 months Active 0.14 vs run in period 2.98	26 Weeks Active 0.21/month vs PBO 1.64/month	26 Weeks Active 0.42/month vs PBO 1.64/month	30 Weeks Active 0.20/month vs PBO 3.04/month 93.4% reduction vs baseline
Mean reduction in attacks	Part A Weeks 1 - 17 90% vs PBO (Weeks 5-17 97% vs PBO	Week 1 – end of on treatment period 96.63 % vs run in baseline	Week 1 to 25 81% vs PBO Week 5 – 25 87% vs PBO	Week 1 -53 93.33 % vs run in baseline	Week 1 – end of on treatment period 82.58% vs run in baseline	Week 1-25 55% vs PBO	Week 1-53 92.01 % vs run in baseline	26 weeks 86.5% vs PBO	13.8 months 95% vs run in period	26 weeks 91% vs PBO	26 weeks 81% vs PBO	30 months 87.4% vs baseline
Attack-free days (AFDs)	N/A	Weeks 5-17 99.83%	-		-	-	-	-	-	26 weeks 27.3 AFDs/month vs 22.6 (PBO) ≈91%	26 weeks 26.9 AFDs/month vs 22.6 (PBO) ≈89.7%	30 months 27.3 AFDs/month

a. Module 2.7.3 Summary of Clinical Efficacy.
b. Craig TJ, Reshef A, Li HH, et al. Efficacy and Safety of garadacimab a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023;401(10382):1079-1090. doi: 10.1016/S0140-6736(23)00350-1.
c. Reshef A, Hsu C, Katelaris CH, et al. Long-term safety and efficacy of garadacimab for preventing hereditary angioedema attacks: Phase 3 open-label extension study. Allergy. 2025;80(2):545-556. doi: 10.1111/all.16351.
d. Banerji A, Riedl MA, Bernstein JA, et al. Effect of Lanadelumab Compared with Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018;320(20):2108-2121. doi: 10.1001/jama.2018.16773.
e. Banerji A, Bernstein JA, Johnston DT, et al. Long-term prevention of hereditary angioedema attacks with lanadelumab: The HELP OLE Study. Allergy. 2022;77(3):979-990. doi:10.1111/all.15011 https://pmc.ncbi.nlm.nih.gov/articles/PMC9292251/.
f. Summary of Product Information Berinert® (Human C1 esterase inhibitor).
g. Summary of Product Information Cinryze C1 Esterase Inhibitor, last update Sept 2024.

Table 4. Presentation of the Key Efficacy Data for Donidalorsen and Currently Approved Prophylaxis Therapies for HAE.

	Donidalorsen (Ionis)							**Cinryze® C1-inhibitor (IV) (Takeda)**		**Berinert® C1-Inhibitor (SQ) (CSL Behring)**			
ROA, Interval	*SC Q4W (80 mg)*				*SC Q8W (80 mg)*			*IV Every 3 or 4 days (1000 IU, 500 IU)[f]*	*IV Every 3 to 7 days (1000 IU)[f]*	*SC BIW (60 IU)[gg]*		*SC BIW (40 IU)[gg]*	
Trial	*Phase 2[a]*	*Phase 2 OLE[a]*	*Phase 3[a]*	*Phase 3 (OLE)*	*Phase 2 OLE[a]*	*Phase 3[a]*	*Phase 3 (OLE)*	*Phase 3[f]*	*Phase 3 OLE[f]*	*Phase 3[g]*	*Phase 3 OLE[g]*	*Phase 3[g]*	*Phase 3 OLE[g]*
HAE Type	*Part A: HAE-1/HAE-2* *Part B: HAE-nC1-INH).*	*HAE-1/HAE-2* *HAE-nC1-INH).*	*HAE-1/HAE-2*	*HAE-1/HAE-2*	*HAE-1/HAE-2*	*HAE-1/HAE-2*	*HAE-1/HAE-2*	*HAE-1/HAE-2*	*HAE-1/HAE-2*	*HAE-1/HAE-2*	*HAE-1/HAE-2*	*HAE-1/HAE-2*	*HAE-1/HAE-2*
Time-normalized number of HAE attacks (the rate of attacks)	Part A Week 1 - 17 Active: 0.22/month vs PBO: 2.29/month Week 5 - 17 Active: 0.06/month vs PBO: 2.13/month Part B Week 1 - 17 Active: 1.52/month vs. 4.23 run in period Week 5 - 17 Active: 1.78/month	Week 1 – to end of on treatment period Active 0.04 vs run in baseline 2.69	Week 1 - 25 Active: 0.44/month vs PBO: 2.26/month Week 5 - 25 Active: 0.30/month vs PBO: 2.25/month	-	Week 1 – to end of on treatment period Active 0.03 vs run in baseline 2.20	Week 1 - 25 Active: 1.02/month vs PBO: 2.26/month Week 5 - 25 Active: 0.90/month vs PBO: 2.25/month	-	12 weeks Active 6.1/12-week treatment period vs PBO 12.7/12-week treatment period	32 months Active 0.50/month vs. baseline (not reported)	16 weeks Active: 0.52/month vs PBO: 4.03/month	-	16 weeks Active: 1.19/month vs PBO: 3.61/month	-
Percentage of HAE Attack-Free Patients	Part A Week 1 - 17 Active 92.3% vs PBO 0 Part B 33.3%	-	Week 5 - 25 Active: 53.3% vs PBO: 9.1%	-	-	Week 5 - 25 Active: 34.8% vs PBO: 9.1%	-	-	-	40%	44.4 %	37.8%	34.9 %
Time-Normalized Moderate or Severe HAE Attack Rate	Part A Week 5 - 17 Active: 0.05/month vs PBO: 1.20/month 96% reduction vs PBO Part B	Week 1 – end of on treatment period Active 0.02 /month vs run in baseline 1.86/month	Week 5 - 25 Active: 0.12/month vs PBO: 1.15/month 89% reduction vs PBO	-	Week 1 – end of on treatment period Active 0.17 /month vs run in baseline 1.62/month	Week 5 - 25 Active: 0.68/month vs PBO: 1.15/month 41% reduction vs PBO	-	-	-				

	Week 1 - 17 Active: 0.76/month Week 5 - 17 Active: 0.89												
HAE Attack Rate Requiring Acute HAE Therapy	Part A Week 5 - 17 Active: 0.06 vs PBO: 1.16 95% reduction vs PBO Part B Week 5 - 17 Active: 0.89	Week 1 – end of on treatment period Active 0.02 /month vs run in baseline 1.57/month	Week 5 - 25 Active: 0.15 vs PBO: 1.80 92% reduction vs PBO	-	Week 1 – end of on treatment period Active 0.29 /month vs run in baseline 1.27/month	Week 5 - 25 Active: 0.59 vs PBO: 1.80	-	-	-	Active 0.32/month vs PBO 3.89/month	-	Active 0.1.13/month vs PBO 5.55/month	-
Mean reduction in attacks	Part A Weeks 1 - 17 90% vs PBO (Weeks 5-1797% vs PBO	Week 1 – end of on treatment period 96.63 % vs run in baseline	Week 1 to 25 81% vs PBO Week 5 – 25 87% vs PBO	Week 1 -53 93.33 % vs run in baseline	Week 1 – end of on treatment period 82.58% vs run in baseline	Week 1-25 55% vs PBO	Week 1-53 92.01 % vs run in baseline	-	-	16 weeks 95.1% vs. PBO	-	16 weeks 88.6 % vs. PBO	-
Attack-free days (AFDs)	N/A	Weeks 5-17 99.83%	-		-	-	-	-	-	-	-	-	-

a. Module 2.7.3 Summary of Clinical Efficacy.
b. Craig TJ, Reshef A, Li HH, et al. Efficacy and Safety of garadacimab a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023;401(10382):1079-1090. doi: 10.1016/S0140-6736(23)00350-1.
c. Reshef A, Hsu C, Katelaris CH, et al. Long-term safety and efficacy of garadacimab for preventing hereditary angioedema attacks: Phase 3 open-label extension study. Allergy. 2025;80(2):545-556. doi: 10.1111/all.16351.
d. Banerji A, Riedl MA, Bernstein JA, et al. Effect of Lanadelumab Compared with Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018;320(20):2108-2121. doi: 10.1001/jama.2018.16773.
e. Banerji A, Bernstein JA, Johnston DT, et al. Long-term prevention of hereditary angioedema attacks with lanadelumab: The HELP OLE Study. Allergy. 2022;77(3):979-990. doi:10.1111/all.15011 https://pmc.ncbi.nlm.nih.gov/articles/PMC9292251/.
f. Summary of Product Characteristic Berinert® (Human C1 esterase inhibitor), Prescribing Information for Berinert / HAEGARDA®.
g. Summary of Product Characteristic Cinryze C1 Esterase Inhibitor, Version Sept 2024.#

To estimate the comparative efficacy and health-related quality of life (HRQoL) of donidalorsen 80 mg every four weeks (Q4W) versus garadacimab (as per its SmPC) and placebo, the sponsor conducted a network meta-analysis (NMA) using data from randomized controlled trials. Donidalorsen 80 mg every eight weeks (Q8W) was also included to contextualize a reduced-frequency dosing regimen.

According to the sponsor, a feasibility assessment confirmed that a RCT-based NMA was appropriate for outcomes aligned across the OASIS-HAE study (donidalorsen) and the VANGUARD study (garadacimab). Outcomes that could be compared in a consistent manner were:

- **Count outcomes:** mean monthly HAE attack rate; mean monthly moderate/severe attacks; mean monthly attacks requiring on-demand treatment.
- **Binary outcomes:** proportions of patients achieving ≥50%, ≥70%, or ≥90% attack reduction from baseline.
- **Continuous outcomes:** change from baseline in AE-QoL total score.

Safety data could not be included in the NMA because disaggregated treatment-emergent adverse event data were either sparse or inconsistently reported across studies, and the sponsor considered that including such data would introduce high uncertainty and risk of misleading inference.

The NMA compared donidalorsen Q4W, donidalorsen Q8W, garadacimab, and placebo. A Bayesian random-effects model was used to account for potential between-study heterogeneity. Poisson, binomial, and normal likelihood functions were used for count, binary, and continuous outcomes, respectively. Because the evidence network was limited, informative priors for between-study variance were applied, based on meta-analytic distributions described by Turner et al. The sponsor notes that, due to this, results may be sensitive to the choice of prior.

Donidalorsen 80 mg Q4W served as the reference treatment, and treatment effects were calculated for the full trial duration reported in each study. The results are summarised in Table 5.

Across the seven prespecified efficacy analyses:

- **Donidalorsen Q8W vs donidalorsen Q4W:** Estimates were inconclusive for all outcomes, with wide 95% credible intervals. No statistically significant difference was observed; however, the results do not demonstrate equivalence, particularly as no equivalence criteria were predefined.
- **Garadacimab vs donidalorsen Q4W:** Estimates were similarly inconclusive, with wide 95% credible intervals. No statistically significant difference was observed; however, the results do not demonstrate equivalence, as no predefined equivalence margin or criteria were applied.
- **Garadacimab vs donidalorsen Q8W:** No estimates or corresponding 95% credible intervals were reported for this comparison are reported.

Table 5. Summary of the of the Comparative Key Primary and Secondary Efficacy Data for Donidalorsen Q8W Versus Garadacimab 400 mg Q4W and Placebo with Donidalorsen Q4W as Reference.

Endpoints	**Donidalorsen Q8W**	**Garadacimab Q4W**	**Placebo**
Median rate ratios for mean number of HAE attacks per month (RE)(95%CrI)	2.33 (0.62, 8.33)	0.69 (0.11, 4.30)	5.17 (1.35, 19.72)*
Median rate ratios for mean number of moderate or severe HAE attacks per month (RE)(95%CrI)	3.24 (0.93, 10.69)	0.53 (0.09, 3.24)	5.60 (1.61, 19.70)*
Median rate ratios for mean number of HAE attacks per month requiring on demand medication (RE)(95%CrI)	1.76 (0.50, 6.30)	0.41 (0.07, 2.36)	3.30 (0.95, 11.39)
Mean difference from baseline in AE-QoL score (RE)(95%CrI)	4.87 (-3.82, 13.59)	-7.68 (-20.80, 5.43)	18.48 (9.43, 27.69)**
Median odds ratio for proportion of patients achieving a ≥50% reduction in HAE attacks from baseline (RE) (95%CrI)	0.45 (0.07, 2.85)	2.07 (0.15, 39.92)	0.04 (0.01, 0.24)*
Median odds ratio for proportion of patients achieving a ≥70% reduction in HAE attacks from baseline (RE)(95%CrI)	0.39 (0.07, 2.07)	2.70 (0.15, 54.63)	0.03 (0.00, 0.22)*

Median odds ratio for proportion of patients achieving a ≥90% reduction in HAE attacks from baseline (RE)(95%CrI)	0.67 (0.13, 3.17)	6.10 (0.38, 119.49)	0.15 (0.02, 0.83)*

*95% CrI does not include 1 and is therefore considered statistically significant.
** 95% CrI does not include 0 and is therefore considered statistically significant
Abbreviations: AE-QOL=Angioedema Quality of Life Questionnaire; CrI=Credible interval; HAE=Hereditary angioedema; Q8W=every 8 weeks; RE=Random effects.
Note: For responder outcomes, OR >1 favours the comparator vs donidalorsen Q4W; for rate ratios >1 indicates higher event rate than donidalorsen Q4W; for AE-QoL, positive values indicate greater improvement vs reference.

The sponsor additionally considers that donidalorsen may offer a clinically relevant advantage by allowing patients to transition directly from other long-term prophylactic therapies without requiring a washout period and resulting in a reduction in the attack activity. Evidence supporting this comes from *Switch patients* in ISIS 721744-CS7, defined as individuals who were donidalorsen-naïve and were previously maintained on prophylaxis with lanadelumab, berotralstat, or a C1-esterase inhibitor (C1-INH). These patients entered the study directly from their prior regimen.

According to the sponsor, a rapid and substantial reduction in attack activity was observed immediately following transition to donidalorsen. At Switch Baseline (defined as the run-in attack rate while on prior prophylaxis), the mean time-normalized, investigator-confirmed HAE attack rate was 0.85 attacks per 4 weeks (SD 1.28). From Week 1 through Week 53 on donidalorsen, the mean attack rate decreased to 0.30 attacks per 4 weeks (SD 0.46), corresponding to a 66.12% reduction (95% CI: −79.69%, −52.55%). When disaggregated by prior therapy, the reduction in attack frequency was consistent across treatment groups (Table 6).

Table 6. Reduction from Week 1 to Week 53 after switch from previous prophylactic therapies.

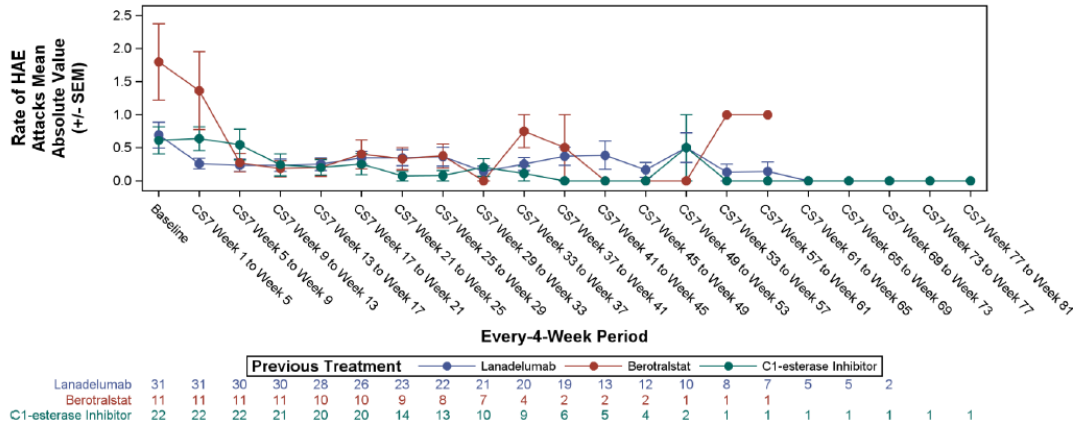
Prior prophylaxis	**% reduction from Switch Baseline**
Lanadelumab (n = 31)	**−51.05%**
Berotralstat (n = 11)	**−76.47%**
C1-esterase inhibitor (n = 22)	**−78.20%**

Some Switch patients had zero attacks during the run-in period; therefore, the sponsor also performed a group-level accumulative analysis, which incorporates data from all patients by summing total attacks and normalizing them to total exposure time. Using this approach:

- Group-level attack rate from Week 1 to Week 53 was **0.30 attacks / 4 weeks**.
- Overall % reduction: **−64.34%**
    - Prior lanadelumab: −60.62%
    - Prior berotralstat: −80.46%
    - Prior C1-INH: −46.57%.

The sponsor highlights that attack reduction appeared early and sustained, with no increase in HAE attacks observed during the transition between treatments. Figure 1 shows a decline in mean attack rate beginning immediately after switch and maintained over successive 4-week intervals through Week 53.

Figure 1. Study ISIS 721744-CS7 - Mean Rate (±SEM) (Absolute Value) of Investigator-confirmed HAE Attacks Over Successive 4-Week Periods (Day 1 to the End of the On-treatment Period) (Full Analysis Set - Switch Patients



C1 = complement 1; HAE = hereditary angioedema; SEM = standard error of mean. Source: ISIS 721744-CS7 CSR Figure 14.2.1.2.2. Note: Lanadelumab = prior lanadelumab; Berotralstat = prior berotralstat; C1-esterase inhibitor = prior C1-esterase inhibitor.
Note: Treatment groups are defined as follows:
Prior lanadelumab = Patients treated previously with lanadelumab who switched to donidalorsen treatment
Prior berotralstat = Patients treated previously with berotralstat who switched to donidalorsen treatment
Prior C1-esterase inhibitor = Patients treated previously with C1-esterase inhibitor who switched to donidalorsen treatment
Switch patients = All patients who did not roll over from another donidalorsen study (donidalorsen-naïve) and were previously maintained on HAE prophylactic therapy with lanadelumab, berotralstat, or a C1-esterase inhibitor.
Note: Baseline is Switch Baseline, defined as the number of HAE attacks that occurred during the Switch Run-In Period divided by the number of days the patient contributed to the Run-In Period multiplied by 28 days. The Switch Run-In Period is defined as the period from Screening to Study Day 1.

Note: The every-4-week HAE attack rate is calculated as the number of HAE attacks occurring during each 4-week period divided by the number of days the patient contributed to this period multiplied by 28 days. Week 1 to Week 5 includes Day 1 to Day 28; Week 5 to Week 9 includes Day 29 to Day 56; Week 9 to Week 13 includes Day 57 to Day 84, and so on.

In addition to the reduction in overall attack frequency, the sponsor reports similar improvements across secondary clinical outcomes. The mean time-normalized rate of moderate or severe attacks decreased from 0.54 to 0.17 attacks per 4 weeks, corresponding to an 81.92% reduction (95% CI: –95.60%, –68.24%). A reduction was also observed in attacks requiring acute rescue therapy, which decreased by 68.99% from baseline (95% CI: –84.33%, –53.65%). From Week 5 through Week 53, 40.6% of patients remained attack-free.

Patient-reported outcomes showed a similar pattern. Following treatment with donidalorsen, the percentage of patients with AECT scores indicating well-controlled disease was higher compared with the percentage at Baseline. At Week 13, of the 58 patients who had poorly controlled disease at Baseline, 94.8% had achieved a well-controlled disease state. At Week 25, of the 43 patients who had poorly controlled disease at Baseline, 90.7% had achieved a well-controlled disease state. AE-QoL total scores improved by 10.4 points at Week 17 and 11.9 points at Week 25, both exceeding the 6-point threshold considered clinically meaningful. According to the sponsor, these improvements were consistent across all prior prophylaxis subgroups, and no increase in breakthrough attacks or unexpected safety findings was observed during or after the transition to donidalorsen.

Conclusion on clinically relevant advantage claims

For the purpose of establishing a clinically relevant advantage under the significant benefit framework, comparisons against all authorised long-term prophylactic treatments are required. While the sponsor provides extensive descriptive comparisons with lanadelumab, berotralstat, danazol and garadacimab, no statistical methodology for formal comparisons was submitted to quantify relative efficacy, to quantify the uncertainty in the estimated relative effects, and to adjust for differences across patient

populations, baseline characteristics, or study designs in the indirect comparisons. Consequently, the relative efficacy of donidalorsen versus these satisfactory treatment methods has not been robustly demonstrated, and a clinically relevant advantage on efficacy grounds cannot be concluded based on the current evidence submitted.

A Bayesian network meta-analysis (NMA) comparing donidalorsen (Q4W and Q8W) with garadacimab and placebo was submitted; however, the comparative outcomes were associated with wide credible intervals across all endpoints for the comparison of donidalorsen Q4W against garadacimab, rendering the NMA inconclusive. These results do not demonstrate equivalence or exclude meaningful treatment effect differences between donidolarsen and garadacimab. In fact, point estimates numerically favoured garadacimab. No estimates of the effect of garadacimab versus donidalorsen Q8W were presented, preventing an assessment of that regimen.

Regarding the switching data presented, showing patients transitioning from prior prophylactic therapies to donidalorsen, these observations may be clinically meaningful and could contribute to the argument of improved patient management. However, the relevance of these findings for patients, as well as the clinical importance of the magnitude of the observed reductions in attack rate and improvements in quality-of-life measures, is not yet sufficiently justified. Further clarification is requested regarding the methodology used to generate these data (including baseline definition and analytical approach) and a clearer clinical interpretation of the observed effects, to enable an assessment of the true patient-relevant benefit of switching to donidalorsen. Particularly, it needs to be demonstrated that the observed behaviour is the effect of donidalorsen, and cannot be attributed to other factors, e.g. regression to the mean.

In summary, donidalorsen demonstrates efficacy within its clinical trials. However, without appropriate comparative analyses versus all currently authorised prophylactic therapies, a clinically relevant advantage on efficacy grounds has not been established.

Major contribution to patient care

In addition to efficacy-related arguments, the sponsor considers that donidalorsen provides a major contribution to patient care by reducing treatment burden, allowing flexibility in dosing intervals, and enabling direct transition from other prophylactic treatments without loss of disease control.

Historically, long-term prophylaxis in hereditary angioedema (HAE) has required frequent or invasive administration. Intravenous plasma-derived C1-INH products were often administered up to twice weekly and could require support from healthcare professionals. The introduction of subcutaneous therapies reduced procedural complexity, though dosing every two weeks (lanadelumab) or every four weeks (garadacimab) remains necessary. According to the sponsor, the ability to individualize treatment intensity and reduce administration frequency further addresses an unmet tolerability and practicality need for patients requiring lifelong therapy.

The sponsor’s MCPC rationale focuses on treatment burden, dose-interval flexibility, and switching practicality.

Dose-interval flexibility (Q4W to Q8W) claim

Donidalorsen is administered as 80 mg subcutaneously every four weeks (Q4W) with the option to extend the dosing interval to every eight weeks (Q8W) in patients who achieve sustained attack control. The sponsor considers this adaptive regimen a key component of the proposed MCPC.

In the open-label extension study ISIS 721744-CS7 (data cut-off 27 January 2025), 12 patients who remained attack-free on Q4W dosing for approximately one year transitioned to Q8W (Table 7):

- Mean time on Q4W: **447 days**.
- Mean time on Q8W: **116 days**.
- Mean reduction in HAE attack rate vs baseline: Q4W **–98.47%**, Q8W **–98.44%**.
- **No patient resumed more frequent dosing** during the evaluation period.

Table 7. Summary of HAE Attack Rate (per 4-weeks) and Duration of Treatment for Patients who Switched from Donidalorsen 80 mg Q4W to Q8W in the Open Label Extension Period in 721744-CS7 Study

Subject ID	**HAE Attack Rate (per 4-weeks)**			**Duration (Days)**		**%Change from Baseline in HAE Attack Rate**	
	Baseline	**Q4W**	**Q8W**	**Q4W**	**Q8W**	**Q4W**	**Q8W**
Patient 1	3	0	0.562871	392.18	198.98	-100	-81.2376
Patient 2	2.709677	0	0	503.96	85	-100	-100
Patient 3	1.333333	0	0	391.98	57	-100	-100
Patient 4	1.166667	0	0	398.97	56	-100	-100
Patient 5	2.333333	0.056804	0	492.92	82	-97.5655	-100
Patient 6	1.435897	0	0	455.2	152	-100	-100
Patient 7	3	0	0	398.09	223	-100	-100
Patient 8	2.333333	0.095196	0	588.26	105	-95.9202	-100
Patient 9	2.545455	0	0	387	257	-100	-100
Patient 10	1.714286	0.12309	0	454.95	18	-92.8197	-100
Patient 11	1.142857	0	0	452.92	84	-100	-100
Patient 12	1.333333	0.062643	0	446.98	76	-95.3018	-100
Mean	2.004014	0.028144	0.046906	446.9508	116.165	-98.4673	-98.4365

A second extension cohort (ISIS 721744-CS3, data cut-off 26 February 2024) supports these findings. Of eight patients who transitioned from Q4W to Q8W after ≥12 attack-free weeks:

- **5/8 remained on Q8W through study completion**.
- **3/8 returned to Q4W** following recurrence of attacks.
- Mean attack rate during Q8W: **0.30 attacks / 4 weeks**.
- Mean reduction from baseline: **82.6%**.
- **Three patients remained completely attack-free**.

The sponsor argues that these observations suggest that extended dosing is feasible in a proportion of patients and that return to Q4W dosing remains available if needed.

Exposure–response modelling would support these clinical findings. Simulations conducted in 10,000 virtual subjects predicted that **56.4%** of patients initiating donidalorsen Q4W would qualify for Q8W extension (no attacks during first 3 months). Estimated reductions in attack burden remained high (Table 8).

Table 8.

Regimen	Median attacks / 4 weeks	Median reduction vs baseline
Continue Q4W	0.01	**99.7%**
Switch to Q8W (Month 1)	0.07	**97.4%**
Switch to Q8W (Month 2)	0.12	**95.5%**

Evidence in HAE-nC1INH (Type 3)

HAE-nC1INH is a rare subgroup characterised by recurrent attacks despite normal C1-INH levels. Few medicinal products are currently authorised for long-term prophylaxis in this population in the EU, and evidence for existing therapies is limited (berotralstat n=7; garadacimab n=6; plasma-derived C1-INH limited to case reports).

Donidalorsen has prospective interventional data in this subgroup (Table 9).

Table 9.

Study	n	Regimen	Duration	Attack rate change vs baseline
ISIS 721744-CS2 (Phase 2)	3	80 mg Q4W	17 weeks	**–76%**
Compassionate use	1	Clinical dosing	–	Symptomatic improvement

Improvements in patient-reported outcomes (AECT, AE-QoL) were also observed, and no treatment discontinuations were reported for safety reasons in this subgroup. Based on this, the sponsor considers donidalorsen to provide a potential new prophylactic option in a group with limited authorised treatment alternatives.

Major Contribution to Patient Care Conclusion

With respect to the MCPC, the EU Orphan Regulation requires that before a MCPC can be considered, the medicinal product must first demonstrate at least equivalent efficacy and safety compared with all existing satisfactory treatment methods. At present, equivalence versus lanadelumab, berotralstat, garadacimab, and danazol have not been demonstrated, as no comparative statistical analyses have been provided against all satisfactory methods. The indirect comparison submitted for garadacimab, based on a network meta-analysis, is inconclusive. Therefore, the analysis cannot confirm equivalence between donidalorsen and garadacimab.

With respect to the major contribution to patient care (MCPC), if equivalence in efficacy and safety to the satisfactory methods can be demonstrated, donidalorsen's potential advantages - such as the possibility of extended dosing intervals, simplified subcutaneous administration, and seamless switching from existing therapies - could support improved convenience and flexibility in long-term disease management. However, it is noted that only a limited number of patients have so far transitioned from the Q4W to the Q8W dosing regimen, which constrains the interpretability of these findings. Moreover, no patient-reported outcome (PRO) data has been submitted to support the clinical relevance of this transition from the patient perspective. The sponsor is therefore invited to further substantiate the MCPC justification by expanding on the available evidence and, where possible, providing quantifiable data on aspects such as adherence, reduction in treatment burden, patient satisfaction, and quality of life. Demonstrating a clear and measurable link between these elements

and patient-relevant outcomes would be essential to determine whether the proposed advantages translate into a meaningful major contribution to patient care.

Overall conclusion

Overall, based on the available evidence, a significant benefit of donidalorsen over the currently authorised satisfactory methods (lanadelumab, berotralstat, danazol) on efficacy grounds has not been demonstrated. Although the sponsor presented point estimates and descriptive summaries comparing donidalorsen with these therapies, no comparative statistical analysis was provided - either direct (within a randomized trial) or indirect (across studies). Consequently, the relative efficacy and the uncertainty associated with these comparisons could not be quantified, and differences in study populations or baseline prognostic factors were not addressed. In the absence of such comparative methodology, superiority or advantage on efficacy grounds cannot be concluded.

With regard to the claim of a major contribution to patient care, the legal framework for significant benefit requires that the new treatment first demonstrates at least equivalent efficacy and safety compared with all existing satisfactory methods before improvements in convenience, dosing, or patient experience may be considered. In this respect, no comparative evidence was provided to assess equivalence versus lanadelumab or berotralstat.

Regarding the switching data presented, showing patients transitioning from prior prophylactic therapies to donidalorsen, may represent clinically meaningful observations and could contribute to the argument of improved patient management. However, the relevance of these findings for patients, as well as the clinical importance of the magnitude of the observed reductions in attack rate and improvements in quality-of-life measures, is not yet sufficiently justified. Further clarification is requested regarding the methodology used to generate these data (including baseline definition and analytical approach) and a clearer clinical interpretation of the observed effects, to enable an assessment of the true patient-relevant benefit of switching to donidalorsen.

Taken together, the evidence does not support the significant benefit, and the absence of comparative data versus all satisfactory methods prevents the demonstration of at least equivalent efficacy and safety needed to support a major contribution to patient care.

4. COMP list of issues

Based on the information submitted so far, significant benefit has not been demonstrated.

The sponsor has provided extensive descriptive clinical data. To enable a robust assessment of the relative efficacy, these comparisons need to be supported by an appropriate comparative statistical approach that quantifies relative efficacy, including the uncertainty in these estimates, and that adequately accounts for variability between studies.

The switching data could be clinically relevant and may contribute to the argument of improved patient management. The sponsor is therefore invited to further elaborate on these findings, including the methodology used and the clinical interpretation of these observations.

For a claim of major contribution to patient care, COMP requires that the new treatment demonstrates at least equivalent efficacy, safety and benefit–risk relative to all authorised satisfactory methods. At this stage, equivalence versus lanadelumab, berotralstat, garadacimab, and danazol has not yet been formally demonstrated.

In summary, additional clarification and comparative analyses - including rationale for the selected methods, interpretation of the indirect evidence, and further support for the claim of a major contribution to patient care are required for a significant benefit conclusion.