Donidalorsen (hereditary angioedema)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Patient and family involvement

No feedback was received within the framework of this dossier assessment.

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
AAS	Angioedema Activity Score
ACE	angiotensin converting enzyme
ACT	appropriate comparator therapy
AE	adverse event
AE-QoL	Angioedema Quality of Life
AECT	Angioedema Control Test
C1-INH	C1 esterase inhibitor
CI	confidence interval
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
DMID	Division of Microbiology and Infectious Diseases
EAACI	European Academy of Allergy and Clinical Immunology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GAD-7	Generalised Anxiety Disorder 7
HAE	hereditary angioedema
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LLN	lower limit of normal
MMRM	mixed-effects model with repeated measures
NCI	National Cancer Institute
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
RCT	randomised controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardised mean difference
VAS	visual analogue scale
WAO	World Allergy Organization
WHO	World Health Organization

Abbreviation	Meaning
WPAI+CIQ:SHP	Work Productivity and Activity Impairment plus Classroom Impairment Questions: Specific Health Problem

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug donidalorsen. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 27 February 2026.

Research question

The aim of this report is to assess the added benefit of donidalorsen in comparison with the appropriate comparator therapy (ACT) for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of donidalorsen

Therapeutic indication	**ACT**[a]
For routine prevention of recurrent attacks of hereditary angioedema in adults and adolescents aged 12 years and older[b, c]	Routine prevention with a C1 esterase inhibitor or lanadelumab or **berotralstat**
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**. b. According to the G-BA, the therapeutic indication of donidalorsen is assumed to comprise only patients with type I or type II HAE. c. Both study arms should offer the possibility of acute treatment of HAE attacks. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HAE: hereditary angioedema	

In addition to the treatment options specified by the G-BA in the ACT, the company designated garadacimab as a comparator therapy. The company conducted the search for studies of direct comparison for donidalorsen versus all treatment options listed by the G-BA in the ACT as well as garadacimab. As the company did not identify any randomised controlled trials (RCTs) that directly compared donidalorsen versus the G-BA's ACT or garadacimab, it conducted a search for RCTs for a potential adjusted indirect comparison. The company selected berotralstat for the search for studies with the comparator therapy. The additional inclusion of garadacimab in the comparator therapy therefore remained without consequence for the benefit assessment. It should be noted that the company did not justify the selection of berotralstat, although studies exist for all 3 treatment options of the ACT as well as for garadacimab, which the company cited as an additional option, that might be suitable for an indirect comparison.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the inclusion criterion of the company.

Study pool and study design

No relevant RCTs were identified for a direct comparison of donidalorsen versus the ACT. The company presented an adjusted indirect comparison using the common comparator placebo, with the OASIS-HAE study on the donidalorsen side and the studies APeX-2 and APeX-J on the berotralstat side.

OASIS-HAE (study with donidalorsen)

OASIS-HAE is a double-blind, randomised study comparing donidalorsen in 2 different dosing intervals (monthly and every 2 months) with placebo in patients aged 12 years and older with type I or type II HAE. The study comprised a screening or run-in phase lasting up to 8 weeks (56 days) and a 24-week (Day 1 to Day 169) placebo-controlled treatment phase.

The study included patients with a documented diagnosis of type I or type II HAE defined as a clinical history consistent with HAE (subcutaneous or mucosal, non-pruritic swelling episodes) and a C1 esterase inhibitor (C1-INH) deficiency (functional level <40% normal level). To be eligible for the study, patients had to have experienced ≥2 HAE attacks during the run-in phase of up to 56 days.

A total of 91 patients were enrolled in the OASIS-HAE study. These were initially randomised into 2 cohorts in a 2:1 ratio: Cohort 1 investigated the monthly administration of 80 mg of donidalorsen, whilst Cohort 2 investigated the administration of 80 mg of donidalorsen every 2 months, in each case compared with placebo. Within each of the 2 cohorts, patients were randomised in a 3:1 ratio to receive either donidalorsen or placebo. 46 patients were allocated to receive monthly treatment with donidalorsen, and 23 patients were allocated to receive donidalorsen every 2 months. It was specified in advance that the 2 placebo arms were to be pooled (N = 22), and there was no explicit information on how many patients were treated with placebo each month or every 2 months. The Cohort 2 intervention arm, with a dosing interval of every 2 months, was not relevant for the benefit assessment and is not shown below.

Monthly treatment with donidalorsen was carried out largely in compliance with the information provided in the summary of product characteristics (SmPC). On-demand therapy of HAE attacks was allowed in the study. Plasma-derived or recombinant C1-INH, bradykinin-2 receptor antagonists (icatibant) or kallikrein inhibitors (ecallantide) could be used.

The primary outcome of the study was the time-normalised number of investigator-confirmed HAE attacks per 4 weeks during the 24-week treatment phase (Day 1 to Day 169). Secondary outcomes were further outcomes in the categories morbidity and health-related quality, as well as adverse events (AEs).

APeX-2 and APeX-J (studies with berotralstat)

The APeX-2 and APeX-J studies are double-blind, randomised studies of berotralstat in patients aged 12 years and older and ≥40 kg body weight with HAE type I or type II. The studies each comprised a 10-week screening phase, including a run-in phase of up to 56 days, and a treatment phase of up to 240 weeks (APeX-2) or up to 104 weeks (APeX-J), divided into 3 phases. The first, 24-week, placebo-controlled treatment phases of the studies APeX-2 and APeX-J, with berotralstat at a dose of 150 mg compared with placebo, were relevant for this benefit assessment.

The APeX-2 and APeX-J studies included patients with a clinical diagnosis of HAE type I or type II, defined as a C1-INH deficiency corresponding to functional C1-INH activity <50% of normal and a C4 concentration <LLN during the screening phase. Patients with a diagnosis of any other type of recurrent angioedema were excluded from participation in the study. Patients had to have had ≥2 HAE attacks during the ≥14 to ≤56-day (APeX2) or the 56-day (APeX-J) run-in phases.

In phase 1 of the APeX-2 study, a total of 121 patients were randomly assigned in a 1:1:1 ratio to receive treatment with 110 mg berotralstat (N = 41), 150 mg berotralstat (N = 40) or placebo (N = 40). One patient in the placebo arm received no study treatment. In phase 1 of the APeX-J study, a total of 19 patients were randomly assigned in a 1:1:1 ratio to receive treatment with 110 mg berotralstat (N = 6), 150 mg berotralstat (N = 7) or placebo (N = 6). In both studies, randomisation was stratified by HAE attack rate at baseline (recorded between first screening visit and start of treatment; ≥2 HAE attacks/month versus <2 HAE attacks/month).

In the APeX-2 and APeX-J studies, treatment with berotralstat in the study arm with the 150 mg dose was in compliance with the SmPC.

On-demand therapy of HAE attacks was allowed in the studies. Plasma-derived or recombinant C1-INH, icatibant and ecallantide were allowed in the APeX-2 study, while plasma-derived C1-INH and icatibant were allowed in the APeX-J study. Prophylaxis with C1-INH for an unforeseen/unplanned procedure was also allowed in both studies. Patients were not allowed to have used androgens or tranexamic acid for prophylaxis of HAE attacks within the 28 days prior to screening, or C1-INH for prophylaxis of HAE attacks within the 14 days prior to screening.

The primary outcome of the studies was the rate of HAE attacks confirmed by the investigator (study APeX-2) or by an independent expert (APeX-J) during the 24-week treatment phase (Day 1 to Day 168). Secondary outcomes were further outcomes in the categories morbidity and health-related quality, as well as AEs.

Similarities of the studies for the indirect comparison

Overall, the OASIS-HAE, APeX-2 and APeX-J studies had a similar design. In addition, the patient populations of the studies were sufficiently similar. Differences in individual demographic and clinical characteristics (sex, family origin, proportion of patients with previous long-term prophylaxis) and the possible concomitant treatments (androgens, tranexamic acid, oestrogen-containing drugs) between the studies OASIS-HAE and APeX-2 and APeX-J also did not call into question the sufficient similarity and thus the performance of an adjusted indirect comparison via the common comparator placebo.

Risk of bias

The risk of bias across outcomes was rated as low for all 3 studies. The risk of bias was rated as low for the results of the outcomes of the studies OASIS-HAE, APeX-2 and APeX-J.

Results

One RCT (OASIS-HAE) was available on the side of the intervention with donidalorsen of the given adjusted indirect comparison. Consequently, there was no need to assess homogeneity for the side of the intervention with donidalorsen. On the side of the comparator berotralstat of the present adjusted indirect comparison, there was no important heterogeneity between the effect estimates of the studies APeX-2 and APeX-J for this benefit assessment. As there was no study of direct comparison of donidalorsen versus berotralstat, it was impossible to check the consistency of results. Therefore, the adjusted indirect comparisons had at most a low certainty of results. Hence, no more than hints, e.g. of an added benefit, could be derived on the basis of the data available from the adjusted indirect comparison.

Mortality

All-cause mortality

The results on all-cause mortality were based on data on fatal AEs. No deaths occurred in any of the studies OASIS-HAE, APeX-2 and APeX-J. There is no hint of an added benefit of donidalorsen compared with berotralstat; an added benefit is therefore not proven.

Morbidity

HAE attacks

Monthly rate

For the monthly rate of HAE attacks, the adjusted indirect comparison showed a statistically significant difference in favour of donidalorsen compared with berotralstat. There is a hint of an added benefit of donidalorsen in comparison with berotralstat.

Freedom from attacks

For freedom from attacks, the adjusted indirect comparison showed no statistically significant difference between donidalorsen and berotralstat. There is no hint of an added benefit of donidalorsen compared with berotralstat; an added benefit is therefore not proven.

Activity impairment (Work Productivity and Activity Impairment [WPAI] question 10 / question 6)

With regard to activity impairment assessed using the Work Productivity and Activity Impairment plus Classroom Impairment Questions: Specific Health Problem (WPAI+CIQ:SHP) question 10 (OASIS-HAE) or WPAI question 6 (APeX-2 and APeX-J), the adjusted indirect comparison showed no statistically significant difference between donidalorsen and berotralstat. There is no hint of an added benefit of donidalorsen compared with berotralstat; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

For health status assessed with the EQ-5D VAS, the adjusted indirect comparison showed no statistically significant difference between donidalorsen and berotralstat. There is no hint of an added benefit of donidalorsen compared with berotralstat; an added benefit is therefore not proven.

Health-related quality of life

Angioedema Quality of Life Questionnaire (AE-QoL)

For health-related quality of life assessed with the AE-QoL, the adjusted indirect comparison showed a statistically significant difference in favour of donidalorsen compared with berotralstat for the AE-QoL total score. The standardised mean difference (SMD) was considered to check the relevance of the result. The 95% confidence interval (CI) of the SMD was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. There is no hint of an added benefit of donidalorsen compared with berotralstat; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

For the outcome SAEs, the adjusted indirect comparison showed no statistically significant difference between donidalorsen and berotralstat. There is no hint of greater or lesser harm of donidalorsen in comparison with berotralstat; greater or lesser harm is therefore not proven.

Severe AEs

For the outcome severe AEs, no suitable data were available for the indirect comparison of donidalorsen versus berotralstat. There is no hint of greater or lesser harm of donidalorsen in comparison with berotralstat; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No discontinuations due to AEs occurred in the OASIS-HAE study. One discontinuation due to AEs occurred in the berotralstat arm of the APeX-2 study, and no discontinuation due to AEs occurred in the berotralstat arm of the APeX-J study. There is no hint of greater or lesser harm of donidalorsen in comparison with berotralstat; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug donidalorsen versus the ACT was assessed as follows:

Overall, there is a positive effect for donidalorsen compared with berotralstat. There was no statistically significant effect for the outcome HAE attacks, operationalised as freedom from attacks, but the operationalisation of the monthly rate of HAE attacks, which is also relevant for the benefit assessment, showed a hint of an added benefit with the extent considerable. In summary, there is a hint of a considerable added benefit of donidalorsen in comparison with the ACT for patients aged 12 years and older for the routine prevention of recurrent HAE attacks.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) 'proof', (2) 'indication', (3) 'hint', or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or lesser benefit). For further details see [1,2].

Table 3 summarizes the probability and extent of added benefit of donidalorsen.

Table 3: Donidalorsen – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
For routine prevention of recurrent attacks of HAE in adults and adolescents aged 12 years and older[b, c]	Routine prevention with a C1 esterase inhibitor or lanadelumab or **berotralstat**	Hint of considerable added benefit

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**.
b. According to the G-BA, the therapeutic indication of donidalorsen is assumed to comprise only patients with type I or type II HAE.
c. Both study arms should offer the possibility of acute treatment of HAE attacks.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HAE: hereditary angioedema

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of donidalorsen in comparison with the appropriate comparator therapy (ACT) for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of donidalorsen

Therapeutic indication	**ACT**[a]
For routine prevention of recurrent attacks of hereditary angioedema in adults and adolescents aged 12 years and older[b, c]	Routine prevention with a C1 esterase inhibitor or lanadelumab or **berotralstat**
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**. b. According to the G-BA, the therapeutic indication of donidalorsen is assumed to comprise only patients with type I or type II HAE. c. Both study arms should offer the possibility of acute treatment of HAE attacks. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HAE: hereditary angioedema	

In addition to the treatment options specified by the G-BA in the ACT, the company designated garadacimab as a comparator therapy. The company conducted the search for studies of direct comparison for donidalorsen versus all treatment options listed by the G-BA in the ACT as well as garadacimab. As the company did not identify any randomised controlled trials (RCTs) that directly compared donidalorsen versus the G-BA's ACT or garadacimab, it conducted a search for RCTs for a potential adjusted indirect comparison (see Chapter I 3). The company selected berotralstat for the search for studies with the comparator therapy. The additional inclusion of garadacimab in the comparator therapy therefore remained without consequence for the benefit assessment. It should be noted that the company did not justify the selection of berotralstat, although studies exist for all 3 treatment options of the ACT as well as for garadacimab, which the company cited as an additional option, that might be suitable for an indirect comparison [3].

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the inclusion criterion of the company.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on donidalorsen (status: 15 December 2025)
- Bibliographical literature search on donidalorsen (last search on 15 December 2025)
- Search of trial registries / trial results databases for studies on donidalorsen (last search on 15 December 2025)
- Search on the G-BA website for donidalorsen (last search on 15 December 2025)
- Bibliographical literature search on the ACT berotralstat (last search on 15 December 2025)
- Search of trial registries / trial results databases for studies on the ACT berotralstat (last search on 15 December 2025)
- Search on the G-BA website for the ACT berotralstat (last search on 15 December 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on donidalorsen (last search on 9 March 2026); for search strategies, see I Appendix A of the full dossier assessment
- Search of trial registries for studies on berotralstat (last search on 12 March 2026); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the review of the completeness of the study pool did not identify any studies of a direct comparison of donidalorsen versus the ACT in the given therapeutic indication.

Indirect comparison

As the company did not identify any RCTs that directly compared donidalorsen versus the ACT, it conducted a search for RCTs for a potential adjusted indirect comparison according to Bucher [4]. For this purpose, the company selected berotralstat as the comparator from the ACT options specified by the G-BA. For the adjusted indirect comparison, the company identified the OASIS-HAE study on the side of the intervention and the APeX-2 and APeX-J studies on the side of berotralstat.

The review of the study pool did not identify any additional relevant studies for the adjusted indirect comparison presented by the company.

I 3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, indirect comparison: donidalorsen vs. berotralstat

Study	Study category			Available sources		
	Study for the marketing authorisation of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
donidalorsen vs. placebo						
ISIS 721744-CS5 (OASIS-HAE[d])	Yes	No[e]	Yes	Yes [5]	Yes [6,7]	Yes [8]
berotralstat vs. placebo						
BCX7353-302 (APeX-2[d])	No	No	Yes	No	Yes [9,10]	Yes [11-13]
BCX7353-301 (APeX-J[d])	No	No	Yes	No	Yes [14]	Yes [12,13,15]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website; European Public Assessment Report.
d. In the following tables, the study is referred to by this acronym.
e. Ionis Pharmaceuticals, Inc. developed donidalorsen and sponsored the OASIS-HAE study. Otsuka Pharma GmbH holds the licence to market donidalorsen in Germany.

CSR: clinical study report; G-BA: Federal Joint Committee; GmBH: company with limited liability; RCT: randomised controlled trial

The study pool was consistent with that selected by the company. The APeX-2 and APeX-J studies had already been submitted and assessed in the previous benefit assessments of berotralstat and garadacimab [3,16,17].

Figure 1 is a schematic representation of the indirect comparison.

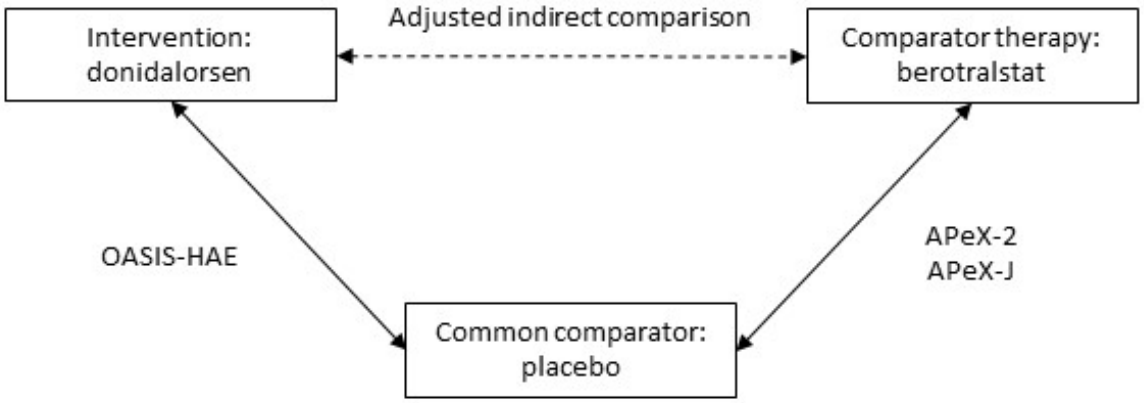


Figure 1: Study pool for the adjusted indirect comparison between donidalorsen and berotralstat via the common comparator placebo

I 3.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, indirect comparison: donidalorsen vs. berotralstat (multipage table)

Study	Study design	Population	Interventions (number of randomised patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
donidalorsen vs. placebo						
OASIS-HAE	RCT, double-blind, parallel	Patients aged ≥12 years with type I or II HAE ▪ Functional C1-INH activity <40% of normal[b] ▪ ≥1 of the following criteria: ▫ Age at reported HAE onset ≤30 years ▫ A family history of type I or II HAE ▫ Complement component 1q within the normal range ▪ ≥2 HAE attacks during run-in phase	▪ donidalorsen[c] monthly (N = 46) ▪ donidalorsen every 2 months (N = 23)[d] ▪ placebo (N = 22)	Screening (including run-in): ≤56 days Treatment: 24 weeks[e] Follow-up: 13 weeks after the last dose of the study medication[f]	39 centres in: Belgium, Bulgaria, Canada, France, Germany, Israel, Italy, Netherlands, Poland, Spain, Turkey, United Kingdom, United States 1/2022–12/2023	Primary: rate of confirmed HAE attacks per 4 weeks during the 24-week treatment phase (Day 1 to Day 169) Secondary: morbidity, health-related quality of life, AEs
berotralstat vs. placebo						
APeX-2	RCT, double-blind, parallel	Patients aged ≥12 years with type I or II HAE ▪ Functional C1-INH activity <50% of normal[g] ▪ C4 concentration <LLN[h] ▪ ≥2 HAE attacks during run-in phase	▪ berotralstat 110 mg (N = 41)[d] ▪ berotralstat 150 mg (N = 40) ▪ placebo (N = 40)	Screening: ≤10 weeks, including run-in (≥14 to ≤56 days) Treatment: 24 weeks[i] Follow-up: 3 weeks after the last dose of the study medication[j]	57 centres in Austria, Canada, Czech Republic, France, Hungary, Germany, North Macedonia, Romania, Spain, United Kingdom, United States 2/2018–4/2022[k]	Primary: rate of confirmed HAE attacks during the 24-week treatment phase (Day 1 to Day 168) Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: donidalorsen vs. berotralstat (multipage table)

Study	Study design	Population	Interventions (number of randomised patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
APeX-J	RCT, double-blind, parallel	Patients aged ≥12 years with type I or II HAE ▪ Functional C1-INH activity <50% of normal[g] ▪ C4 concentration <LLN[h] ▪ ≥2 HAE attacks during run-in phase	▪ berotralstat 110 mg (N = 6)[d] ▪ berotralstat 150 mg (N = 7) ▪ placebo (N = 6)	Screening: ≤10 weeks, including run-in (56 days) Treatment: 24 weeks[i] Follow-up: 3 weeks after the last dose of the study medication[j]	10 centres in Japan 12/2018–7/2021[l]	Primary: rate of confirmed HAE attacks during the 24-week treatment phase (Day 1 to Day 168) Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: donidalorsen vs. berotralstat (multipage table)

Study	Study design	Population	Interventions (number of randomised patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. If the C1-INH functional level was 40% to 50%, a complement factor C4 level <LLN or a demonstrated pathogenic mutation in the SERPING-1 gene were additionally required for inclusion.
c. The patients included in the study were initially randomised in a 2:1 ratio into 2 cohorts: Cohort 1 received a monthly dose and Cohort 2 received a dose every 2 months. The patients were then randomised within the cohorts in a 3:1 ratio to receive either donidalorsen or placebo. For the analysis, patients who were treated with placebo on a monthly and bimonthly basis were pooled.
d. This arm is not relevant for the assessment and is not shown in the following tables.
e. In Module 4 A, the company referred to the analysis period as 'Week 1 to Week 25'. According to the study protocol, the treatment duration is 24 weeks in total (Day 1 to Day 169). In this benefit assessment, the treatment period is referred to as '24 weeks'.
f. Following completion of the randomised controlled treatment phase (24 weeks), patients were able to take part in an open-label extension phase. Follow-up was carried out only in patients who did not take part in the open-label extension phase after the end of the treatment phase. Only one patient in the relevant donidalorsen arm completed the follow-up.
g. For C1-INH functional level between 50% and LLN, the following criterion was necessary for inclusion: SERPING-1 gene mutation or (only in APeX-2) a repeat C1-INH functional level <50%.
h. In the absence of a low C4 value drawn during the intercritical period (i.e. patient is not having an HAE attack), 1 of the following is acceptable to confirm the diagnosis of HAE: a SERPING-1 gene mutation known or likely to be associated with HAE type I or II (assessed during the screening period); a confirmed family history of C1-INH deficiency; a C4 retested during an HAE attack in the screening period with the results <LLN.
i. After the 24-week placebo-controlled, double-blind treatment phase, all patients received berotralstat until Week 240 (Week 144 in the United States; study APeX-2) or until Week 104 or until berotralstat became commercially available (study APeX-J). Berotralstat 110 mg vs. berotralstat 150 mg was investigated in treatment phase 2 (double-blind); only berotralstat 150 mg was given in treatment phase 3 (open-label).
j. After completion of treatment phase 3 or premature discontinuation of treatment.
k. Last visit in the placebo-controlled phase 1: 10 April 2019.
l. Last visit in the placebo-controlled phase 1: 15 November 2019.

AE: adverse event; C1-INH: C1 esterase inhibitor; C4: complement factor C4; HAE: hereditary angioedema; LLN: lower limit of normal; N: number of randomised patients; RCT: randomised controlled trial

Table 7: Characteristics of the intervention – RCT, indirect comparison: donidalorsen vs. berotralstat (multipage table)

Study	Intervention	Comparison
donidalorsen vs. placebo		
OASIS-HAE	donidalorsen 80 mg, SC, monthly	placebo, SC, monthly or every 2 months[a]
	▪ Dose modifications not allowed ▪ Treatment interruption or discontinuation[b] were allowed in case of toxicity or for safety reasons in consultation with the sponsor	
	Prohibited prior and concomitant treatment ▪ Long-term prophylaxis with lanadelumab, C1 esterase inhibitors or berotralstat during the study and ≤5 half-lives prior to screening ▪ ACE inhibitors or oestrogen-containing medications with systemic absorption (e.g. oral contraceptive or hormone replacement therapy) ≤4 weeks prior to screening and during the study ▪ Other oligonucleotides within 4 months of screening if administered as a single dose, or within 12 months of screening if administered as multiple doses ▪ Plasmapheresis during the study ▪ Investigational products or biological agents within 1 month or 5 half-lives (whichever is longer) of screening and during the study **Allowed prior and concomitant treatment** ▪ Acute medications to treat HAE attacks: plasma-derived or recombinant C1-INH concentrate, bradykinin-2 receptor antagonists or kallikrein inhibitors) ▪ Androgens or tranexamic acid, each at a stable dose, as long-term prophylaxis ▪ Stable medications (if not prohibited in the study) provided the dose and type are not expected to change during the study	
berotralstat vs. placebo		
APeX-2 and APeX-J	Berotralstat 150 mg daily, orally	Placebo daily, orally
	▪ Dose modifications not allowed ▪ Interruption of treatment allowed for certain AEs potentially related to the study medication, or other extenuating circumstances[c]	

Table 7: Characteristics of the intervention – RCT, indirect comparison: donidalorsen vs. berotralstat (multipage table)

Study	Intervention	Comparison
	Prohibited prior and concomitant treatment ▪ Short-term prophylaxis of HAE attacks for a preplanned procedure during the screening or during the study ▪ C1-INH for prophylaxis of HAE attacks within the 14 days prior to screening or during the study ▪ ACE inhibitors within 7 days before treatment start or during the study ▪ APeX-2 study: lanadelumab for the prophylaxis of HAE attacks during the study ▪ Drugs metabolized by CYP2D6, CYP2C9, CYP2C19 or CYP3A4, and with narrow therapeutic range, within 7 days before treatment start or during the study ▪ Drugs transported by P-gp, and with narrow therapeutic range, within 7 days before treatment start or during the study ▪ Initiation of an oestrogen-containing hormonal contraceptive within 56 days of screening or during the study[d] ▪ Investigational products within 30 days of screening or during the study ▪ Androgens[e] or tranexamic acid for prophylaxis of HAE attacks within the 28 days prior to screening or during the study **Allowed concomitant treatment** ▪ On-demand therapy for the treatment of HAE attacks with plasma-derived C1-INH, icatibant; in study APeX-2 additionally: recombinant C1-INH, ecallantide ▪ Prophylaxis with C1-INH for an unforeseen/unplanned procedure	

a. The comparator side was pooled from patients who were treated with placebo on a monthly and bimonthly basis.
b. In case of a platelet count <50 000/µL and markedly elevated liver values, treatment was to be discontinued.
c. The investigator and the patient may decide to continue treatment if the patient has a grade 1 or 2 rash that is related to the study medication but the treatment is considered to be beneficial. If the rash does not improve or worsens, as well as for grade 3 or 4 rash related to the study medication, treatment should be discontinued. Study APeX-2: If treatment is interrupted for >10 days due to rash related to the study medication, treatment should not be resumed.
d. Established use (initiation ≥56 days prior to screening) was allowed during the study.
e. Testosterone replacement therapy was allowed during the study.

ACE: angiotensin converting enzyme; AE: adverse event; C1-INH: C1 esterase inhibitor; CYP2D6: cytochrome P450 2D6; CYP2C9: cytochrome P450 2C9; CYP2C19: cytochrome P450 2C19; CYP3A4: cytochrome P450 3A4; HAE: hereditary angioedema; P-gp: P-glycoprotein; RCT: randomised controlled trial; SC: subcutaneous

OASIS-HAE (study with donidalorsen)

OASIS-HAE is a double-blind, randomised study comparing donidalorsen in 2 different dosing intervals (monthly and every 2 months) with placebo in patients aged 12 years and older with type I or type II HAE. The study comprised a screening or run-in phase lasting up to 8 weeks (56 days) and a 24-week (Day 1 to Day 169) placebo-controlled treatment phase.

The study included patients with a documented diagnosis of type I or type II HAE defined as a clinical history consistent with HAE (subcutaneous or mucosal, non-pruritic swelling episodes)

and a C1 esterase inhibitor (C1-INH) deficiency (functional level <40% normal level). Patients with a functional level of 40% to 50% of normal could be enrolled if their complement factor C4 level was below the lower limit of normal (LLN) or if a pathogenic mutation in the SERPING-1 gene had been demonstrated. In addition, at least one of the following criteria had to be met for a diagnosis: age at reported HAE onset ≤30 years, a family history of type I or type II HAE, or complement component 1q within the normal range. Patients with a diagnosis of any other type of angioedema, such as idiopathic angioedema or type III HAE, were excluded from participation in the study. To be eligible for the study, patients had to have experienced ≥2 HAE attacks during the run-in phase of up to 56 days.

The extent to which patients met the inclusion criterion regarding the number of HAE attacks/month in the run-in phase was checked on the basis of the patients' daily entries in the Angioedema Activity Score (AAS), a diary-type questionnaire. The documented HAE attacks had to be confirmed by the investigator. An episode was classified as an HAE attack if at least one symptom occurred in a location typical of HAE (peripheral, abdominal or laryngeal). A discrete attack was counted if there was an at least 24-hour symptom-free period between attacks.

A total of 91 patients were enrolled in the OASIS-HAE study. These were initially randomised into 2 cohorts in a 2:1 ratio: Cohort 1 investigated the monthly administration of 80 mg of donidalorsen, whilst Cohort 2 investigated the administration of 80 mg of donidalorsen every 2 months, in each case compared with placebo. Within each of the 2 cohorts, patients were randomised in a 3:1 ratio to receive either donidalorsen or placebo (see Figure 2). 46 patients were allocated to receive monthly treatment with donidalorsen, and 23 patients were allocated to receive donidalorsen every 2 months. It was specified in advance that the 2 placebo arms were to be pooled (N = 22), and there was no explicit information on how many patients were treated with placebo each month or every 2 months. The Cohort 2 intervention arm, with a dosing interval of every 2 months, was not relevant for the benefit assessment and is not shown below. One patient who had been randomised to monthly treatment with donidalorsen did not receive any study treatment. Randomisation was not stratified.

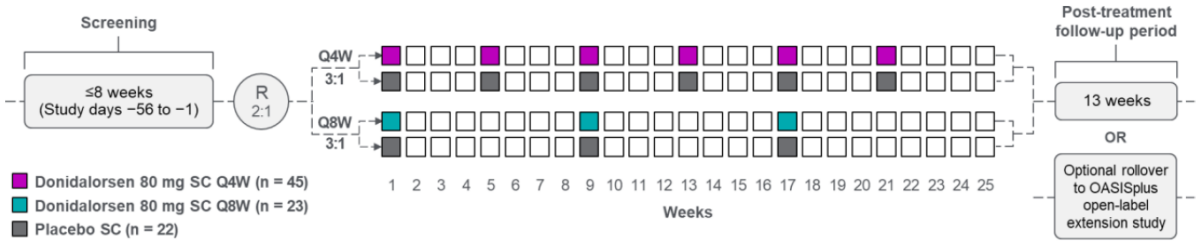


Figure 2: Design of the OASIS-HAE study

Treatment with donidalorsen was carried out largely in compliance with the information provided in the summary of product characteristics (SmPC) [18]. According to the SmPC, switching from monthly dosing to a dosing interval once every 2 months may be considered if the patient is well controlled (e.g. attack-free) for at least 3 months. In total, 22% of patients experienced no HAE attacks during the course of the study, and for these patients at least, a reduction in the dosing interval would potentially have been possible according to the SmPC. However, a switch to a dosing interval of every 2 months could only have taken place from Month 4 at the earliest. The lack of an option to adjust the dosing interval was considered negligible for the purposes of the benefit assessment for the following reasons: The placebo-controlled treatment duration relevant to the benefit assessment lasted only 24 weeks, the adjustment of the dosing interval is not mandatory according to the SmPC, and it can be assumed that the majority of patients would not have been eligible for this adjustment.

On-demand therapy of HAE attacks was allowed in the study. Plasma-derived or recombinant C1-INH, bradykinin-2 receptor antagonists (icatibant) or kallikrein inhibitors (ecallantide) could be used. Whilst long-term prophylaxis with lanadelumab, C1-INH or berotralstat was not permitted from 5 half-lives prior to screening, long-term prophylaxis with a stable dose of androgens or tranexamic acid was permitted.

The primary outcome of the study was the time-normalised number of investigator-confirmed HAE attacks per 4 weeks during the 24-week treatment phase (Day 1 to Day 169). Secondary outcomes were further outcomes in the categories morbidity and health-related quality, as well as adverse events (AEs).

APeX-2 and APeX-J (studies with berotralstat)

The APeX-2 and APeX-J studies are double-blind, randomised studies of berotralstat in patients aged 12 years and older and ≥40 kg body weight with HAE type I or type II. The studies each comprised a 10-week screening phase, including a run-in phase of up to 56 days, and a treatment phase of up to 240 weeks (APeX-2) or up to 104 weeks (APeX-J), divided into 3 phases. In the first double-blind treatment phase of 24 weeks (Day 1 to Day 168), berotralstat at 2 different doses (110 mg and 150 mg) was compared with placebo. In the second, double-blind treatment phase (Week 24 to Week 48 [APeX-2] or Week 24 to Week 52 [APeX-J]), all patients received berotralstat at doses of 110 mg or 150 mg. In the third, open-label treatment phase (Week 48 to Week 240 [APeX-2] or Week 52 to Week 104 [APeX-J]), all patients received berotralstat at a dose of 150 mg. The first, 24-week, placebo-controlled treatment phases of the studies APeX-2 and APeX-J, with berotralstat at a dose of 150 mg compared with placebo, were relevant for this benefit assessment.

The APeX-2 and APeX-J studies included patients with a clinical diagnosis of HAE type I or type II, defined as a C1-INH deficiency corresponding to functional C1-INH activity <50% of

normal and a C4 concentration <LLN during the screening phase. The inclusion of patients with a C1-INH functional level between 50% and LLN was acceptable if a SERPING-1 gene mutation known or likely to be associated with HAE type I or II was determined; in APex-2, a repeat C1-INH level <50% could alternatively be determined. In both studies, in the absence of a low C4 value drawn during the intercritical period (i.e. patient is not having an HAE attack), one of the following criteria was acceptable to confirm the diagnosis of HAE: 1) SERPING-1 gene mutation known or likely to be associated with HAE type I or II, 2) a confirmed family history of C1-INH deficiency, 3) a C4 retested during an HAE attack in the screening period with the results <LLN. Patients with a diagnosis of any other type of recurrent angioedema were excluded from participation in the study. Patients had to have had ≥2 HAE attacks during the ≥14 to ≤56-day (APeX-2) or the 56-day (APeX-J) run-in phases.

The extent to which the inclusion criterion for the number of HAE attacks/month was met during the run-in phase was checked on the basis of the patients' entries in an electronic diary. The investigator (study APeX-2) or the independent expert (study APeX-J) reviewed the entries and assessed whether the reported symptoms, taking into account clinical characteristics and any additional clarifying questions for the patient, were an HAE attack. An HAE attack was considered as such if it included symptoms of swelling. Symptoms of swelling, in addition to visible swelling, could also include symptoms in the oropharyngeal or abdominal regions that are indicative of internal swelling. In addition, the HAE attack had to have either been treated, required medical attention, or been documented to have caused functional impairment.

In phase 1 of the APeX-2 study, a total of 121 patients were randomly assigned in a 1:1:1 ratio to receive treatment with 110 mg berotralstat (N = 41), 150 mg berotralstat (N = 40) or placebo (N = 40). One patient in the placebo arm received no study treatment. In phase 1 of the APeX-J study, a total of 19 patients were randomly assigned in a 1:1:1 ratio to receive treatment with 110 mg berotralstat (N = 6), 150 mg berotralstat (N = 7) or placebo (N = 6). In both studies, randomisation was stratified by HAE attack rate at baseline (recorded between first screening visit and start of treatment; ≥2 HAE attacks/month versus <2 HAE attacks/month).

In the APeX-2 and APeX-J studies, treatment with berotralstat in the study arm with the 150 mg dose was in compliance with the SmPC [19]. The berotralstat arm with the 110 mg dose was not relevant for the assessment and is not presented further below.

On-demand therapy of HAE attacks was allowed in the studies. Plasma-derived or recombinant C1-INH, icatibant and ecallantide were allowed in the APeX-2 study, while plasma-derived C1-INH and icatibant were allowed in the APeX-J study. Prophylaxis with C1-INH for an unforeseen/unplanned procedure was also allowed in both studies. Patients were not allowed to have used androgens or tranexamic acid for prophylaxis of HAE attacks

within the 28 days prior to screening, or C1-INH for prophylaxis of HAE attacks within the 14 days prior to screening.

The primary outcome of the studies was the rate of HAE attacks confirmed by the investigator (study APeX-2) or by an independent expert (APeX-J) during the 24-week treatment phase (Day 1 to Day 168). Secondary outcomes were further outcomes in the categories morbidity and health-related quality, as well as AEs.

Table 8 shows the characteristics of the patients in the studies included.

Table 8: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: donidalorsen vs. berotralstat (multipage table)

Study	donidalorsen vs. placebo		berotralstat vs. placebo			
Characteristic	OASIS-HAE		APeX-2		APeX-J	
Category	donidalorsen	placebo	berotralstat	placebo	berotralstat	placebo
	N = 45[a]	N = 22	N = 40	N = 40	N = 7	N = 6
Age [years], mean (SD)	40 (15)	35 (11)	40 (14)	45 (14)	37 (9)	42 (14)
Sex [F/M], %	62/38	36/64	58/43	68/33	86/14	83/17
Family origin, n (%)						
White	42 (93)	18 (82)	38 (95)	37 (93)	0 (0)	0 (0)
Black or African American	1 (2)	1 (5)	1 (3)	2 (5)	0 (0)	0 (0)
Asian	1 (2)	0 (0)	0 (0)	0 (0)	6 (86)	6 (100)
Other	1 (2)[b]	3 (14)[c]	1 (3)[b]	1 (3)[b]	1 (14)[b]	0 (0)[b]
BMI at screening [kg/m²], mean (SD)	28.0 (6.7)	28.9 (9.2)	30.4 (6.7)	29.3 (6.8)	22.3 (5.0)	28.3 (5.9)
HAE type, n (%)						
Type I	42 (93)	20 (91)	ND	ND	ND	ND
Type II	3 (7)	2 (9)	ND	ND	ND	ND
History of laryngeal attack, n (%)	22 (49)	12 (55)	26 (65)	34 (85)	4 (57)	5 (83)
Family history of HAE, n (%)	41 (91)	17 (77)	ND	ND	ND	ND
Time since diagnosis [years], mean (SD)	18.9 (13.2)	18.2 (10.2)	28.7 (13.1)	33.4 (14.0)	17.7 (9.1)	22.3 (11.4)
Time since diagnosis [years], median [min; max]	17.0 [0; 52]	18.0 [2; 36]	26.5 [4.0; 53.0]	32.5 [2.0; 62.0]	21.0 [4.0; 26.0]	21.5 [10.0; 37.0]
Age at symptom onset, mean (SD)	11.6 (9.9)	12.9 (7.2)	11.2 (5.9)	11.0 (8.9)	19.6 (7.2)	20.0 (15.8)
Prior long-term prophylaxis, n (%)[d]	6 (13)	5 (23)	30 (75)[e]	29 (73)[e]	6 (86)	4 (67)
Number of attacks in the last 12 months, median [Q1, Q3]	36 [15; 57]	24 [12; 47]	ND	ND	ND	ND
Rate of HAE attacks [attacks/month][f]						
Mean (SD)	3.6 (2.2)	2.9 (1.7)	3.1 (1.6)	2.9 (1.1)	2.0 (1.1)	2.5 (1.5)

Table 8: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: donidalorsen vs. berotralstat (multipage table)

Study	donidalorsen vs. placebo		berotralstat vs. placebo			
Characteristic	OASIS-HAE		APeX-2		APeX-J	
Category	donidalorsen	placebo	berotralstat	placebo	berotralstat	placebo
	N = 45[a]	N = 22	N = 40	N = 40	N = 7	N = 6
Median [min; max]	3.3 [0.5; 10.0]	2.5 [1.0; 8.1]	2.7 [0.9; 6.7]	3.0 [1.3; 6.2]	2.2 [0.8; 3.9]	2.2 [0.9; 5.3]
Number of patients with, n (%)						
≥2 attacks per month	33 (73)	16 (73)	30 (75)	27 (68)	4 (57)	3 (50)
<2 attacks per month	12 (27)	6 (27)	10 (25)	12 (30)	3 (43)	3 (50)
Treatment discontinuation, n (%)	1 (2)[g]	4 (18)[g]	3 (8[h])[i]	5 (13[h])[i]	0 (0)	1 (17[h])[j]
Study discontinuation, n (%)	ND[k]	ND[k]	ND[l]	ND[l]	ND[l]	ND[l]

a. Number of randomised patients who received at least one dose of the respective treatment.
b. Includes the category 'Other'.
c. Institute's calculation; included the categories 'American Indian or Alaska Native' and 'Multiple'.
d. OASIS-HAE: first-choice prophylactic treatments, except for androgens and tranexamic acid; APeX-2 and APeX-J: any previous prophylactic treatment for HAE.
e. 12 (30%) patients in the intervention arm vs. 11 (28%) patients in the control arm had prophylactic treatment within 30 days before screening.
f. Period of recording between screening and the start of study medication.
g. Common reasons for treatment discontinuation in the intervention arm vs. the control arm were the following: lack of efficacy (2% vs. 14%) and pregnancy (0 vs. 4.5%).
h. Institute's calculation.
i. Common reasons for treatment discontinuation in the intervention vs. control arm were the following: AEs (3% each), lack of efficacy (3% vs. 5%), withdrawal of consent (3% each) (percentages: Institute's calculation, based on number of randomised patients). In addition, one patient in the control arm did not receive any study treatment.
j. The reason for treatment discontinuation in the control arm was the following: AE.
k. There are no data on patients with study discontinuation.
l. There are no explicit data on patients with study discontinuation. Module 4 A on berotralstat shows that 38 vs. 36 patients in the intervention vs. control arm (APeX-2 study) and 7 vs. 6 patients (APeX-J study) completed all assessments in the placebo-controlled phase 1.

BMI: body mass index; F: female; HAE: hereditary angioedema; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomised patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomised controlled trial; SD: standard deviation

The characteristics of the patient populations were largely comparable across the individual studies and study arms, with the exception of the characteristic sex in the OASIS-HAE study and prior long-term prophylaxis (see below). The mean age of the patients in the 3 studies was about 40 years. Most patients in OASIS-HAE and APeX-2 were white, whilst most patients in the smaller APeX-J study were Asian. In OASIS-HAE, approximately 53% of participants were female; in the APeX-2 study, 63%; and in the APeX-J study, 85%. A history of laryngeal attacks was slightly more common in the placebo arms of the studies than in the intervention arms. The majority of patients in APeX-2 and APeX-J had already received prior long-term prophylaxis (including androgens and tranexamic acid) (approximately 74%), whilst approximately 16% of patients in OASIS-HAE had received prior long-term prophylaxis (excluding androgens and tranexamic acid). No data were available on previous long-term prophylaxis in a comparable operationalisation. The time since diagnosis was approximately 19 years in OASIS-HAE, approximately 30 years in APeX-2 and approximately 20 years in APeX-J. The patients in the studies had an average rate of 2.0 to 3.6 HAE attacks/month in the run-in phase (OASIS-HAE) or between screening and start of the study medication (APeX-2 and APeX-J).

In all 3 studies, more patients in the placebo arms (13% to 18%) discontinued treatment prematurely than in the intervention arms (0 to 8%). There are no explicit data on the number of patients with study discontinuation. For the APeX-2 and APeX-J studies, The information in Module 4 A regarding berotralstat showed that the majority of patients completed all assessments in the placebo-controlled phase 1.

I 3.3 Similarities of the studies for the indirect comparison

Study design

The studies OASIS-HAE, APeX-2 and APeX-J are multicentre, double-blind RCTs, each of which included patients aged 12 years and older with HAE type I or type II. There were marginal differences in the diagnostic criteria relevant to inclusion in the studies. Patients with a C1-INH functional level <40% normal level could be included in OASIS-HAE. For patients with a functional level of 40% to 50% of normal to be included, a complement factor C4 level <LLN or a pathogenic mutation in the SERPING-1 gene had to be demonstrated. For inclusion in the APeX-2 and APeX-J studies, patients had to have a C1-INH functional level <50% as well as a C4 level <LLN. However, patients with C1-INH ≥50%, but <LLN, could also be included if a pathogenic SERPING-1 gene mutation was demonstrated. Overall, there were no indications that the marginal differences in the inclusion criteria resulted in different patient populations being included. All 3 studies included a run-in phase of a maximum of 56 days, in which patients had to have ≥2 HAE attacks to be eligible for transition to the treatment phase with the study medication.

In all 3 studies, the placebo-controlled treatment phase was 24 weeks. The study implementation periods differed only marginally. While the OASIS-HAE study started in 2022 and was completed in 2023, the APeX-2 and APeX-J studies started in 2018 and completed their placebo-controlled phases in 2019. The APeX-J study was conducted exclusively in Japan, while OASIS-HAE and APeX-2 recruited patients globally. There was no indication that the characteristic region had a substantial influence on the results. The difference in the characteristic region in the APeX-J study therefore did not call into question the sufficient similarity of the studies overall.

Similarities of the patient populations

Information on the patient characteristics can be found in Section I 3.2; information on the location of HAE attacks before study start and on previous and concomitant treatments of the patient populations is also presented as supplementary information in I Appendix B of the full dossier assessment.

Differences in patient characteristics with regard to the proportions of women and regarding family origin were shown between APeX-J versus APeX-2 and OASIS-HAE (Table 8). Although the proportion of women in the study population was slightly higher in the APeX-J study than in OASIS-HAE and APeX-2, overall more women than men were included in all studies. In line with the fact it was conducted in Japan, the APeX-J study mainly included Asian patients, whereas most patients in OASIS-HAE and APEX-2 were white. There were no indications that the characteristic family origin had a substantial influence on the results. Overall, the demographic and clinical characteristics of the included patients were assessed as sufficiently comparable between the studies OASIS-HAE and APeX-2 as well as APeX-J.

Differences between the studies related to the proportion of patients who had previously received long-term prophylaxis (APeX-2 intervention arm: 75%; placebo arm: 73%; APeX-J intervention arm: 86%; placebo arm: 67%; OASIS-HAE intervention arm: 13%; placebo arm: 23%). However, the operationalisations differed between the studies (androgens and tranexamic acid were taken into account in APeX-2 and APeX-J, but not in OASIS-HAE). At baseline, patients in all 3 studies were not receiving long-term prophylaxis with other medications (except for 1 patient receiving tranexamic acid and 3 patients receiving androgens in OASIS-HAE; see below). Both the rate of HAE attacks at baseline (OASIS-HAE: 2.9 to 3.6 HAE attacks/month; APeX-2: 2.9 to 3.1 HAE attacks/month; APeX-J: 2.0 to 2.5 attacks/month; see Table 8), as well as the baseline values for the morbidity outcomes (recorded using the EQ-5D visual analogue scale [VAS]) and for health-related quality of life (recorded using the Angioedema Quality of Life Questionnaire [AE-QoL]; see Table 14) showed that patients had a comparable burden of disease at study entry. There were therefore no indications that the characteristic of previous long-term prophylaxis had a substantial influence on the results.

There was no information on the number of patients with HAE type I or type II for the APeX-2 and APeX-J studies. This was of no consequence for this benefit assessment, however. This is due to the fact that, firstly, HAE type I and type II do not differ in terms of their clinical symptoms, prognosis and treatment options. Secondly, assuming a frequency of type I and type II in accordance with the guidelines [20,21] and the use of sufficiently comparable inclusion criteria in the studies, the distribution of type I and type II was presumed to be comparable to that in the OASIS-HAE study. There was also a lack of information regarding the family history of HAE for the studies APeX-2 and APeX-J. A family history is relevant for the diagnosis of HAE [20,21]. However, there were no indications that the characteristic family history had a substantial influence on the results. Furthermore, taking into account the inclusion and exclusion criteria of the studies – which were considered to be sufficiently comparable – it was not assumed that the differences in the individual characteristics called into question the performance of an adjusted indirect comparison based on the studies OASIS-HAE, APeX-2 and APeX-J.

Similarities in the common comparator and concomitant treatment

The common comparator in the presented indirect comparison was placebo. The OASIS-HAE study as well as the APeX-2 and APeX-J studies allowed on-demand medication with C1-INH and icatibant to treat HAE attacks. The studies OASIS-HAE and APeX-2 also allowed ecallantide as on-demand medication, but this drug is not approved in Germany. However, ecallantide was not used as concomitant medication for HAE attacks in any patients in either the OASIS-HAE study or the APeX-2 study [12].

Long-term prophylaxis of HAE attacks with C1-INH, androgens or antifibrinolytics or tranexamic acid was not permitted in APeX-2 and APeX-J within defined periods before screening or the run-in phase, or during the studies. In the OASIS-HAE study, prophylaxis with C1-INH was also not permitted; however, long-term prophylaxis with androgens and tranexamic acid at a stable dose was permitted. However, this affected no more than 3 patients in the intervention arm and 1 patient in the placebo arm. In addition, angiotensin converting enzyme (ACE) inhibitors were not allowed to be administered during the studies, or in the OASIS-HAE study within 4 weeks before the run-in phase, or in the APeX-2 and APeX-J studies within 7 days before the start of treatment. This concurs with the recommendations of the German S1 guideline [21] and the recommendations of the World Allergy Organization (WAO) and the European Academy of Allergy and Clinical Immunology (EAACI) [20], according to which ACE inhibitors can increase the frequency or severity of HAE attacks and should therefore be discontinued and avoided in future.

The APeX-2 and APeX-J studies differed from the OASIS-HAE study with regard to pre- and concomitant treatment with oestrogen-containing medications. In the OASIS-HAE study, oestrogen-containing medications with systemic absorption (e.g. oral contraceptives or

hormone replacement therapy) were not allowed within 4 weeks prior to screening and during the study. This concurs with the recommendations of the guidelines [20,21], according to which oestrogen-containing oral contraceptives and oestrogen hormone replacement therapies can increase the frequency or severity of HAE attacks and should therefore be discontinued and avoided in future. In the APeX-2 and APeX-J studies, in contrast, only the initiation of oestrogen-containing hormonal contraception within 56 days of the screening visit or during the study was not allowed. Established use (initiation ≥56 days prior to screening) was allowed to be continued during the studies. However, no information was available on how many patients in the APeX-2 and APeX-J studies received oestrogen-containing drugs.

To assess the potential influence of the different specifications regarding oestrogen-containing medications on the study results, this benefit assessment examined the extent to which the effects for the outcome HAE attacks (operationalised as monthly rate) in men (no potential use of oestrogen-containing drugs) differed from those in the total study population. As in the overall study population (Table 12), the indirect comparison of donidalorsen versus berotralstat in men also showed an effect estimate that was notably <1 (rate ratio [95% CI]: 0.62 [0.24; 1.59]; p = 0.323; based on available results from OASIS-HAE and APeX-2). There was no substantial difference in the monthly rate of HAE attacks among women in the respective placebo arms at the end of the study (OASIS-HAE: 2.17 HAE attacks/month; APeX-2: 2.16 HAE attacks/month; APeX-J: no data). For the OASIS-HAE study, no data broken down by sex were available on the baseline values for the morbidity outcomes (recorded using the EQ-5D VAS) and for health-related quality of life (recorded using the AE-QoL). However, these baseline values were comparable when considering the overall populations in the 3 studies (>50 to 85% women). Overall, the uncertainty arising from any differences in concomitant treatment with oestrogen in the studies was assessed as low.

The use of on-demand medications administered during the studies was assessed as sufficiently comparable between the studies (see Table 19 in I Appendix B of the full dossier assessment), although no data were available for the APeX-J study. In the studies OASIS-HAE and APeX-2, the main drugs used for on-demand treatment of HAE were C1-INH and icatibant [12]. Based on the specifications in the study design regarding allowed and disallowed concomitant treatments, it can be assumed that C1-INH and icatibant were also administered as on-demand medication in the APeX-J study.

Summary of the similarity of the studies

Similarity is a key requirement for the consideration of studies in the adjusted indirect comparison. The studies had a similar design. In addition, the patient populations of the studies were sufficiently similar. The described differences in individual demographic and clinical characteristics (sex, family origin, proportion of patients with previous long-term

prophylaxis) and the possible concomitant treatments (androgens, tranexamic acid, oestrogen-containing drugs) between the studies OASIS-HAE and APeX-2 and APeX-J also did not call into question the sufficient similarity and thus the performance of an adjusted indirect comparison via the common comparator placebo.

I 3.4 Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, indirect comparison: donidalorsen vs. berotralstat

Comparison Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
donidalorsen vs. placebo							
OASIS-HAE	Yes	Yes	Yes	Yes	Yes	Yes	Low
berotralstat vs. placebo							
APeX-2	Yes	Yes	Yes	Yes	Yes	Yes	Low
APeX-J	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomised controlled trial							

The risk of bias across outcomes was rated as low for all 3 studies.

Transferability of the study results to the German health care context

According to the company, the OASIS-HAE study was conducted mainly in Western study centres, and as such, also involved participants from Germany. It added that the study population corresponded to the German target population in terms of key demographic and disease-specific characteristics, and that the treatment of patients concurred with the health care standard in Germany. According to the company, the APeX-2 study was also conducted primarily in Western study centres, and the study population corresponded to the German target population in terms of its key characteristics; for example, 90% of the patients included in the study were of Caucasian family origin. The company explained that the APeX-J study was conducted in Japan and that it could therefore be assumed that the health care standard there is sufficiently similar to that in Germany. It added that patients in APeX-2 and APeX-J had access to the same drugs for the acute treatment of HAE attacks as those that represent

standard of care in Germany. It concluded that the results of the studies OASIS-HAE, APeX-2 and APeX-J were fully transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - HAE attacks
  - Activity impairment, recorded using the Work Productivity and Activity Impairment plus Classroom Impairment Questions: Specific Health Problem (WPAI+CIQ:SHP) question 10, or the Work Productivity and Activity Impairment (WPAI) Question 6
  - Health status, recorded with the EQ-5D VAS
- Health-related quality of life
  - recorded with the Angioedema Quality of Life Questionnaire (AE-QoL)
- Side effects
  - Serious adverse events (SAEs)
  - Severe AEs
  - Discontinuation due to AEs
  - Other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 10 shows for which outcomes data were available in the included studies and whether an indirect comparison was possible based on the available data.

Table 10: Matrix of outcomes – RCT, indirect comparison: donidalorsen vs. berotralstat

Comparison / Study	Outcomes								
	All-cause mortality[a]	HAE attacks[b]	Activity impairment (WPAI[c])	Health status (EQ-5D VAS)	Health-related quality of life (AE-QoL)	SAEs	Severe AEs	Discontinuation due to AEs	Specific AEs
donidalorsen vs. placebo									
OASIS-HAE	Yes	Yes	Yes	Yes	Yes	Yes	No[d]	Yes	No[e]
berotralstat vs. placebo									
APeX-2	Yes	Yes	Yes	Yes	Yes	Yes	Yes[f]	Yes	No[e]
APeX-J	Yes	Yes	Yes	Yes	Yes	Yes	Yes[f]	Yes	No[e]
Indirect comparison feasible	Yesg	Yes	Yes	Yes	Yes	Yes	No[h]	Yes	No[h]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalised as the monthly rate of HAE attacks during the treatment period and as the proportion of patients without HAE attacks during the treatment phase (attack-free).
c. For OASIS-HAE, question 10 of the WPAI+CIQ:SHP is used; for APeX-2 and APeX-J, question 6 of the WPAI is used, which corresponds to question 10 of the WPAI+CIQ:SHP.
d. No suitable data available; see the following text sections for reasons.
e. No specific AEs were identified based on the AEs occurring in the relevant study/studies.
f. Severe AEs are operationalised as DMID grade 3 (severe) or DMID grade 4 (life-threatening).
g. The company presented no indirect comparison in Module 4 A.
h. Not feasible because no suitable data are available for at least one side of the indirect comparison.

AE: adverse event; AE-QoL: Angioedema Quality of Life Questionnaire; DMID: Division of Microbiology and Infectious Diseases; HAE: hereditary angioedema; RCT: randomised controlled trial; SAE: serious adverse event; VAS: visual analogue scale; WPAI+CIQ:SHP: Work Productivity and Activity Impairment plus Classroom Impairment Questions: Specific Health Problem

HAE attacks

For patients in the given therapeutic indication, the treatment goal according to the expired German S1 guideline on HAE due to C1-INH deficiency from 2019 [21] is to prevent suffocation, prevent attacks or reduce disease activity (frequency, severity and duration of attacks) and, as a result, normalise quality of life. According to the more recent international WAO and EAACI recommendations for the treatment of HAE from 2021, the goals of long-term

prophylaxis are to achieve complete control of the disease and to normalise patients' lives. Complete control means that the patient no longer has any attacks [20].

In the given therapeutic indication, HAE attacks are patient-relevant events, and avoiding HAE attacks is a central treatment goal as described above. The HAE attack rate (operationalised as the average monthly rate during the treatment phase) and attack-free status (operationalised as the proportion of patients without HAE attacks during the treatment phase) were considered to be meaningful operationalisations of the outcome HAE attacks and were used for this benefit assessment. The recording and operationalisation of HAE attacks in the studies is explained below.

Recording of HAE attacks

In the OASIS-HAE study, HAE attacks were recorded using the Angioedema Activity Score (AAS), a diary-type questionnaire. Patients were instructed to complete this questionnaire daily, regardless of whether they had an HAE attack or not. It includes, among other questions, questions on the burden of symptoms (how severely the patient experienced any physical symptoms such as pain and burning, and any cosmetic impairment) and on the impact of an HAE attack on daily activities. If an HAE attack occurred, patients were also instructed to report details to the study centre within 72 hours, where the location, the perceived severity, the need for medical intervention, as well as the time of start and end of the attack were recorded. In addition, the study staff were to contact the patients once a week in order to enquire about any HAE attack that may have occurred. In the APeX2 and APeX-J studies, patients were asked to complete their electronic diary daily and indicate whether or not symptoms of an HAE attack had occurred within the last 24 hours. The diary was completed regardless of the occurrence of an HAE attack. If the patients reported an HAE attack, they had to enter additional information about the attack (onset and end, symptoms, location, severity, administration of treatments, use of additional medical assistance). The investigator had to contact the patient within approximately 2 working days after the HAE attack. In case of poor compliance in completing the electronic diary, a follow-up training session on how to complete it was to be arranged.

In the event of premature discontinuation of the study medication in the APeX-2 and APeX-J studies, the occurrence of HAE attacks was still to be documented in the diary until Week 24. The study design of OASIS-HAE also provided for the continued documentation of HAE attacks in the event of premature discontinuation (up to 13 weeks after the last dose of the study medication).

The extent to which the reported symptoms constituted an HAE attack was confirmed by the investigator based on the information provided by the patients (OASIS-HAE and APeX-2) or verified by the investigator and confirmed by an independent expert (APeX-J). In accordance

with the criteria set out in the OASIS-HAE study, an HAE attack was rated as such if there was at least one defined symptom in at least one defined location. A list of typical symptoms and locations was included in the study design. The investigator made the final decision of whether the event was in fact an HAE attack or whether it was caused by something else. According to the criteria in the APeX-2 and APeX-J studies, an HAE attack was considered as such if it was accompanied by symptoms of swelling. Prodromal symptoms in the absence of swelling did not count as an HAE attack. Symptoms of swelling, in addition to visible swelling, could also include symptoms in the oropharyngeal or abdominal regions that are indicative of internal swelling. In addition, the HAE attack had to have either been treated, required medical attention, or been documented to have caused functional impairment. A new attack had to be temporally separated from a previous attack, i.e. was not allowed to have begun within 24 hours (OASIS-HAE) or 48 hours (APeX-2 and APeX-J) of the end of a previous HAE attack. The recording of HAE attacks by the patients in all 3 studies was considered suitable for the practically complete recording of HAE attacks, in particular due to the regular contact with the study staff and clear protocol requirements.

The severity of the HAE attacks was additionally classified in the studies. In the APeX-2 and APeX-J studies, the patients were asked to indicate the severity of the HAE attack in the diary; however, information on the severity classification was not available for the APeX-2 and APeX-J studies. In the OASIS-HAE study, the severity (mild, moderate, severe) was classified by the investigator on the basis of criteria defined in the study design (including the degree of limitation in daily activities and the need for assistance).

Overall, the recording of HAE attacks was considered to be sufficiently similar in the studies OASIS-HAE, APeX-2 and APeX-J. The differences described did not call into question the performance of an adjusted indirect comparison via the common comparator placebo. However, it remained unclear to what extent the classification of severity was comparable in the studies, so that analyses of any HAE attacks regardless of severity were used in this data situation (see next section).

Operationalisations used for the benefit assessment

With regard to the treatment goals to avoid HAE attacks and achieve complete control of the disease (defined as being attack-free) described in the guidelines [20,21], the operationalisations of the monthly rate of HAE attacks and freedom from attacks were used in this benefit assessment. In the OASIS-HAE study, as well as in the APeX-2 and APeX-J studies, analyses of the monthly rate of HAE attacks over the entire study period were predefined in the study design. For the operationalisation of freedom from attacks, analyses from Week 5 to Week 24 (Days 29 to 169) were predefined in the OASIS-HAE study. The company presented a post hoc analysis from Week 1 to Week 24 (Day 1 to Day 169) in Module 4 A, which was used

for the benefit assessment. The recording of freedom from attacks over the entire study period was predefined in the APeX-2 and APeX-J studies.

In the available analyses for the indirect comparison, 'freedom from attacks' was defined as the proportion of patients without HAE attacks during the treatment phase. A patient's monthly rate of HAE attacks during the treatment phase was calculated as the number of HAE attacks divided by the observation period (in days) of the patient from the start of treatment, multiplied by 28 days.

All confirmed HAE attacks, regardless of severity and location, were included in the analyses used for the operationalisation of the monthly rate of HAE attacks and freedom from attacks. This is appropriate, as HAE attacks are accompanied by tangible symptoms regardless of their severity and location and are therefore relevant to the patient. Due to the previously described differences in the assessment of the severity of HAE attacks and the lack of information on severity classification, it was not possible to consider the severity of HAE attacks in the given data situation. In Module 4 A, the company also provided analyses of the monthly rate of laryngeal HAE attacks. The criteria for recording a laryngeal HAE attack were sufficiently similar across the 3 studies and included, amongst other things, dysphagia, swelling of the mouth and dyspnoea. Laryngeal attacks are very rare, and the monthly rate of laryngeal HAE attacks was already included in the overall rate of monthly HAE attacks. However, as laryngeal HAE attacks can be potentially life-threatening, they are presented as supplementary information.

Activity impairment (recorded using WPAI)

The outcome activity impairment, recorded using the WPAI, is patient relevant and was used for this benefit assessment. The WPAI+CIQ:SHP was used in the OASIS-HAE study, whilst the WPAI was used in APeX-2 and APeX-J. Question 6 of the WPAI is 'During the past seven days, how much did health problems affect your ability to do your regular daily activities, other than work at a job?'. Question 10 of the WPAI+CIQ:SHP also states that attending classes should not be taken into account ('other than work at a job or attending classes'). The patient assesses their health on a scale of 0 to 10, where 0 means 'health problems had no effect on my daily activities' and 10 means 'health problems completely prevented me from doing my daily activities'. Question 10 of the WPAI+CIQ:SHP and question 6 of the WPAI are sufficiently comparable.

The WPAI+CIQ:SHP was recorded weekly in the OASIS-HAE study. In the APeX-2 and APeX-J studies, recordings took place on Day 1, Day 29, Day 57, Day 85, Day 127 and Day 169. Overall, the recordings were carried out more frequently in OASIS-HAE than in APeX-2 and APeX-J. Given the chronic nature of the disease and the continuous treatment, any potential bias caused by the different time points of recording was assessed as negligible. The average return

rates in the intervention and placebo arms at all timepoints were 85% in OASIS-HAE, ≥90% in APeX-2 and 100% in APeX-J.

The analyses of the change at the end of treatment compared with baseline presented by the company for the WPAI using a mixed-effects model with repeated measures (MMRM) for the indirect comparison of donidalorsen versus berotralstat were used for this benefit assessment.

Health status (recorded using the EQ-5D VAS)

The outcome health status, recorded by means of the EQ-5D VAS, is patient relevant and was used for this benefit assessment. The EQ-5D VAS was recorded on Day 1, Day 85 and Day 169 in the OASIS-HAE study, and on Day 1, Day 29, Day 57, Day 85, Day 127 and Day 169 in APeX-2 and APeX-J. Overall, the recordings were carried out less frequently in OASIS-HAE than in APeX-2 and APeX-J. Given the chronic nature of the disease and the continuous treatment, any potential bias caused by the different time points of recording was assessed as negligible. The return rates in the intervention and placebo arms at all timepoints were ≥80% in OASIS-HAE, ≥90% in APeX-2 and 100% in APeX-J.

In addition to the recordings conducted during the previously mentioned planned study visits, the APeX-2 and APeX-J studies also included a recording – starting in Week 4 – if the patient experienced an HAE attack after the last visit. According to the statistical analysis plan, these additional recordings were not included in the MMRM analyses, but only the recordings from the planned visits.

The analyses of the change at the end of treatment compared with baseline presented by the company for health status using MMRM for the indirect comparison of donidalorsen versus berotralstat were used for the benefit assessment.

Health-related quality of life (recorded using AE-QoL)

The AE-QoL is an instrument for recording patients' impairment due to HAE-specific symptoms [22-24]. The questionnaire consists of 17 questions in 4 domains (functioning, fatigue/mood, fear/shame, and food). Each question is answered on a 5-point Likert-scale (never, rarely, sometimes, often, very often) regarding the period of the last 4 weeks.

The scores of the individual domains as well as the total score (mean of the individual domains) are transformed linearly to a score range of 0 to 100; higher scores mean a greater impairment. The questionnaire was developed to assess the patients' health-related quality of life. The dimensions of mental, physical and social functioning are represented by the various items in the questionnaire. The AE-QoL was assessed to be a valid instrument for recording the health-related quality of life in adult – but not adolescent – patients with HAE and was used for this benefit assessment.

In each of the studies OASIS-HAE and APeX-2, only 4 patients were under 18 years of age; in the APeX-J study, none of the patients were under 18 years of age. Due to the small number of patients for whom the AE-QoL was recorded, but the questionnaire was unvalidated (<18 years), this was of no consequence for this benefit assessment.

The AE-QoL was recorded on Day 1, Day 85 and Day 169 in the OASIS-HAE study, and on Day 1, Day 29, Day 57, Day 85, Day 127 and Day 169 in APeX-2 and APeX-J. Overall, the recordings were carried out less frequently in OASIS-HAE than in APeX-2 and APeX-J. Given the chronic nature of the disease and the continuous treatment, any potential bias caused by the different time points of recording was assessed as negligible. The average return rates in the intervention and placebo arms at all timepoints were 95% in OASIS-HAE, ≥90% in APeX-2 and 100% in APeX-J.

The analyses of the change at the end of treatment compared with baseline presented by the company for the AE-QoL using MMRM for the indirect comparison of donidalorsen versus berotralstat were used for this benefit assessment.

Additional patient-reported outcomes

AAS, AECT, GAD-7, PGI-C and PGI-S

As part of the OASIS-HAE study, additional patient-reported outcomes were recorded, such as the AAS, the Angioedema Control Test (AECT) and the Generalised Anxiety Disorder 7 (GAD-7). These are potentially patient relevant; however, their validity was not assessed further for this benefit assessment, as they were not recorded in APeX-2 and APeX-J, making an indirect comparison impossible. Furthermore, no information on the wording of the items was found in the study documentation for the patient-reported single-item scales Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC); hence it was impossible to assess the patient relevance of these 2 instruments.

Side effects

Severe AEs

The operationalisation of the outcome severe AEs differed between OASIS-HAE and APeX-2/APeX-J. According to the information provided in Module 4 A, the severity in the OASIS-HAE study was generally classified based on the Common Terminology Criteria for Adverse Events (CTCAE). However, there is no information on this in the study documents. According to the study protocol, the severity of AEs relating to laboratory tests and AEs at the injection site was to be graded based on the criteria from the 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials'. Laboratory AEs not included in this list were graded by the investigator as mild, moderate or severe, taking into account the extent to which they interfered with daily activities. The study documents did not indicate the criteria used to classify the severity grading for all other AEs.

This was not an adequate operationalisation of severe AEs as distinct from non-severe AEs and was therefore unsuitable for the benefit assessment.

In the APeX-2 and APeX-J studies, the severity of AEs was classified in accordance with the Division of Microbiology and Infectious Diseases (DMID) adult toxicity tables, version: November 2007 [25,26]. The DMID criteria are adapted from the toxicity tables of the Division of Acquired Immunodeficiency Syndrome (DAIDS), the Common Toxicity Criteria (CTC) of the National Cancer Institute (NCI), and the World Health Organization (WHO). The severity classification of AEs according to DMID was predefined in the APeX-2 and APeX-J study protocols, operationalising severe AEs as DMID grade 3 (severe) or DMID grade 4 (life-threatening).

Irrespective of the fact that the severity classification according to DMID potentially represents an adequate operationalisation of severe AEs as distinct from non-severe AEs in the given therapeutic indication, there were no suitable data for an indirect comparison for the outcome severe AEs for the side of the intervention with donidalorsen from the OASIS-HAE study. Thus, the indirect comparison presented by the company for the outcome severe AEs was not used for the benefit assessment.

I 4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, indirect comparison: donidalorsen vs. berotralstat

Comparison Study	Study level	Outcomes								
		All-cause mortality[a]	HAE attacks[b]	Activity impairment (WPAI)[c]	Health status (EQ-5D VAS)	Health-related quality of life (AE-QoL)	SAEs	Severe AEs	Discontinuation due to AEs	Specific AEs
donidalorsen vs. placebo										
OASIS-HAE	L	L	L	L	L	L	L	–[d]	L	–
berotralstat vs. placebo										
APeX-2	L	L	L	L	L	L	L	L[e]	L	–
APeX-J	L	L	L	L	L	L	L	L[e]	L	–

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalised as the monthly rate of HAE attacks during the treatment period and as the proportion of patients without HAE attacks during the treatment phase (attack-free).
c. For OASIS-HAE, question 10 of the WPAI+CIQ:SHP is used; for APeX-2 and APeX-J, question 6 of the WPAI is used, which corresponds to question 10 of the WPAI+CIQ:SHP.
d. No suitable data available; see the following text sections for reasons.
e. Severe AEs are operationalised as DMID grade 3 (severe) or DMID grade 4 (life-threatening).

AE: adverse event; AE-QoL: Angioedema Quality of Life Questionnaire; DMID: Division of Microbiology and Infectious Diseases; HAE: hereditary angioedema; RCT: randomised controlled trial; SAE: serious adverse event; VAS: visual analogue scale; WPAI+CIQ:SHP: Work Productivity and Activity Impairment plus Classroom Impairment Questions: Specific Health Problem

The risk of bias was rated as low for the results of the outcomes of the studies OASIS-HAE, APeX-2 and APeX-J.

In the 3 studies, daily recordings were planned, regardless of whether HAE attacks occurred. The company did not provide any information on missing values were dealt with or on the extent of missing values. In the given situation, however, it was assumed that the recording of HAE attacks was sufficiently reliable and almost complete (see Section I 4.1). In addition, the size of the observed effect for the outcome HAE attacks must be taken into account, which could not be explained solely by potential bias due to missing values. The existing

uncertainties regarding the handling and extent of potentially missing values therefore were of no consequence for the benefit assessment.

I 4.3 Results

Table 12, Table 13 and Table 14 summarise the results comparing donidalorsen with berotralstat in patients aged 12 years and older for the routine prevention of recurrent HAE. Where necessary, calculations conducted by the Institute or information from Module 4 A on berotralstat are provided in addition to the data from the company's dossier.

For the OASIS-HAE study, tables on common AEs and common SAEs are presented in I Appendix C of the full dossier assessment. There were no discontinuations due to AEs in OASIS-HAE. For the APeX-2 and APeX-J studies, the tables on common AEs, common SAEs (only for the APeX-2 study; no SAEs occurred in the APeX-J study), common severe AEs and discontinuations due to AEs are also presented in I Appendix C of the full dossier assessment.

Table 12: Results (morbidity: HAE attacks) – RCT, indirect comparison: donidalorsen vs. berotralstat (multipage table)

Outcome category outcome	donidalorsen/berotralstat		placebo		Group difference
Comparison Study	N	Mean monthly rate [95% CI][a]	N	Mean monthly rate [95% CI][a]	Rate ratio [95% CI]; p-value
Morbidity					
HAE attacks					
Monthly rate[b, c]					
donidalorsen vs. placebo					
OASIS-HAE	45	0.44 [0.27; 0.73]	22	2.26 [1.66; 3.09]	0.19 [0.11; 0.35]; <0.001
berotralstat vs. placebo					
APeX-2	40	1.33 [ND]	39	2.35 [ND]	0.56 [0.41; 0.78]; <0.001
APeX-J	7	1.08 [ND]	6	2.12 [ND]	0.51 [0.33; 0.79]; <0.003
Total[d]					0.54 [0.42; 0.70]; <0.001
Indirect comparison using common comparatorse:					
donidalorsen vs. berotralstat					0.36 [0.19; 0.69]; 0.002
Monthly rate of laryngeal HAE attacks [b, c] (supplementary information)					
donidalorsen vs. placebo					
OASIS-HAE	*45*	*0.01 [0.00; 0.05]*	*22*	*0.05 [0.02; 0.14]*	*0.22 [0.04; 1.31]; 0.097*
berotralstat vs. placebo					
APeX-2	*40*	*0.07 [ND]*	*39*	*0.17 [ND]*	*0.39 [0.16; 0.97]; 0.044*
APeX-J	*7*	*NC*	*6*	*NC*	*NC*
Indirect comparison using common comparators[e, f]					*0.56 [0.08; 4.17]; 0.573*
donidalorsen vs. berotralstat					
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI][g]; p-value**
Freedom from attacks[b, h]					
donidalorsen vs. placebo					
OASIS-HAE	45	14 (31.1)	22	1 (4.5)	6.84 [0.96; 48.77]; 0.055
berotralstat vs. placebo					
APeX-2	40	2 (5.0)	39	1 (2.6)	1.95 [0.18; 20.64]; 0.579
APeX-J	7	0 (0)	6	0 (0)	0.88 [0.02; 38.59]; 0.945
Total[d]					1.56 [0.21; 11.54]; 0.664
Indirect comparison using common comparatorse:					
donidalorsen vs. berotralstat					4.39 [0.27; 72.53]; 0.302

Table 12: Results (morbidity: HAE attacks) – RCT, indirect comparison: donidalorsen vs. berotralstat (multipage table)

Outcome category outcome	donidalorsen/berotralstat		placebo		Group difference
Comparison Study	N	Mean monthly rate [95% CI][a]	N	Mean monthly rate [95% CI][a]	Rate ratio [95% CI]; p-value

a. OASIS-HAE: Poisson model with the rate of HAE attacks at baseline and the interaction between treatment arm and HAE attacks at baseline as covariables, and the logarithm of the observation period as an offset variable. APeX-2 and APeX-J: negative binomial model; the covariable 'confirmed HAE attack rate at baseline' was taken into account. The logarithm of the treatment duration was used as an offset variable.
b. OASIS-HAE and APeX-2: HAE attacks confirmed by the investigator; APeX-J: HAE attacks confirmed by the independent expert.
c. In OASIS-HAE, APeX-2 and APeX-J, 1 month was defined as 28 days.
d. Meta-analysis using a fixed-effect model (inverse variance method).
e. Indirect comparison according to Bucher [4].
f. No suitable data for the indirect comparison are available for the APeX-J study. Only the data from the APeX-2 study are used for the comparator side for the indirect comparison.
g. Calculation with 2x2 table; in case of 0 events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms.
h. 100% reduction in the number of HAE attacks during the treatment period compared with the run-in phase.

CI: confidence interval; HAE: hereditary angioedema; n: number of patients with event; N: number of analysed patients; NC: not calculable; RCT: randomised controlled trial; RR: relative risk

Table 13: Results (mortality, side effects) – RCT, indirect comparison: donidalorsen vs. berotralstat (multipage table)

Outcome category outcome Comparison Study	donidalorsen/berotralstat N	 Patients with event n (%)	placebo N	 Patients with event n (%)	Group difference RR [95% CI]; p-value[a]
Mortality					
All-cause mortality[b]					
donidalorsen vs. placebo					
OASIS-HAE	45	0 (0)	22	0 (0)	–
berotralstat vs. placebo					
APeX-2	40	0 (0)	39	0 (0)	–
APeX-J	7	0 (0)	6	0 (0)	–
Indirect comparison using common comparators[c]:					Not submitted
Side effects					
AEs (supplementary information)					
donidalorsen vs. placebo					
OASIS-HAE	45	33 (73.3)	22	18 (81.8)	–
berotralstat vs. placebo					
APeX-2	40	34 (85.0)	39	30 (76.9)	–
APeX-J	7	7 (100)	6	6 (100)	–
SAEs					
donidalorsen vs. placebo					
OASIS-HAE	45	0 (0.0)	22	1 (4.5)	0.17 [0.01; 3.93]; 0.267
berotralstat vs. placebo					
APeX-2	40	0 (0)	39	3 (7.7)	0.14 [0.01; 2.61]; 0.188
APeX-J	7	0 (0)	6	0 (0)	–
Indirect comparison using common comparators[c, d]:					
donidalorsen vs. berotralstat					1.20 [0.02; 91.20]; 0.935
Severe AEs	No suitable data for the indirect comparison[e]				
Discontinuation due to AEs					
donidalorsen vs. placebo					
OASIS-HAE	45	0 (0.0)	22	0 (0.0)	–
berotralstat vs. placebo					
APeX-2	40	1 (2.5)	39	1 (2.6)	0.98 [0.06; 15.05]; 0.986
APeX-J	7	0 (0)	6	1 (16.7)	0.29 [0.01; 6.07]; 0.426
Total[f]					0.57 [0.07; 4.34]; ND
Indirect comparison using common comparators[c]:					
donidalorsen vs. berotralstat					NC

Table 13: Results (mortality, side effects) – RCT, indirect comparison: donidalorsen vs. berotralstat (multipage table)

Outcome category outcome	donidalorsen/berotralstat		placebo		Group difference
Comparison Study	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
a. Calculation with 2x2 table; in case of 0 events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms. b. The results on all-cause mortality are based on the data on fatal AEs. c. Indirect comparison according to Bucher [4]. d. Only the data from the APeX-2 study are used for the comparator side for the indirect comparison. e. See Section I 4.1 for an explanation. f. Meta-analysis using a fixed-effect model (inverse variance method). AE: adverse event; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; ND: no data; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event					

Table 14: Results (morbidity, health-related quality of life) – RCT, indirect comparison: donidalorsen vs. berotralstat (multipage table)

Outcome category outcome Comparison Study	donidalorsen/berotralstat N[a]	 Values at baseline mean (SD)	 Mean change at the end of treatment Mean (SE)[b]	placebo N[a]	 Values at baseline mean (SD)	 Mean change at the end of treatment Mean (SE)[b]	Group difference Mean difference [95% CI][b]; p-value
Morbidity							
Activity impairment (WPAI[c])							
donidalorsen vs. placebo							
OASIS-HAE	44	ND[d]	–2.2 (0.4)	22	N D[d]	–1.4 (0.5)	−0.83 [−2.09; 0.43]; 0.192
berotralstat vs. placebo							
APeX-2	38[e]	3.6 (2.8)	–1.6 (0.4)	36[e]	4.1 (2.8)	–1.2 (0.4)	−0.5 [−1.7; 0.7]; 0.406
APeX-J	7	3.3 (2.8)	1.0 (1.0)	6	1.3 (3.3)	−1.0 (1.1)	2.1 [−1.2; 5.4]; 0.200
Total[f]							−0.20 [−1.32; 0.93]; 0.733
Indirect comparison using common comparators[g]:							
donidalorsen vs. berotralstat							−0.63 [−2.32; 1.06]; 0.463
Health status (EQ-5D VAS[h])							
donidalorsen vs. placebo							
OASIS-HAE	44	82.8 (15.0)	–0.9 (2.0)	22	86.8 (10.1)	–2.5 (3.0)	1.53 [−5.53; 8.59]; 0.668
berotralstat vs. placebo							
APeX-2	38[e]	82.9 (12.6)	2.7 (1.8)	36[e]	85.2 (10.8)	3.3 (1.8)	−0.6 [−5.8; 4.5]; 0.807
APeX-J	7	75.7 (30.6)	8.4 (4.7)	6	80.5 (26.3)	–3.6 (5.1)	12.0 [−3.7; 27.8]; 0.120
Total[f]							0.62 [−4.28; 5.51]; 0.805
Indirect comparison using common comparators[g]:							

Table 14: Results (morbidity, health-related quality of life) – RCT, indirect comparison: donidalorsen vs. berotralstat (multipage table)

Outcome category outcome Comparison Study	donidalorsen/berotralstat N[a]	Values at baseline mean (SD)	Mean change at the end of treatment Mean (SE)[b]	placebo N[a]	Values at baseline mean (SD)	Mean change at the end of treatment Mean (SE)[b]	Group difference Mean difference [95% CI][b]; p-value
donidalorsen vs. berotralstat							0.91 [−7.68; 9.50]; 0.836[i]
Health-related quality of life							
AE-QoL[j]							
Total score							
donidalorsen vs. placebo							
OASIS-HAE	45	45.6 (16.8)	−24.8 (2.6)	22	45.4 (17.0)	−6.2 (3.8)	−18.56 [−27.67; −9.45]; 0.001
berotralstat vs. placebo							
APeX-2	38[e]	43.0 (16.9)	−15.8 (2.7)	36[e]	45.9 (20.1)	−11.0 (2.7)	−4.83 [−12.39; 2.74]; 0.207
APeX-J	7	39.5 (24.8)	−17.1 (6.5)	6	40.4 (16.0)	0.1 (7.0)	−17.26 [-38.68; 4.15]; 0.103
Total[f]							−6.21 [−13.34; 0.92]; 0.088
Indirect comparison using common comparators[g]:							
donidalorsen vs. berotralstat							−12.35 [−23.92; −0.79]; 0.036
					SMD [95% CI]:		−0.45 [−0.87; −0.02]
Functioning							
donidalorsen vs. placebo							
OASIS-HAE	45	45.2 (22.2)	−36.7 (3.4)	22	46.6 (19.6)	−12.2 (5.0)	−24.46 [−36.42; −12.51]
berotralstat vs. placebo							
APeX-2	38[e]	47.1 (21.0)	−22.0 (3.4)	36[e]	45.3 (24.1)	−13.0 (3.5)	−8.97 [−18.72; 0.78]
APeX-J	7	42.0 (28.3)	−14.8 (7.0)	6	32.3 (18.3)	−1.5 (7.5)	−13.26 [−35.97; 9.45]
Fatigue/mood							
donidalorsen vs. placebo							

Table 14: Results (morbidity, health-related quality of life) – RCT, indirect comparison: donidalorsen vs. berotralstat (multipage table)

Outcome category outcome Comparison Study	donidalorsen/berotralstat			placebo			Group difference
	N[a]	Values at baseline mean (SD)	Mean change at the end of treatment Mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change at the end of treatment Mean (SE)[b]	Mean difference [95% CI][b]; p-value
OASIS-HAE	45	41.9 (20.2)	−11.6 (3.0)	22	34.1 (20.2)	−3.5 (4.6)	−8.07 [−19.04; 2.89]
berotralstat vs. placebo							
APeX-2	38[e]	38.5 (19.3)	−12.7 (3.3)	36[e]	44.5 (23.2)	−10.5 (3.3)	−2.13 [−11.41; 7.15]
APeX-J	7	21.4 (15.5)	−3.2 (7.2)	6	32.5 (18.1)	2.9 (7.8)	−6.12 [−30.56; 18.31]
Fear/shame							
donidalorsen vs. placebo							
OASIS-HAE	45	53.3 (21.0)	−29.8 (3.3)	22	57.0 (25.8)	−5.9 (5.0)	−23.91 [−35.80; −12.03]
berotralstat vs. placebo							
APeX-2	38[e]	47.9 (22.9)	−16.2 (3.5)	36[e]	51.5 (26.1)	−11.2 (3.5)	−5.09 [−15.03; 4.85]
APeX-J	7	57.1 (33.1)	−32.6 (7.6)	6	61.8 (25.1)	−4.4 (8.2)	−28.21 [−53.57; −2.86]
Food							
donidalorsen vs. placebo							
OASIS-HAE	45	32.7 (20.7)	−21.4 (2.6)	22	36.4 (23.4)	−5.8 (3.9)	−15.65 [−24.90; −6.39]
berotralstat vs. placebo							
APeX-2	38[e]	31.6 (24.0)	−10.0 (3.2)	36[e]	34.0 (25.0)	−7.4 (3.3)	−2.57 [−11.68; 6.54]
APeX-J	7	26.8 (29.3)	−4.3 (8.6)	6	12.5 (15.8)	2.9 (9.3)	−7.24 [−36.49; 22.01]

Table 14: Results (morbidity, health-related quality of life) – RCT, indirect comparison: donidalorsen vs. berotralstat (multipage table)

Outcome category outcome Comparison Study	donidalorsen/berotralstat			placebo			Group difference
	N[a]	Values at baseline mean (SD)	Mean change at the end of treatment Mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change at the end of treatment Mean (SE)[b]	Mean difference [95% CI][b]; p-value
a. Number of patients taken into account in the effect estimation; baseline values may be based on different patient numbers. b. OASIS-HAE: mean (SE) and mean difference [95% CI]: based on an MMRM model with the treatment group, the visit and an interaction variable between visit and treatment group defined as fixed effects. The effect represents the difference in changes (from baseline) between the treatment groups at Week 25. APeX-2 and APeX-J: mean (SE) and mean difference [95% CI]: based on an MMRM model with baseline, the treatment group, the visit and an interaction variable between visit and treatment group defined as fixed effects. The effect represents the difference in changes (from baseline) between the treatment groups at Week 24. c. For OASIS-HAE, question 10 of the WPAI+CIQ:SHP is used; for APeX-2 and APeX-J, question 6 of the WPAI is used, which corresponds to question 10 of the WPAI+CIQ:SHP. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 10 points). d. According to the OASIS-HAE study protocol, the weekly scores for each 4-week period were to be pooled in the analysis of the WPAI+CIQ:SHP. For the dossier and the indirect comparison, the last 7 days were taken into account in the analysis, similar to the approach used for APeX-2 and APeX-J. The company did not specify any baseline values for these in Module 4 A. e. Number of patients with values at the end of treatment; unclear how many patients were included in the model. f. Meta-analysis using a fixed-effect model (inverse variance method). g. Indirect comparison according to Bucher [4]. h. Higher (increasing) values indicate improved symptoms; positive effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 100 points). i. Institute's calculation; the company's calculation in Module 4 A takes into account only the OASIS-HAE and APeX-J studies, and not the results of the meta-analysis of APeX-2 and APeX-J. j. Lower values indicate better health-related quality of life; negative effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 100 points). AE-QoL: Angioedema Quality of Life Questionnaire; CI: confidence interval; HAE: hereditary angioedema; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; SMD: standardised mean difference; VAS: visual analogue scale; WPAI+CIQ:SHP: Work Productivity and Activity Impairment plus Classroom Impairment Questions: Specific Health Problem						

One RCT (OASIS-HAE) was available on the side of the intervention with donidalorsen of the given adjusted indirect comparison. Consequently, there was no need to assess homogeneity for the side of the intervention with donidalorsen. On the side of the comparator berotralstat of the adjusted indirect comparison, 2 RCTs were available (APeX-2 and APeX-J). The review of the homogeneity of the pairwise meta-analysis of the studies APeX-2 and APeX-J showed a heterogeneity measure $I^2$of 0% for the patient-relevant outcomes in the operationalisations used for the benefit assessment, with the exception of health status (EQ-5D VAS) and activity

impairment (WPAI question 6). The heterogeneity measure I^2 was 55% for health status (EQ-5D VAS) and 53% for activity impairment (WPAI question 6). In both cases, however, the p-value of the heterogeneity test was above 0.05 (EQ-5D VAS: p = 0.14; WPAI question 6: p = 0.15), which was classified as no relevant heterogeneity, in accordance with IQWiG's General Methods [1]. Overall, there was thus no relevant heterogeneity between the effect estimations of the studies APeX-2 and APeX-J for this benefit assessment. As there was no study of direct comparison of donidalorsen versus berotralstat, it was impossible to check the consistency of results. Therefore, the adjusted indirect comparisons had at most a low certainty of results. Hence, no more than hints, e.g. of an added benefit, could be derived on the basis of the data available from the adjusted indirect comparison.

Mortality

All-cause mortality

The results on all-cause mortality were based on data on fatal AEs. No deaths occurred in any of the studies OASIS-HAE, APeX-2 and APeX-J. There is no hint of an added benefit of donidalorsen compared with berotralstat; an added benefit is therefore not proven.

Morbidity

HAE attacks

Monthly rate

For the monthly rate of HAE attacks, the adjusted indirect comparison showed a statistically significant difference in favour of donidalorsen compared with berotralstat. There is a hint of an added benefit of donidalorsen in comparison with berotralstat.

Freedom from attacks

For freedom from attacks, the adjusted indirect comparison showed no statistically significant difference between donidalorsen and berotralstat. There is no hint of an added benefit of donidalorsen compared with berotralstat; an added benefit is therefore not proven.

Activity impairment (WPAI question 10 / question 6)

With regard to activity impairment assessed using WPAI+CIQ:SHP question 10 (OASIS-HAE) or WPAI question 6 (APeX-2 and APeX-J), the adjusted indirect comparison showed no statistically significant difference between donidalorsen and berotralstat. There is no hint of an added benefit of donidalorsen compared with berotralstat; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

For health status assessed with the EQ-5D VAS, the adjusted indirect comparison showed no statistically significant difference between donidalorsen and berotralstat. There is no hint of

an added benefit of donidalorsen compared with berotralstat; an added benefit is therefore not proven.

Health-related quality of life

AE-QoL

For health-related quality of life assessed with the AE-QoL, the adjusted indirect comparison showed a statistically significant difference in favour of donidalorsen compared with berotralstat for the AE-QoL total score. The standardised mean difference (SMD) was considered to check the relevance of the result. The 95% confidence interval (CI) of the SMD was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. There is no hint of an added benefit of donidalorsen compared with berotralstat; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome SAEs, the adjusted indirect comparison showed no statistically significant difference between donidalorsen and berotralstat. There is no hint of greater or lesser harm of donidalorsen in comparison with berotralstat; greater or lesser harm is therefore not proven.

Severe AEs

For the outcome severe AEs, no suitable data were available for the indirect comparison of donidalorsen versus berotralstat (for an explanation see Section I 4.1). There is no hint of greater or lesser harm of donidalorsen in comparison with berotralstat; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No discontinuations due to AEs occurred in the OASIS-HAE study. One discontinuation due to AEs occurred in the berotralstat arm of the APeX-2 study, and no discontinuation due to AEs occurred in the berotralstat arm of the APeX-J study. There is no hint of greater or lesser harm of donidalorsen in comparison with berotralstat; greater or lesser harm is therefore not proven.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for this benefit assessment:

- Age
- Sex
- Monthly HAE attack rate at baseline

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value <0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

In the APeX-2 study (or for pooled analyses of the studies APeX-2 and APeX-J), the age categories <18 years (or 12 to 17 years), 18 to 65 years (or 18 to 64 years) and >65 years (or ≥65 years) were predefined for subgroup analyses. In the OASIS-HAE study, the age categories were predefined as 12 to 17 years, 18 to 39 years, 40 to 64 years and ≥65 years. The company stated that, when the age categories from APeX-2 and APeX-J were applied to OASIS-HAE, some age categories included fewer than 10 patients. Consequently, subgroup analyses for the characteristic age were not carried out for the indirect comparison. This approach was appropriate.

The company did not present any subgroup analyses for the indirect comparison of donidalorsen versus berotralstat for the subgroup characteristic monthly HAE attack rate at baseline. The company justified this on the grounds that there is no measure for assessing the severity of HAE attacks. In APeX-2 and APeX-J, the categories for the subgroup characteristic of monthly HAE attack rate at baseline were prespecified as ≥2 attacks/month versus <2 attacks/month, in accordance with the stratification factor. The company's approach was not comprehensible. In the indirect comparison presented by the company in the dossier, subgroups according to the monthly HAE attack rate at baseline could have been analysed post hoc for the OASIS-HAE study concurring with the categories in the APeX-2 and APeX-J studies.

For the subgroup characteristic sex (male versus female), the company presented subgroup analyses for the indirect comparison of donidalorsen versus berotralstat in Module 4 A of the dossier. Applying the methods described above, there were no effect modifications for the characteristic sex. Due to the small numbers of events, the company did not conduct any subgroup analyses for the outcomes all-cause mortality, SAEs and discontinuation due to AEs. This approach was appropriate.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 15).

Determination of the outcome category for the symptom outcome

It cannot be inferred from the dossier whether the following symptoms outcome is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

HAE attacks

For the outcome HAE attacks, operationalised as monthly rate, insufficient severity data were available for a classification as serious/severe. The outcome HAE attacks, operationalised as monthly rate, was therefore allocated to the outcome category of non-serious/non-severe symptoms/late complications.

Table 15: Extent of added benefit at outcome level: donidalorsen vs. berotralstat (multipage table)

Outcome category **outcome**	**donidalorsen (OASIS-HAE) vs. berotralstat (APeX-2 or APeX-J)** **Mean monthly rate or proportion of events (%) or mean change (mean value)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% or 0% RR: –[c]	Lesser benefit not proven / added benefit not proven
Morbidity		
HAE attacks Monthly rate	0.44 vs. 1.33 or 1.08 Rate ratio: 0.36 [0.19; 0.69]; p = 0.002 Probability: hint	Outcome category: non-serious / non-severe symptoms / late complications CI_u <0.80 Added benefit, extent: considerable
Freedom from attacks	31.1% vs. 5.0% or 0% Rate ratio: 4.39 [0.27; 72.53]; p = 0.302	Lesser benefit not proven / added benefit not proven
Activity impairment (WPAI[d])	−2.2 vs. −1.6 or 1.0 MD: −0.63 [−2.32; 1.06]; p = 0.463	Lesser benefit not proven / added benefit not proven
Health status (EQ-5D VAS)	−0.9 vs. 2.7 or 8.4 MD: 0.91 [−7.68; 9.50][e]; p = 0.836	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
AE-QoL total score	−24.8 vs. −15.8 or −17.1 MD: −12.35 [−23.92; −0.79]; p = 0.036 SMD [95% CI]: −0.45 [−0.87; −0.02][f]	Lesser benefit not proven / added benefit not proven
Side effects		
SAEs	0% vs. 0% or 0% RR: 1.20 [0.02; 91.20]; p = 0.935	Greater/lesser harm not proven
Severe AEs	No suitable data for the indirect comparison[g]	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 2.5% vs. 0% RR: NC	Greater/lesser harm not proven

Table 15: Extent of added benefit at outcome level: donidalorsen vs. berotralstat (multipage table)

Outcome category **outcome**	**donidalorsen (OASIS-HAE) vs. berotralstat (APeX-2 or APeX-J)** **Mean monthly rate or proportion of events (%) or mean change (mean value)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
a. Probability provided if statistically significant differences are present. b. Depending on the outcome category and the scale level of the outcome, the effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L). c. No indirect comparison was submitted by the company. d. For OASIS-HAE, question 10 of the WPAI+CIQ:SHP is used; for APeX-2 and APeX-J, question 6 of the WPAI is used, which corresponds to question 10 of the WPAI+CIQ:SHP. e. Institute's calculation; the company's calculation in Module 4 A takes into account only the OASIS-HAE and APeX-J studies, and not the results of the meta-analysis of APeX-2 and APeX-J. f. If the CI for the SMD is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived. g. See Section I 4.1 for an explanation. AE: adverse event; AE-QoL: Angioedema Quality of Life Questionnaire; CI: confidence interval; Ci_u: upper limit of the confidence interval; CI_L: lower limit of the confidence interval; HAE: hereditary angioedema; MD: mean difference; RR: relative risk; NC: not calculable; SAE: serious adverse event; SMD: standardised mean difference; VAS: visual analogue scale; WPAI+CIQ:SHP: Work Productivity and Activity Impairment plus Classroom Impairment Questions: Specific Health Problem		

I 5.2 Overall conclusion on added benefit

Table 16 summarises the results taken into account for the overall conclusion on the extent of the added benefit.

Table 16: Positive and negative effects from the assessment of donidalorsen in comparison with berotralstat

Positive effects	**Negative effects**
Non-serious/non-severe symptoms/late complications ▪ HAE attacks (monthly rate): hint of an added benefit – extent: considerable	–
HAE: hereditary angioedema	

Overall, there is a positive effect for donidalorsen compared with berotralstat. There was no statistically significant effect for the outcome HAE attacks, operationalised as freedom from attacks (see Table 12), but the operationalisation of the monthly rate of HAE attacks, which is also relevant for the benefit assessment, showed a hint of an added benefit with the extent

considerable. In summary, there is a hint of a considerable added benefit of donidalorsen in comparison with the ACT for patients aged 12 years and older for the routine prevention of recurrent HAE attacks.

The result of the assessment of the added benefit of donidalorsen in comparison with the ACT is summarised in Table 17.

Table 17: Donidalorsen – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
For routine prevention of recurrent attacks of HAE in adults and adolescents aged 12 years and older[b, c]	Routine prevention with a C1 esterase inhibitor or lanadelumab or **berotralstat**	Hint of considerable added benefit

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**.
b. According to the G-BA, the therapeutic indication of donidalorsen is assumed to comprise only patients with type I or type II HAE.
c. Both study arms should offer the possibility of acute treatment of HAE attacks.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HAE: hereditary angioedema

The assessment described above differs from that of the company, which derived an indication of a considerable added benefit of donidalorsen in comparison with berotralstat.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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