Garadacimab (hereditary angioedema)

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

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

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I List of abbreviations

Abbreviation	Meaning
ACE	angiotensin converting enzyme
ACT	appropriate comparator therapy
AE	adverse event
AE-QoL	Angioedema Quality of Life Questionnaire
C1-INH	C1 esterase inhibitor
CI	confidence interval
CTC	Common Toxicity Criteria
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)
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
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SmPC	summary of product characteristics
WAO	World Allergy Organization
WHO	World Health Organization
WPAI:GH	Work Productivity and Activity Impairment: General Health
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) 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 garadacimab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 3 March 2025.

Research question

The aim of this report is to assess the added benefit of garadacimab in comparison with the appropriate comparator therapy (ACT) for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients 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 garadacimab

Therapeutic indication	**ACT**[a]
For routine prevention of recurrent attacks of HAE[b] in adults and adolescents aged 12 years and older	Routine prevention with a C1 esterase inhibitor or lanadelumab or **berotralstat**[c]
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 garadacimab 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 company followed the G-BA's specification of the ACT. The company conducted the search for studies of direct comparison for garadacimab versus all treatment options designated by the G-BA in the ACT. As the company did not identify any RCTs that directly compared garadacimab versus the ACT, 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 assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used to derive the added benefit.

Study pool and study design

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

VANGUARD study (study with garadacimab)

The VANGUARD study is a double-blind, randomized study comparing garadacimab with placebo in patients aged 12 years and older with HAE type I or type II. The study consisted of a 1-month screening phase, a maximum 2-month run-in phase and a 6-month double-blind, placebo-controlled treatment phase.

The study included patients with a documented clinical history of HAE and documented C1 esterase inhibitor (C1-INH) deficiency. Patients with a diagnosis of any other type of angioedema were excluded from participation in the study. Patients had to have had ≥ 3 HAE attacks during the ≥ 3 months before screening. Patients who had started HAE prophylaxis within the 3 months before screening had to have ≥ 3 HAE attacks within 3 consecutive months before starting prophylaxis. For the transition to the treatment phase of the VANGUARD study, ≥ 2 HAE attacks were required during the run-in phase.

In the VANGUARD study, a total of 64 patients were randomly assigned in a 3:2 ratio to treatment with 200 mg garadacimab (N = 39) or placebo (N = 26). According to the company, one patient in the placebo arm was mistakenly assigned to blinded treatment (although they did not attend the visit at the start of treatment and withdrew their consent) and never received study treatment. Randomization was stratified according to age (≤ 17 years versus > 17 years) and, in adults, additionally according to HAE attack rate observed during the run-in phase (1 to < 3 HAE attacks/month versus ≥ 3 HAE attacks/month).

In the VANGUARD study, treatment with garadacimab was in compliance with the summary of product characteristics (SmPC).

On-demand therapy of HAE attacks was allowed in the study. Plasma-derived or recombinant C1-INH, icatibant and ecallantide were allowed. In addition, short-term prophylaxis with intravenous C1-INH before medically indicated procedures was allowed. Adults were not allowed to have received long-term prophylaxis of HAE attacks with C1-INH, androgens, antifibrinolytics or other small-molecule medications within 2 weeks before the run-in phase. For adolescents aged 12 to 17 years, any long-term prophylaxis prior to screening led to exclusion from study participation.

The primary outcome of the study was the rate of investigator-confirmed HAE attacks during the 6-month treatment phase. 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, randomized 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 ≥ 14 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 phase of the studies APeX-2 and APeX-J, with berotralstat at a dose of 150 mg compared with placebo, was 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 complement factor C4 concentration < lower limit of normal (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 run-in phase.

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, randomization was stratified by HAE attack rate at baseline (≥ 2 HAE attacks/month vs. < 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.

Secondary outcomes were further outcomes in the categories morbidity and health-related quality, as well as AEs.

Similarity of the studies for the indirect comparison

Overall, the studies VANGUARD, APeX-2 and APeX-J had a very similar study design, which ultimately differed only marginally in the duration of the placebo-controlled treatment phase. In addition, the patient populations of the studies were sufficiently similar. The described differences in individual demographic and clinical characteristics (sex, family origin) and the possible concomitant treatments (oestrogen-containing drugs) between the studies VANGUARD and APeX2 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 VANGUARD, APeX-2 and APeX-J.

Results

One RCT (VANGUARD) was available on the side of the intervention garadacimab of the present adjusted indirect comparison. Thus, there was no homogeneity check for the side of the intervention garadacimab. 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 garadacimab versus berotralstat, it is 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

No deaths occurred in any of the studies VANGUARD, APeX-2 and APeX-J. There was no hint of an added benefit of garadacimab in comparison with berotralstat; an added benefit was 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 garadacimab compared with berotralstat. There was a hint of an added benefit of garadacimab in comparison with berotralstat.

Freedom from attack

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

Activity impairment (Work Productivity and Activity Impairment: General Health [WPAI:GH] question 6)

The company did not present an adjusted indirect comparison of garadacimab versus berotralstat for activity impairment assessed using WPAI:GH question 6. There was no hint of an added benefit of garadacimab in comparison with berotralstat; an added benefit was therefore not proven.

Health status (EQ-5D VAS)

For health status assessed with the EQ-5D VAS, the adjusted indirect comparison showed a statistically significant difference in favour of garadacimab compared with berotralstat. The 95% CI for the SMD was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. There was a hint of an added benefit of garadacimab in comparison with berotralstat.

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 garadacimab compared with berotralstat for the AE-QoL total score. The 95% CI of the SMD was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. There was a hint of an added benefit of garadacimab in comparison with berotralstat.

Side effects

Serious adverse events (SAEs)

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

Severe AEs

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

Discontinuation due to AEs

No discontinuations due to AEs occurred in the VANGUARD 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 was no hint of greater or lesser harm of garadacimab in comparison with berotralstat; greater or lesser harm was 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 garadacimab in comparison with the ACT was assessed as follows:

Overall, only positive effects were shown for garadacimab in comparison with berotralstat. There was no statistically significant effect for the outcome HAE attacks, operationalized as freedom from attacks, but the operationalization 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. For the outcome health status (EQ-5D VAS) and the AE-QoL total score, there was a hint of an added benefit with the extent minor in each case. In summary, there is a hint of a considerable added benefit of garadacimab in comparison with the ACT for patients aged 12 years and older for the routine prophylaxis of recurrent attacks of HAE.

Table 3 presents a summary of the probability and extent of the added benefit of garadacimab.

[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 less benefit). For further details see [1,2].

Table 3: Garadacimab – probability and extent of the added benefit

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

G-BA: Federal Joint Committee

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 garadacimab in comparison with the ACT for routine prevention of recurrent attacks of HAE in adult and adolescent patients 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 garadacimab

Therapeutic indication	**ACT**[a]
For routine prevention of recurrent attacks of HAE[b] in adults and adolescents aged 12 years and older	Routine prevention with a C1 esterase inhibitor or lanadelumab or **berotralstat**[c]
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 garadacimab 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 company followed the G-BA's specification of the ACT. The company conducted the search for studies of direct comparison for garadacimab versus all treatment options designated by the G-BA in the ACT. As the company did not identify any RCTs that directly compared garadacimab versus the ACT, 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 company did not justify this selection, although studies existed for all 3 ACT options that could have been suitable for an indirect comparison [3-5]. In its description of the added benefit (Module 4 A, Section 4.4.2), the company mentioned a network meta-analysis in which garadacimab was compared with C1 esterase inhibitor (C1-INH), lanadelumab and berotralstat, but it did not present any data on this in the dossier.

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

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 lists on garadacimab (status: 3 January 2025 and 6 January 2025)
- Bibliographical literature search on garadacimab (last search on 3 January 2025)
- Search of trial registries/trial results databases for studies on garadacimab (last search on 6 January 2025)
- Search on the G-BA website for garadacimab (last search on 18 February 2025)
- Bibliographical literature search on berotralstat (last search on 3 January 2025)
- Search of trial registries/trial results databases for studies on berotralstat (last search on 6 January 2025)
- Search on the G-BA website for berotralstat (last search on 19 February 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on garadacimab (last search on 18 March 2025); for search strategies, see I Appendix A of the full benefit assessment
- Search of trial registries for studies on berotralstat (last search on 21 March 2025); for search strategies, see I Appendix A of the full benefit assessment

Direct comparison

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

Indirect comparison

As the company did not identify any RCT that directly compared garadacimab and the ACT of routine prevention with C1-INH or lanadelumab or berotralstat, it conducted a search for RCTs for a potential adjusted indirect comparison according to Bucher [6] . 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 VANGUARD 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: garadacimab vs. berotralstat

Study	Study category			Available sources		
	Study for the marketing authorization 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])
Garadacimab vs. placebo						
CSL312_3001 (VANGUARD[d])	Yes	Yes	No	Yes [7]	Yes [8,9]	Yes [10]
Berotralstat vs. placebo						
BCX7353-302 (APeX-2[d])	Yes	No	Yes	No	Yes [11,12]	Yes [13-15]
BCX7353-301 (APeX-J[d])	Yes	No	Yes	No	Yes [16]	Yes [14,15,17]

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.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool was consistent with that selected by the company. The studies APeX-2 und APeX-J had already been presented and assessed in a previous benefit assessment of berotralstat [18].

Figure 1 is a schematic representation of the indirect comparison.

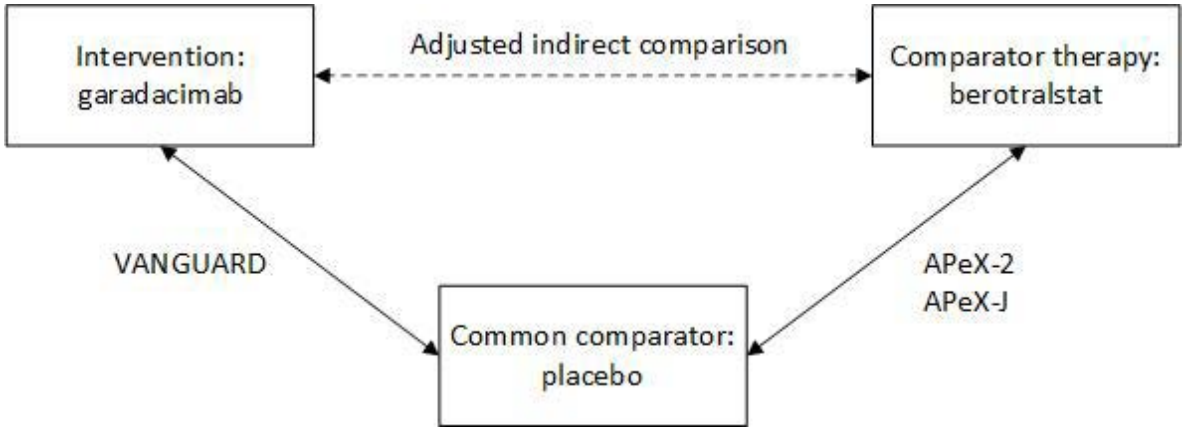

Figure 1: Study pool for the adjusted indirect comparison between garadacimab and berotralstat via the common comparator placebo

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: garadacimab vs. berotralstat (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Garadacimab vs. placebo						
VANGUARD	RCT, double-blind, parallel	Patients aged ≥ 12 years with type I or II HAE ▪ C1-INH concentration and/or functional C1-INH activity ≤ 50% of normal ▪ C4 concentration < LLN ▪ ≥ 3 HAE attacks during the 3 months before screening[b] ▪ ≥ 2 HAE attacks during run-in phase	▪ garadacimab (N = 39) ▪ placebo (N = 26)	Screening: ≤ 1 month Run-in: ≥ 1 to ≤ 2 months[c] Treatment: 6 months Follow-up: 3 months after the last dose of the study medication[d]	28 centres in Canada, Germany, Hungary, Israel, Japan, Netherlands, United States 1/2021–9/2022	Primary: rate of confirmed HAE attacks during the 6-month treatment phase (Day 1 to Day 182) 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[e] ▪ C4 concentration < LLN[f] ▪ ≥ 2 HAE attacks during run-in phase	▪ berotralstat 110 mg (N = 41)[g] ▪ berotralstat 150 mg (N = 40) ▪ placebo (N = 40)	Screening: ≤ 10 weeks, including run-in (≥ 14 to ≤ 56 days) Treatment: 24 weeks (placebo-controlled phase[h]) Follow-up: 3 weeks after the last dose of the study medication[i]	57 centres in Austria, Canada, Czech Republic, France, Hungary, Germany, North Macedonia, Romania, Spain, United Kingdom, United States 2/2018–4/2022[j]	Primary: rate of confirmed HAE attacks during the 24-week treatment phase (Day 1 to 168) Secondary: morbidity, health-related quality of life, AEs

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

Study	Study design	Population	Interventions (number of randomized 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[e] ▪ C4 concentration < LLN[f] ▪ ≥ 2 HAE attacks during run-in phase	▪ berotralstat 110 mg (N = 6)[g] ▪ berotralstat 150 mg (N = 7) ▪ placebo (N = 6)	Screening: ≤ 10 weeks, including run-in (≥ 14 to ≤ 56 days) Treatment: 24 weeks (placebo-controlled phase[h]) Follow-up: 3 weeks after the last dose of the study medication[i]	10 centres in Japan 12/2018–7/2021[k]	Primary: rate of confirmed HAE attacks during the 24-week treatment phase (Day 1 to 168) Secondary: morbidity, health-related quality of life, AEs

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. Patients who had started HAE prophylaxis within the 3 months before screening had to have ≥ 3 HAE attacks within 3 consecutive months before starting prophylaxis.
c. The run-in phase could begin parallel to the screening. If the patient had ≥ 2 HAE attacks within the first month of the run-in phase, the treatment phase could begin, otherwise the run-in phase was extended by 1 month.
d. The follow-up visit took place in patients who did not participate in the open-label extension study CSL312_3002 [19] after the end of the treatment phase.
e. For functional C1-INH activity between 50% and LLN, the following was acceptable as a criterion for inclusion:
  ▫ a SERPING-1 gene mutation (assessed during the screening period) known or likely to be associated with HAE type I or II, or
  ▫ retested functional C1-INH activity < 50%.
f. In the absence of a low C4 concentration during the intercritical period (i.e. the patient is not having an HAE attack), one of the following criteria is acceptable to confirm the diagnosis of HAE:
  ▫ a SERPING-1 gene mutation (assessed during the screening period) known or likely to be associated with HAE type I or II
  ▫ a confirmed family history of C1-INH deficiency
  ▫ a C4 concentration retested during an HAE attack in the screening period with a result < LLN.
g. The arm is irrelevant for the assessment and is disregarded in the following tables.

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
h. 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). i. After completion of treatment phase 3 or premature discontinuation of treatment j. Last visit in the placebo-controlled phase 1: 10 April 2019. k. 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 randomized patients; RCT: randomized controlled trial						

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

Study	Intervention	Comparison
Garadacimab vs. placebo		
VANGUARD	garadacimab 400 mg on Day 1, then 200 mg every 4 weeks, SC	Placebo, every 4 weeks, SC
	▪ Dose modifications not allowed ▪ Interruption of treatment allowed in case of severe hypersensitivity related to the study medication, confirmed thromboembolic events or abnormal bleeding episodes, or any event or laboratory abnormality that poses an unacceptable risk to the patient	
	Prohibited prior and concomitant treatment ▪ Adults: long-term prophylaxis of HAE attacks with C1-INH, androgens, antifibrinolytics or other small-molecule medications within 2 weeks before the run-in phase and during the study ▪ Adolescents (12–17 years): long-term prophylaxis of HAE before screening and during the study ▪ Monoclonal antibodies such as lanadelumab within 3 months before the run-in period and during the study ▪ Oestrogen-containing medications with systemic absorption (e.g. oral contraceptives or hormone replacement therapy), ACE inhibitors within 4 weeks before the run-in phase and during the study ▪ Investigational products within 30 days before screening or within 5 half-lives of the last dose of the investigational product **Allowed concomitant treatment** ▪ On-demand therapy for the treatment of HAE attacks with plasma-derived or recombinant C1-INH, icatibant, ecallantide ▪ Short-term prophylaxis with intravenous C1-INH before medically indicated procedures	

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

Study	Intervention	Comparison
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[a]	
	Prohibited prior and concomitant treatment ▪ Short-term prophylaxis of HAE attacks for a preplanned procedure during the screening or during the study ▪ Androgens[b] or tranexamic acid for prophylaxis of HAE attacks within the 28 days prior to screening or during the study ▪ C1-INH for prophylaxis of HAE attacks within the 14 days prior to screening 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 ▪ ACE inhibitors within 7 days before treatment start or during the study ▪ Initiation of an oestrogen-containing hormonal contraceptive within 56 days of the screening visit or during the study[c] ▪ Investigational products within 30 days of the screening visit or during the study **Allowed concomitant treatment** ▪ On-demand therapy for the treatment of HAE attacks with plasma-derived or recombinant C1-INH, icatibant; in study APeX-2 additionally: recombinant C1-INH, ecallantide ▪ Prophylaxis with C1-INH for an unforeseen/unplanned procedure	

a. 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.
b. Testosterone replacement therapy was allowed during the study.
c. Established use (initiation ≥ 56 days prior to screening) 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; IV: intravenous; P-gp: P-glycoprotein; RCT: randomized controlled trial; SC: subcutaneous

VANGUARD study (study with garadacimab)

The VANGUARD study is a double-blind, randomized study comparing garadacimab with placebo in patients aged 12 years and older with HAE type I or type II. The study consisted of a 1-month screening phase, a maximum 2-month run-in phase and a 6-month double-blind, placebo-controlled treatment phase.

The study included patients with a documented clinical history of HAE (episodes of subcutaneous or mucosal swelling without accompanying urticaria) and documented C1-INH deficiency according to C1-INH concentration and / or functional C1-INH activity ≤ 50% of normal and complement factor C4 concentration < LLN. The C1-INH deficiency had to be confirmed before randomization. Patients with a diagnosis of any other form of angioedema, such as idiopathic or acquired angioedema, recurrent angioedema associated with urticaria or HAE type III, were excluded from participation in the study. Patients had to have had ≥ 3 HAE attacks in the 3 months before screening (according to documentation in the patient's medical record). Patients who had started HAE prophylaxis within the 3 months before screening had to have ≥ 3 HAE attacks within 3 consecutive months before starting prophylaxis. For the transition to the treatment phase of the VANGUARD study, ≥ 2 HAE attacks were required during the run-in phase (≥ 1 to ≤ 2 months). The run-in phase could begin parallel to the screening. If the patient had ≥ 2 HAE attacks within the first month of the run-in phase, the treatment phase could begin, otherwise the run-in phase was extended by 1 month.

The extent to which the inclusion criterion for the number of HAE attacks/month was met in the run-in phase was checked on the basis of the patients' entries in an electronic diary. The investigator reviewed the entries and assessed whether the reported symptoms, taking into account all available medical information and any additional clarifying questions for the patient, were an HAE attack. An HAE attack was considered as such if it included at least one symptom or location or a combination of several symptoms or locations that occurred simultaneously or consecutively within 24 hours. In addition, there had to be noticeable swelling and/or corresponding symptoms. A prodromal symptom alone or the use of on-demand medication alone was not to be assessed as an attack.

In the VANGUARD study, a total of 64 patients were randomly assigned in a 3:2 ratio to treatment with 200 mg garadacimab (N = 39) or placebo (N = 26). According to the company, one patient in the placebo arm was mistakenly assigned to blinded treatment (although they did not attend the visit at the start of treatment and withdrew their consent) and never received study treatment. Randomization was stratified according to age (≤ 17 years versus > 17 years) and, in adults, additionally according to HAE attack rate observed during the run-in phase (1 to < 3 HAE attacks/month versus ≥ 3 HAE attacks/month).

In the VANGUARD study, treatment with garadacimab was in compliance with the SmPC [20].

On-demand therapy of HAE attacks was allowed in the study. Plasma-derived or recombinant C1-INH, icatibant and ecallantide were allowed. In addition, short-term prophylaxis with intravenous C1-INH before medically indicated procedures was allowed. Adults were not allowed to have received long-term prophylaxis of HAE attacks with C1-INH, androgens, antifibrinolytics or other small-molecule medications within 2 weeks before the run-in phase. For adolescents aged 12 to 17 years, any long-term prophylaxis prior to screening led to exclusion from study participation.

The primary outcome of the study was the rate of investigator-confirmed HAE attacks during the 6-month treatment phase (Day 1 to Day 182). 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, randomized 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 ≥ 14 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 phase of the studies APeX-2 and APeX-J, with berotralstat at a dose of 150 mg compared with placebo, was 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 functional C1-INH activity between 50% and LLN was acceptable if a SERPING-1 gene mutation known or likely to be associated with HAE type I or II, or retested functional C1-INH activity < 50% was determined. In the absence of a low C4 concentration during the intercritical period (i.e. the patient was not having an HAE attack), one of the following criteria was acceptable to confirm the diagnosis of HAE: 1). A 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 concentration retested during an HAE attack in the screening period with a result < 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 run-in phase.

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, randomization was stratified by HAE attack rate at baseline (recorded between first screening visit and start of treatment; ≥ 2 HAE attacks/month vs. < 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 [21]. 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.

Characteristics of the study populations

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: garadacimab vs. berotralstat (multipage table)

Study	Garadacimab vs. placebo		Berotralstat vs. placebo			
Characteristic	VANGUARD		APeX-2		APeX-J	
Category	Garadacimab	Placebo	Berotralstat	Placebo	Berotralstat	Placebo
	N[a] = 39	N[a] = 25	N = 40	N = 40	N = 7	N = 6
Age [years], mean (SD)	43 (17)	38 (13)	40 (14)	45 (14)	37 (9)	42 (14)
Sex [F/M], %	62/38	56/44	58/43	68/33	86/14	83/17
Family origin, n (%)						
White	33 (85)	22 (88)	38 (95)	37 (93)	0 (0)	0 (0)
Black or African American	0 (0)	1 (4)	1 (3)	2 (5)	0 (0)	0 (0)
Asian	4 (10)	2 (8)	0 (0)	0 (0)	6 (86)	6 (100)
Other	2 (5)[b]	0 (0)[b]	1 (3)[c]	1 (3)[c]	1 (14)[c]	0 (0)[c]
BMI at screening [kg/m²], mean (SD)	27.9 (6.0)	28.4 (7.6)	30.4 (6.7)	29.3 (6.8)	22.3 (5.0)	28.3 (5.9)
HAE type, n (%)						
Type I	34 (87)	22 (88)	ND	ND	ND	ND
Type II	5 (13)	3 (12)	ND	ND	ND	ND
History of laryngeal attack, n (%)	21 (54)	17 (68)	26 (65)	34 (85)	4 (57)	5 (83)
Family history of HAE, n (%)	34 (87)	23 (92)	ND	ND	ND	ND
Time since diagnosis [years], mean (SD)	ND	ND	28.7 (13.1)	33.4 (14.0)	17.7 (9.1)	22.3 (11.4)
Time since diagnosis [years], median [min; max]	ND	ND	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 first diagnosis, n (%)						
≤ 17 years	18 (46)	12 (48)	18 (45)[d]	16 (40)[d]	1 (14)[d]	1 (17)[d]
> 17 years	21 (54)[d]	13 (52)[d]	22 (55)[d]	24 (60)[d]	6 (86)[d]	5 (83)[d]
Prior long-term prophylaxis, n (%)[e]	14 (36)	7 (28)	30 (75)[f]	29 (73)[f]	6 (86)	4 (67)
Rate of HAE attacks [attacks/month], mean (SD)[g]	2.9 (2.3)	3.1 (2.3)	3.1 (1.6)	2.9 (1.1)	2.0 (1.1)	2.5 (1.5)
Rate of HAE attacks [attacks/month], median [min; max][g]	1.8 [1; 10]	2 [1; 10]	2.7 [0.9; 6.7]	3.0 [1.3; 6.2]	2.2 [0.8; 3.9]	2.2 [0.9; 5.3]

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

Study Characteristic Category	Garadacimab vs. placebo		Berotralstat vs. placebo			
	VANGUARD		APeX-2		APeX-J	
	Garadacimab	Placebo	Berotralstat	Placebo	Berotralstat	Placebo
	N[a] = 39	N[a] = 25	N = 40	N = 40	N = 7	N = 6
Treatment discontinuation, n (%)	0 (0)	3 (12[d])[h]	3 (8[d])[i]	5 (13[d])[i]	0 (0)	1 (17[d])[j]
Study discontinuation, n (%)	1 (3[d])[k]	3 (12[d])[k]	ND[l]	ND[l]	ND[l]	ND[l]

a. Number of randomized patients who received at least one dose of the respective study medication.
b. Includes the categories “Native Hawaiian or Other Pacific Islander” and “Other”.
c. Includes the category “Other”.
d. Institute’s calculation.
e. VANGUARD: in the past 3 months before the screening phase; APeX-2 and APeX-J: any prior prophylactic treatment of HAE.
f. 12 patients (30%) in the intervention arm vs. 11 patients (28%) in the control arm had prophylactic treatment within 30 days before the screening phase.
g. VANGUARD: in the last 3 months before the screening phase (but for patients with HAE prophylaxis in the last 3 months before the screening phase: in the 3 months before the start of HAE prophylaxis); APeX-2 and APeX-J: between screening and start of study medication.
h. In all cases, the reason for treatment discontinuation in the control arm was patient decision.
i. During the placebo-controlled phase 1; 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), other reasons (0 vs. 3%) (percentages: Institute’s calculation, based on number of randomized patients). In addition, one patient in the control arm did not receive any study treatment.
j. During the placebo-controlled phase 1; the reason for treatment discontinuation in the control arm was AEs.
k. No information on the reason for discontinuation.
l. There are no explicit data on patients with study discontinuation. Module 4 A 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 randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the study populations were largely balanced between the individual studies and study arms. The mean age of the patients in the 3 studies was about 40 years. The majority of the patients in the VANGUARD and APeX-2 studies were white and around 60% were female. The majority of the patients in the smaller APeX-J study were Asian and around 85% were female. In the VANGUARD study, 87.5% of the patients had HAE type I, and 12.5% of the patients had HAE type II. This is of a similar order of magnitude compared with the data on the frequencies of type I and type II in the guidelines [22,23]. There was no information on the number of patients with HAE type I or type II for the APeX-2 and APeX-J studies. A history of laryngeal attacks was slightly more common in the placebo arms of the studies than in the intervention arms. Common locations of previous HAE attacks in the patients included in the studies included extremities, abdomen, (uro)genital tract and head or face (see Table 18 in I Appendix B of the full benefit assessment). The majority of patients in the APeX-2 and APeX-J studies had been pretreated with long-term prophylaxis, with approximately 30% of patients in the APeX-2 study receiving long-term prophylaxis within 30 days prior to screening (data on this period was not available for the APeX-J study). In the VANGUARD study, around one-third of patients had received long-term prophylaxis in the 3 months prior to screening. The proportion of patients with any previous long-term prophylaxis in the VANGUARD study remained unclear due to a lack of data. The patients in the studies had an average rate of around 2 to 3 HAE attacks/month in the 3 months before the screening phase (VANGUARD) or between screening and start of the study medication (APeX-2 and APeX-J).

In all 3 studies, more patients (12% to 17%) in the placebo arm discontinued treatment prematurely. In the VANGUARD study, this was also shown in the study discontinuations (3% in the intervention arm versus 12% in the placebo arm). For the APeX-2 and APeX-J studies, there were no explicit data on patients with study discontinuation. Module 4 A showed that the majority of patients completed all assessments in the placebo-controlled phase 1.

I 3.3 Similarity of the studies for the indirect comparison

Study design

The studies VANGUARD, 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. All 3 studies included a run-in phase, in which patients had to have ≥ 2 HAE attacks to be eligible for transition to the treatment phase with the study medication.

The duration of the placebo-controlled treatment phase, which was 6 months (26 weeks) in VANGUARD and 24 weeks in both APeX-2 and APeX-J, was assessed as sufficiently comparable. The study implementation periods differed only marginally. While the VANGUARD study started in 2021 and was completed in 2022, 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 VANGUARD and APeX-2 recruited patients globally (including Japan

in the VANGUARD study). 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.

Similarity of the patient population

Information on the patient characteristics can be found in Section I 3.2; information on the location of HAE attacks at baseline and on previous and concomitant treatment of the patient populations is also presented as supplementary information in I Appendix B of the full benefit assessment.

Differences in patient characteristics with regard to the proportion of women and family origin were shown between APeX-J versus APeX-2 and VANGUARD. Although the proportion of women in the study population was slightly higher in the APeX-J study than in VANGUARD 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 VANGUARD 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 VANGUARD and APeX-2 as well as APeX-J.

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 [22,23] 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 VANGUARD 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 [22,23]. 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 potential differences in these individual characteristics existed to such an extent that they called into question the performance of an adjusted indirect comparison based on the studies VANGUARD, APeX-2 and APeX-J.

Similarity of the common comparator

The common comparator in the presented indirect comparison was placebo. The VANGUARD study as well as the APeX-2 and APeX-J studies allowed on-demand medication with C1-INH and icatibant to treat HAE attacks, and short-term prophylaxis with C1-INH before medically indicated procedures. The studies VANGUARD 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 VANGUARD study or the APeX-2 study [15].

Long-term prophylaxis of HAE attacks with C1-INH, androgens or antifibrinolytics or tranexanic acid was not permitted in the studies within defined periods before screening or the run-in phase, or during the studies. Treatment with lanadelumab for prophylaxis was also not allowed in any of the 3 studies. In addition, angiotensin converting enzyme (ACE) inhibitors were not allowed to be administered during the studies, or in the VANGUARD 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 [23] and the recommendations of the World Allergy Organization (WAO) and the European Academy of Allergy and Clinical Immunology (EAACI) [22], 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 VANGUARD study with regard to pre- and concomitant treatment with oestrogen-containing drugs. In the VANGUARD study, oestrogen-containing medications with systemic absorption (e.g. oral contraceptives or hormone replacement therapy) were not allowed within 4 weeks before the run-in phase and during the study. This concurs with the recommendations of the guidelines [22,23], 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 (operationalized as monthly rate) in men (no potential use of oestrogen-containing drugs) differed from those in the total study population (potential use of oestrogen-containing drugs). The effects of garadacimab versus berotralstat shown in men (Institute's calculation of an indirect comparison according to Bucher [6], rate ratio [95% CI]: 0.08 [0.02; 0.39]; p = 0.002; based on available results for VANGUARD and APeX-2), were comparable to the effects based on the total study populations (rate ratio [95% CI]: 0.20 [0.09; 0.47]; p < 0.001; see Table 12). Thus, it can be excluded with sufficient certainty that a potential treatment with oestrogen-containing drugs in the studies APeX-2 and APeX-J, which can trigger HAE attacks, had a relevant influence on the results of the indirect comparison. The potential influence of the difference between the studies with

regard to the administration of oestrogen-containing drugs on the results of the present indirect comparison was therefore assessed as negligible.

Overall, 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 benefit assessment), although no data were available for the APeX-J study. In the studies VANGUARD and APeX-2, the main drugs used for on-demand treatment of HAE were C1-INH and icatibant. 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 very similar study design, which ultimately differed only marginally in the duration of the placebo-controlled treatment phase. In addition, the patient populations of the studies were sufficiently similar. The described differences in individual demographic and clinical characteristics (sex, family origin) and the possible concomitant treatments (oestrogen-containing drugs) between the studies VANGUARD 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: garadacimab 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			
garadacimab vs. placebo							
VANGUARD	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: randomized 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 results of the studies VANGUARD and APeX-2 and APeX-J were fully transferable to the German health care context on the basis of the study design and patient characteristics. It referred to the fact that the study centres of the VANGUARD study included centres in Germany (approx. 21% of randomized patients) and other Western industrialized countries (Europe and North America), and that the APeX-2 study was also conducted in study centres in North America and Europe, including in Germany, while the APeX-J study was conducted in Japanese study centres. It added that the majority of patients included in the VANGUARD as well as the APeX-2 and APeX-J studies were of Caucasian family origin (approx. 85% and approx. 81% respectively). It pointed out that treatment of HAE followed a comparable standard in these countries and was based on the specifications of the international guideline [22]. The company added that the same drugs that are used to treat acute HAE attacks in everyday clinical practice in Germany were available in the studies. It concluded that the results of the studies VANGUARD, APeX-2 and APeX-J were therefore 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, measured using the WPAI:GH question 6
  - Health status, measured using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - Health-related quality of life, measured using the 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 (yes/no) and whether an indirect comparison was possible based on the available data (yes/no).

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

Comparison / Study	Outcomes								
	All-cause mortality[a]	HAE attacks[b]	Activity impairment (WPAI:GH question 6)	Health status (EQ-5D VAS)	Health-related quality of life (AE-QoL)	SAEs	Severe AEs	Discontinuation due to AEs	Specific AEs
garadacimab vs. placebo									
VANGUARD	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	Yes	No[d]
berotralstat vs. placebo									
APeX-2	Yes	Yes	Yes	Yes	Yes	Yes	Yes[e]	Yes	No[d]
APeX-J	Yes	Yes	Yes	Yes	Yes	Yes	Yes[e]	Yes	No[d]
Indirect comparison feasible	Yes[f]	Yes	Yes[f]	Yes	Yes	Yes	No[g]	Yes[f]	No[g]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalized 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. No suitable data available; see the following text sections for reasons.
d. No specific AEs were identified based on the AEs occurring in the relevant study/studies.
e. Severe AEs are operationalized as DMID grade 3 (severe) or DMID grade 4 (life-threatening).
f. The company presented no indirect comparison in Module 4 A.
g. 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: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; WPAI:GH: Work Productivity and Activity Impairment: General Health

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 [23] is to prevent suffocation, prevent attacks or reduce disease activity (frequency, severity and duration of attacks) and, as a result, normalize 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 normalize patients' lives. Complete control means that the patient no longer has any attacks [22].

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 (operationalized

as the average monthly rate during the treatment phase) and attack-free status (operationalized as the proportion of patients without HAE attacks during the treatment phase) were considered to be meaningful operationalizations of the outcome HAE attacks and were used for this benefit assessment. The recording and operationalization of HAE attacks in the studies is explained below.

Recording of HAE attacks

Both in the VANGUARD study and in the APeX-2 and APeX-J studies, HAE attacks were recorded via entries made by patients in an electronic diary. In the VANGUARD study, patients were asked to fill in their diary when they had symptoms of a potential HAE attack. The patients had to enter additional information about the attack (start and end, location, impairment of daily activities, use of on-demand medication) and contact the study centre within 72 hours of the onset of symptoms. If additional symptoms occurred within 24 hours, these had to be entered in the diary as updates (symptoms were recorded as new symptoms if they occurred ≥ 24 hours after previous symptoms had resolved). In the APeX-2 and APeX-J studies, however, patients were asked to complete their diary daily and indicate whether or not symptoms of an HAE attack had occurred within the last 24 hours. The diary was therefore completed independently 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 all studies, training was provided on how to use the diary and further measures were taken to ensure that the diary was completed in accordance with the protocol, such as repeated training and telephone calls between visits. In the event of premature discontinuation of the study medication in the APeX-2 and APeX-J studies, the occurrence of HAE attacks was to be documented in the diary until the follow-up visit (3 weeks after the last dose of the study medication). The study design of VANGUARD also provided for the continued documentation of HAE attacks in the event of premature discontinuation (up to 3 months 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 diary entries (VANGUARD and APeX-2) or verified by the investigator and confirmed by an independent expert (APeX-J). All available medical information and clinical characteristics were taken into account in the studies and the patients were asked additional clarifying questions if necessary. According to the criteria in the VANGUARD study, an HAE attack was considered as such if it included at least one symptom or location or a combination of several symptoms or locations that occurred simultaneously or consecutively within 24 hours. In addition, there had to be noticeable swelling and/or corresponding symptoms. A list of typical symptoms and locations was provided in the study design to help investigators identify the symptoms associated with an

HAE attack and their locations. A prodromal symptom alone or the use of on-demand medication alone was not to be assessed as an attack. 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 separated in time from a previous attack, i.e. it did not begin within 24 hours (VANGUARD) 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 recording HAE attacks almost completely, in particular due to the comprehensive training measures, regular visits with review and completion of the diaries 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 VANGUARD study, the severity of the attacks (mild, moderate, severe) was classified by the investigator based on criteria defined in the study design (degree of interference in daily activities, need for [medical] assistance, use of on-demand therapy or other concomitant treatments).

Overall, the recording of HAE attacks was considered to be sufficiently similar in the studies VANGUARD, APeX-2 and APeX-J. The differences described (particularly with regard to daily versus event-related recording) 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).

Operationalization 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 [22,23], the operationalizations of the monthly rate of HAE attacks and freedom from attacks were used in this benefit assessment. In the VANGUARD study as well as in the APeX-2 and APeX-J studies, analyses of both operationalizations were predefined in the study design.

In the studies, freedom from attacks was defined as the proportion of patients without HAE attacks during the treatment phase (26 weeks in the VANGUARD study and 24 weeks in the APeX-2 and APeX-J studies). 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 30.4375 days (VANGUARD) or 28 days (APeX-2 and APeX-J). Overall, it was assumed that the operationalizations of the monthly rate of HAE attacks and freedom from attacks were sufficiently similar between the studies VANGUARD, APeX-2 and APeX-J.

All confirmed HAE attacks, regardless of severity and location, were included in the analyses used for the operationalization 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. Since information on the location (abdominal, peripheral, mixed, laryngeal) of the confirmed HAE attacks was only available for the APeX-2 and APeX-J studies (in the dossier on berotralstat [14]), it was not possible to draw conclusions separately according to the locations of the HAE attacks.

Activity impairment (recorded using WPAI:GH question 6)

The outcome activity impairment, recorded by means of question 6 of the WPAI:GH, is patient relevant and was used for this benefit assessment. Question 6 of the WPAI:GH is 'During the past seven days, not including today, how much did your health problems affect your ability to do your regular, daily, non-work activities?'. 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'.

The WPAI:GH was recorded in the VANGUARD study in patients aged ≥ 16 years. In the VANGUARD study, only 2 patients in the intervention arm and 2 patients in the placebo arm were < 16 years old and therefore did not complete a WPAI:GH questionnaire. In the APeX-2 and APeX-J studies, the recording was independent of the age of the patients.

The WPAI:GH was recorded on Day 1, Day 31, Day 61, Day 91, Day 121, Day 151 and Day 182 in the VANGUARD study, and on Day 1, Day 29, Day 57, Day 85, Day 127 and Day 169 in the APeX-2 and APeX-J studies. The average response rates in the intervention and placebo arms at all time points were 90% in VANGUARD, ≥ 90% in APeX-2 and 100% in APeX-J.

For the APeX-2 and APeX-J studies, the company presented an analysis of the change at the end of treatment compared with baseline for the WPAI:GH question 6, using a mixed-effects model with repeated measures (MMRM; predefined in the study documents), in Module 4 A for the berotralstat procedure. According to information provided by the company in Module 4 A of the dossier, in contrast, a responder analysis was conducted in the VANGUARD study. The company explained that an MMRM analysis requires a continuous outcome criterion to provide reliable and interpretable results. According to the company, an

(approximately) continuous outcome criterion was not assumed to be present in the analysis of the individual question 6 of the WPAI:GH, so it did not perform an analysis using MMRM. The company's reasoning was not substantive. Question 6 of the WPAI:GH is assessed by circling the appropriate value on a scale of 0 to 10. These data, measured on a scale of 11 values, can be considered approximately linear and an MMRM analysis can be conducted. As the company did not conduct an analysis using MMRM for the VANGUARD study, no adjusted indirect comparison of garadacimab versus berotralstat was available for the outcome activity impairment (WPAI:GH question 6).

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 91 and Day 182 in the VANGUARD study, and on Day 1, Day 29, Day 57, Day 85, Day 127 and Day 169 in the APeX-2 and APeX-J studies. The average response rates in the intervention and placebo arms at all time points were 90% in VANGUARD, ≥ 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. Overall, there were more recordings in APeX-2 and APeX-J than in VANGUARD. 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 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 garadacimab 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 [24-26]. 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.

The AE-QoL was recorded in the VANGUARD study in patients aged ≥ 18 years. According to the information provided by the company in Module 4 A of the dossier, the questionnaire was not completed for only 4 patients due to the age limit, but in the VANGUARD study 4 patients in the intervention arm and 2 patients in the placebo arm were < 18 years old at baseline. In the APeX-2 and APeX-J studies, the recording was independent of the age of the patients. In the APeX-2 study, only 4 patients were under 18 years of age at baseline; 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), and the overall small proportion of patients for whom no recording was conducted and who were therefore not included in the analyses, this was of no consequence for this benefit assessment.

The AE-QoL was recorded on Day 1, Day 31, Day 61, Day 91, Day 121, Day 151 and Day 182 in the VANGUARD study, and on Day 1, Day 29, Day 57, Day 85, Day 127 and Day 169 in the APeX-2 and APeX-J studies. The average response rates in the intervention and placebo arms at all time points were 80% in VANGUARD, ≥ 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 garadacimab versus berotralstat were used for this benefit assessment.

Side effects

Symptoms of the underlying disease

The symptoms underlying a confirmed HAE attack were not recorded as AEs in the VANGUARD, APeX-2 and APeX-J studies. This approach was appropriate.

Severe AEs

In the VANGUARD study, the severity of AEs was assessed by the investigator as mild, moderate or severe, taking into account the need for treatment and impairment of the activities of daily living. This was not an adequate operationalization of severe AEs in distinction from non-severe AEs and was 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 [27,28]. 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, operationalizing 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 operationalization 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 garadacimab from the VANGUARD 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: garadacimab vs. berotralstat

Comparison Study	Study level	Outcomes								
		All-cause mortality[a]	HAE attacks[b]	Activity impairment (WPAI:GH question 6)	Health status (EQ-5D VAS)	Health-related quality of life (AE-QoL)	SAEs	Severe AEs	Discontinuation due to AEs	Specific AEs
garadacimab vs. placebo										
VANGUARD	L	L	L	L	L	L	L	–[c]	L	–
berotralstat vs. placebo										
APeX-2	L	L	L	L	L	L	L	L[d]	L	–
APeX-J	L	L	L	L	L	L	L	L[d]	L	–

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalized 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. No suitable data available; for justification see Section I 4.1 of this dossier assessment.
d. Severe AEs are operationalized 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; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; WPAI:GH: Work Productivity and Activity Impairment: General Health

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

In the APeX-2 and APeX-J studies, daily diary entries on HAE attacks were required. The company did not provide any information on how to deal with missing values or on the extent of missing values. In the VANGUARD study, patients were asked to fill in their diary when they had symptoms of a potential HAE attack. With this type of data recording, it is not possible to estimate the extent to which data is missing or to quantify the missing data. In the given situation, however, it was assumed that the recording of HAE attacks was sufficiently reliable and almost complete in the APeX-2 and APeX-J studies as well as in the VANGUARD study (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 summarize the results comparing garadacimab with berotralstat in patients aged 12 years and older for the routine prophylaxis of recurrent attacks of 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 VANGUARD study, tables on common AEs and common SAEs are presented in I Appendix C of the full benefit assessment. There were no discontinuations due to AEs in the VANGUARD study. 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 benefit assessment.

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

Outcome category Outcome Comparison Study	Garadacimab or berotralstat N	Garadacimab or berotralstat Mean monthly rate [95% CI][a]	Placebo N	Placebo Mean monthly rate [95% CI][a]	Group difference Rate ratio [95% CI]; p-value[a]
Morbidity					
HAE attacks					
Monthly rate[b, c]					
Garadacimab vs. placebo					
VANGUARD	39	0.22 [0.11; 0.46]	25	2.07 [1.50; 2.86]	0.11 [0.05; 0.24]; < 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 comparators[e]:					
Garadacimab vs. berotralstat					0.20 [0.09; 0.47]; < 0.001
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[f]**
Attack-free[b, g]					
Garadacimab vs. placebo					
VANGUARD	39	24 (61.5)	25	0 (0)	31.85 [2.02; 501.25]; 0.014
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 comparators[e]:					
Garadacimab vs. berotralstat					20.42 [0.68; 616.19]; 0.083

a. VANGUARD: Poisson model calculated with stratification according to the observed HAE attack rate during the run-in period (1 to < 3 HAE attacks/month and ≥ 3 HAE attacks/month)
APeX-2 and APeX-J: negative binomial model; the covariable baseline HAE attack rate confirmed by the investigator was taken into account. The logarithm of the treatment duration was used as an offset variable.
b. VANGUARD and APeX-2: HAE attacks confirmed by the investigator; APeX-J: HAE attacks confirmed by the independent expert.
c. In the VANGUARD study, 1 month was defined as 30.4375 days, in the APEX-2 and APEX-J studies as 28 days.
d. Meta-analysis using a fixed-effect model (inverse variance method).
e. Indirect comparison according to Bucher [6].
f. 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.
g. 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; RCT: randomized controlled trial; RR: relative risk

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

Outcome category Outcome Comparison Study	Garadacimab or berotralstat N	Garadacimab or berotralstat Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Group difference RR [95% CI]; p-value[a]
Mortality					
All-cause mortality[b]					
Garadacimab vs. placebo					
VANGUARD	39	0 (0)	25	0 (0)	–
Berotralstat vs. placebo					
APeX-2	40	0 (0)	40	0 (0)	–
APeX-J	7	0 (0)	6	0 (0)	–
Indirect comparison using common comparators[c]:					Not submitted
Side effects					
AEs (supplementary information)					
Garadacimab vs. placebo					
VANGUARD	39	25 (64.1)	25	15 (60.0)	–
Berotralstat vs. placebo					
APeX-2	40	34 (85.0)	40	30 (76.9)	–
APeX-J	7	7 (100)	6	6 (100)	–
SAEs					
Garadacimab vs. placebo					
VANGUARD	39	1 (2.6)	25	0 (0)	1.95 [0.08; 46.07]; 0.679
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]:					
Garadacimab vs. berotralstat					14.03 [0.19; 1065.76]; 0.232
Severe AEs	No suitable data for the indirect comparison[d]				
Discontinuation due to AEs					
Garadacimab vs. placebo					
VANGUARD	39	0 (0)	25	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[e]					0.57 [0.07; 4.34]; ND
Indirect comparison using common comparators[c]:					Not submitted

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

Outcome category Outcome	Garadacimab or 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 [6].
d. See Section I 4.1 for an explanation.
e. Meta-analysis using a fixed-effect model (inverse variance method).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

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

Outcome category Outcome Comparison Study	Garadacimab or berotralstat			Placebo			Group difference
	N[a]	Values at baseline mean (SD)	Mean change at the end of treatment[b] Mean (SD/SE)[c]	N[a]	Values at baseline mean (SD)	Mean change at the end of treatment[b] Mean (SD/SE)[c]	MD [95% CI][c]; p-value
Morbidity							
Activity impairment (WPAI:GH question 6[d])							
Garadacimab vs. placebo							
VANGUARD	34	32.6 (31.9)	−23.2 [−31.5; −14.8][e]	20	24.5 (26.0)	7.4 [−3.5; 18.3][e]	ND; p < 0.001[f]
Berotralstat vs. placebo							
APeX-2	38[g]	3.6 (2.8)	−1.6 (0.4)	36[g]	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[h]							−0.20 [−1.32; 0.93]; 0.733
Indirect comparison using common comparators[i]:						Not submitted	
Health status (EQ-5D VAS[j])							
Garadacimab vs. placebo							
VANGUARD	38[g]	85.8 (15.7)	6.1 (1.3)	23[g]	82.6 (18.7)	−6.9 (1.7)	14.99 [9.80; 20.18]; < 0.001
Berotralstat vs. placebo							
APeX-2	38[g]	82.9 (12.6)	2.7 (1.8)	36[g]	85.2 (10.8)	3.3 (1.8)	−0.6 [−5.8; 4.5]; 0.807
APeX-J	7	75.7 (30.61)	8.4 (4.7)	6	80.5 (26.3)	−3.6 (5.1)	12.0 [−3.7; 27.8]; 0.120
Total[h]							0.62 [−4.28; 5.51]; 0.805
Indirect comparison using common comparators[i]:							
Garadacimab vs. berotralstat							14.37 [7.24; 21.50]; < 0.001
						SMD [95% CI]:	0.85 [0.40; 1.29]

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

Outcome category Outcome Comparison Study	Garadacimab or berotralstat			Placebo			Group difference
	N[a]	Values at baseline mean (SD)	Mean change at the end of treatment[b] Mean (SD/SE)[c]	N[a]	Values at baseline mean (SD)	Mean change at the end of treatment[b] Mean (SD/SE)[c]	MD [95% CI][c]; p-value
Health-related quality of life							
AE-QoL[k]							
Total score							
Garadacimab vs. placebo							
VANGUARD	33[g]	38.8 (15.0)	−26.5 (17.9)	20[g]	43.7 (21.4)	−2.2 (19.1)	−25.95 [−35.61; −16.29]; 0.001
Berotralstat vs. placebo							
APeX-2	38[g]	43.0 (16.9)	−15.8 (2.7)	36[g]	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[h]							−6.21 [−13.34; 0.92]; 0.088
Indirect comparison using common comparators[i]:							
Garadacimab vs. berotralstat							–19.74 [–31.75; –7.73]; < 0.001
						SMD [95% CI]:	−0.74 [−1.21; −0.27]
Functioning							
Garadacimab vs. placebo							
VANGUARD	33[g]	43.2 (21.0)	−35.8 (23.2)	20[g]	42.0 (26.0)	1.9 (29.6)	–
Berotralstat vs. placebo							
APeX-2	38[g]	47.1 (21.0)	−22.0 (3.4)	36[g]	45.3 (24.1)	−13.0 (3.5)	–
APeX-J	7	42.0 (28.3)	−14.8 (7.0)	6	32.3 (18.3)	−1.5 (7.5)	–

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

Outcome category Outcome Comparison Study	Garadacimab or berotralstat			Placebo			Group difference
	N[a]	Values at baseline mean (SD)	Mean change at the end of treatment[b] Mean (SD/SE)[c]	N[a]	Values at baseline mean (SD)	Mean change at the end of treatment[b] Mean (SD/SE)[c]	MD [95% CI][c]; p-value
Fatigue/mood							
Garadacimab vs. placebo							
VANGUARD	33[g]	34.6 (19.4)	−21.1 (22.9)	20[g]	42.3 (28.0)	−5.8 (27.1)	–
Berotralstat vs. placebo							
APeX-2	38[g]	38.5 (19.3)	−12.7 (3.3)	36[g]	44.5 (23.2)	−10.5 (3.3)	–
APeX-J	7	21.4 (15.5)	−3.2 (7.2)	6	32.5 (18.1)	2.9 (7.8)	–
Fear/shame							
Garadacimab vs. placebo							
VANGUARD	33[g]	44.2 (20.1)	−28.0 (24.1)	20[g]	51.5 (24.2)	−2.5 (18.6)	–
Berotralstat vs. placebo							
APeX-2	38[g]	47.9 (22.9)	−16.2 (3.5)	36[g]	51.5 (26.1)	−11.2 (3.5)	–
APeX-J	7	57.1 (33.1)	−32.6 (7.6)	6	61.8 (25.6)	−4.4 (8.2)	–
Diet							
Garadacimab vs. placebo							
VANGUARD	33[g]	23.9 (20.3)	−16.7 (23.3)	20[g]	26.7 (30.0)	−0.6 (16.5)	–
Berotralstat vs. placebo							
APeX-2	38[g]	31.6 (24.0)	−10.0 (3.2)	36[g]	34.0 (25.0)	−7.3 (3.3)	–
APeX-J	7	26.8 (29.3)	−4.3 (8.6)	6	12.5 (15.8)	2.9 (9.3)	–

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

Outcome category Outcome Comparison Study	Garadacimab or berotralstat			Placebo			Group difference
	N[a]	Values at baseline mean (SD)	Mean change at the end of treatment[b] Mean (SD/SE)[c]	N[a]	Values at baseline mean (SD)	Mean change at the end of treatment[b] Mean (SD/SE)[c]	MD [95% CI][c]; p-value

a. Number of patients taken into account in the effect estimation; baseline values may be based on different patient numbers.
b. VANGUARD: Week 26; APeX-2 and APeX-J: Week 24
c. Unless otherwise stated: VANGUARD: mean (SD) and MD [95% CI]: MMRM model adjusted for baseline value, visit and the interaction term visit and treatment. The effect represents the difference in changes (from baseline) between the treatment groups at Week 26.
APeX-2 and APeX-J: mean (SE) and MD [95% CI]: MMRM model adjusted for baseline value, baseline HAE attack rate, visit and the interaction term of visit and treatment, patient ID was included in the model as a random variable. The effect represents the difference in changes (from baseline) between the treatment groups at Week 24.
d. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 10 points; in the VANGUARD study the values are given in percentages).
e. Changes and 95% CI at Week 26 from ANCOVA model with baseline value as covariate and treatment as categorical variable.
f. p-value: F-test from ANCOVA model at Week 26, adjusted for baseline values.
g. Number of patients with values at the end of treatment; unclear how many patients were included in the model.
h. Meta-analysis using a fixed-effect model (inverse variance method).
i. Indirect comparison according to Bucher [6].
j. Higher (increasing) values indicate improved symptoms; positive effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 100 points).
k. 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: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; VAS: visual analogue scale; WPAI:GH: Work Productivity and Activity Impairment: General Health

One RCT (VANGUARD) was available on the side of the intervention garadacimab of the present adjusted indirect comparison. Thus, there was no homogeneity check for the side of the intervention garadacimab. On the side of the comparator berotralstat of the present 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 operationalizations used for the benefit assessment, with the exception of health status (EQ-5D VAS) and activity impairment (WPAI:GH question 6). The heterogeneity measure I^2 was 55% for health status (EQ-5D VAS) and 53% for activity impairment (WPAI:GH question 6). In both cases, however, the p-value of the heterogeneity test was above 0.05 (EQ-5D VAS: $p = 0.14$; WPAI:GH

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 garadacimab versus berotralstat, it is 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 VANGUARD, APeX-2 and APeX-J. There was no hint of an added benefit of garadacimab in comparison with berotralstat; an added benefit was 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 garadacimab compared with berotralstat. There was a hint of an added benefit of garadacimab in comparison with berotralstat.

Freedom from attack

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

Activity impairment (WPAI:GH question 6)

The company did not present an adjusted indirect comparison of garadacimab versus berotralstat for activity impairment assessed using WPAI:GH question 6 (see Section I 4.1 for an explanation). There was no hint of an added benefit of garadacimab in comparison with berotralstat; an added benefit was therefore not proven.

Health status (EQ-5D VAS)

For health status assessed with the EQ-5D VAS, the adjusted indirect comparison showed a statistically significant difference in favour of garadacimab compared with berotralstat. The 95% confidence interval (CI) of the standardized mean difference (SMD) was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. There was a hint of an added benefit of garadacimab in comparison with berotralstat.

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 garadacimab compared with berotralstat for the AE-QoL total score. The 95% CI of the SMD was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. There was a hint of an added benefit of garadacimab in comparison with berotralstat.

Side effects

SAEs

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

Severe AEs

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

Discontinuation due to AEs

No discontinuations due to AEs occurred in the VANGUARD 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 was no hint of greater or lesser harm of garadacimab in comparison with berotralstat; greater or lesser harm was 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 1 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 Module 4 A, the company stated that it conducted subgroup analyses for the indirect comparison only for subgroups with comparable definitions. The subgroup analyses presented by the company were incomplete overall. The available and missing subgroup analyses are described below.

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 VANGUARD study, no subgroup analyses by age were predefined; the median age of the patient population (≤ 41 years versus > 41 years) was defined post hoc for group classification. The company stated in Module 4 A of the dossier that an indirect comparison for the characteristic age could not be conducted due to the different definitions of the subgroups. The company's reasoning was not substantive. In the indirect comparison presented by the company in the dossier, age groups could have been defined post hoc for the VANGUARD study concurring with the categories in the APeX-2 and APeX-J studies.

For the subgroup characteristic of the monthly HAE attack rate at baseline, the categories were defined according to the respective stratification factor in the studies as 1 to < 3 attacks/month versus ≥ 3 attacks/month (VANGUARD; post hoc) or ≥ 2 attacks/month versus < 2 attacks/month (APeX-2 and pooled analyses of APeX-2 and APeX-J; predefined). However, the company did not present any subgroup analyses for the indirect comparison of garadacimab versus berotralstat for the characteristic monthly HAE attack rate at baseline. In the indirect comparison presented by the company in the dossier, subgroups according to the monthly HAE attack rate at baseline could have been defined post hoc for the VANGUARD 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 garadacimab 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. However, for the outcome of health-related quality of life (AE-QoL), subgroup analyses for the indirect comparison of garadacimab versus berotralstat were also lacking for the characteristic of sex for the relevant operationalization of the change at the end of treatment.

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 symptom outcomes

For the symptom outcomes below, it could not be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

HAE attacks

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

Health status (EQ-5D VAS)

For the outcome health status (EQ-5D VAS), insufficient severity data were available for a classification as serious/severe. In the VANGUARD study, as well as in the APeX-2 and APeX-J studies, the EQ-5D VAS values at baseline were between 76 and 86 (scale range: 0 to 100, with higher values indicating better symptoms). The outcome of health status (EQ-5D VAS) was therefore allocated to the outcome category of non-serious/non-severe symptoms/late complications.

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

Outcome category **Outcome**	**Garadacimab (VANGUARD) 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/added benefit not proven
Morbidity		
HAE attacks Monthly rate	0.22 vs. 1.33 or 1.08 Rate ratio: 0.20 [0.09; 0.47]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: considerable
Freedom from attack	61.5% vs. 5.0% or 0% Rate ratio: 20.42 [0.68; 616.19]; p = 0.083	Lesser benefit/added benefit not proven
Activity impairment (WPAI:GH question 6)	–23.2 vs. −1.6 or 1.0 MD: –[c]	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	6.1 vs. 2.7 or 8.4 MD: 14.37 [7.24; 21.50]; p < 0.001 SMD [95% CI]: 0.85 [0.40; 1.29][d] Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications 0.20 < CI_L ≤ 0.40 Added benefit, extent: minor
Health-related quality of life		
AE-QoL total score	−26.5 vs. −15.8 or −17.1 MD: −19.74 [−31.75; −7.73]; p < 0.001 SMD [95% CI]: −0.74 [−1.21; −0.27] SMD [95% CI]: 0.74 [0.27; 1.21][d, e] Probability: hint	Outcome category: health-related quality of life 0.20 < CI_L ≤ 0.30 Added benefit, extent: minor
Side effects		
SAEs	2.6% vs. 0% or 0% RR: 14.03 [0.19; 1065.76]; p = 0.232	Greater/lesser harm not proven
Severe AEs	No suitable data for the indirect comparison[f]	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 2.5% or 0% RR: –[c]	Greater/lesser harm not proven

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

Outcome category **Outcome**	**Garadacimab (VANGUARD) 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, 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. 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. e. Institute's calculation, to determine the extent of the added benefit, the mean difference is formed in such a way that the effect estimates and confidence intervals are above 0. f. 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; SAE: serious adverse event; SMD: standardized mean difference; VAS: visual analogue scale; WPAI:GH: Work Productivity and Activity Impairment: General Health		

I 5.2 Overall conclusion on added benefit

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

Table 16: Positive and negative effects from the assessment of garadacimab compared with berotralstat

Positive effects	**Negative effects**
Non-serious/non-severe symptoms/late complications ▪ HAE attacks (monthly rate): hint of an added benefit – extent: considerable ▪ Health status (EQ-5D VAS): hint of an added benefit – extent: minor	–
Health-related quality of life ▪ AE-QoL total score: hint of an added benefit – extent: minor	–
AE-QoL: Angioedema Quality of Life Questionnaire; HAE: hereditary angioedema; VAS: visual analogue scale	

Overall, only positive effects were shown for garadacimab in comparison with berotralstat. There was no statistically significant effect for the outcome HAE attacks, operationalized as

freedom from attacks (see Table 12), but the operationalization 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. For the outcome health status (EQ-5D VAS) and the AE-QoL total score, there was a hint of an added benefit with the extent minor in each case. In summary, there is a hint of a considerable added benefit of garadacimab in comparison with the ACT for patients aged 12 years and older for the routine prophylaxis of recurrent attacks of HAE.

The result of the assessment of the added benefit of garadacimab in comparison with the ACT is summarized in Table 17.

Table 17: Garadacimab – probability and extent of the added benefit

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

G-BA: Federal Joint Committee

The assessment described above differs from that of the company, which derived an indication of a considerable added benefit of garadacimab 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.

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