30 July 2025
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EMADOC-1700519818-2331715
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for marketing authorisation application

Ekterly (sebetralstat)
Treatment of hereditary angioedema
EU/3/22/2625

Sponsor: Kalvista Pharmaceuticals (Ireland) Limited

Note

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

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1. Product and administrative information

Product	
Designated active substance(s)	Sebetralstat
Other name(s)	--
International Non-Proprietary Name	Sebetralstat
Tradename	Ekterly
Orphan condition	Treatment of hereditary angioedema
Sponsor's details:	Kalvista Pharmaceuticals (Ireland) Limited Block C Magennis Place Dublin 2 D02 FK76 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Kalvista Pharmaceuticals (Ireland) Limited
COMP opinion	12 May 2022
EC decision	21 June 2022
EC registration number	EU/3/22/2625
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Jean-Michel Race / Selma Arapovic Dzakula
Applicant	Kalvista Pharmaceuticals (Ireland) Limited
Application submission	25 July 2024
Procedure start	15 August 2024
Procedure number	EMA/H/C/006211
Invented name	Ekterly
Therapeutic indication	Ekterly is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older. Further information on Ekterly can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/ekterly
CHMP opinion	24 July 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Olimpia Neagu
Sponsor's report submission	6 December 2024
COMP discussion and adoption of list of questions	10-12 June 2025
Oral explanation	15 July 2025
COMP opinion (adoption via written procedure)	30 July 2025

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2022 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing sebetralstat was considered justified based on preliminary clinical data showing that their product prolonged the time to use of conventional treatment;
- the condition is life-threatening and chronically debilitating due to recurrent attacks of oedema in various parts of the body that may cause airway obstruction leading to asphyxia;
- the condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sebetralstat will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that their oral product prolonged the time to use of conventional treatment. The Committee considered that this constitutes a clinically relevant advantage.

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

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

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

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

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

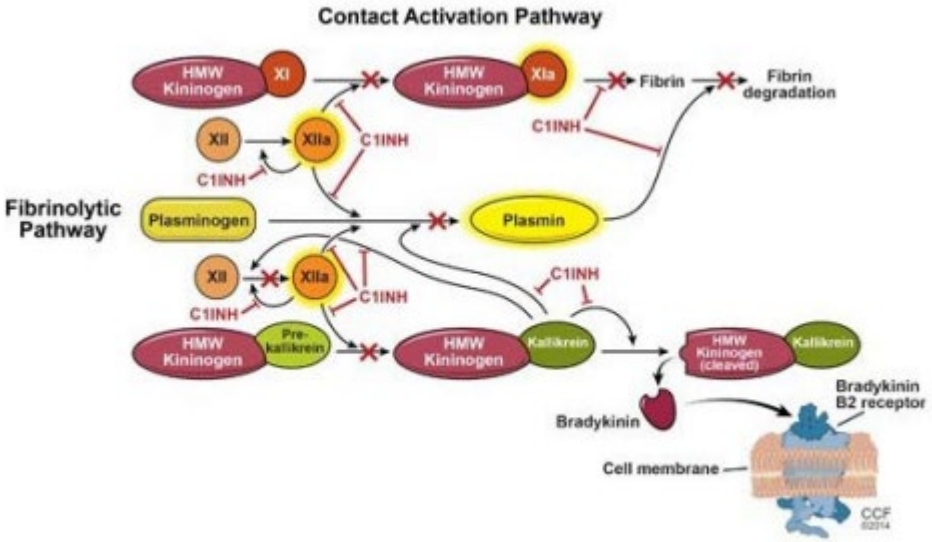
Condition

Hereditary angioedema (HAE) is a genetic, rare, chronic, debilitating and potentially life-threatening disorder characterised by recurrent, and often unpredictable, attacks of swelling in any subcutaneous or submucosal part of the body, without the presence of hives (Bernstein 2018). The type of swelling seen in HAE is bradykinin mediated rather than histaminergic and therefore is not responsive to the use of steroids and/or antihistamines. HAE attacks often occur without a trigger; however, precipitating factors shown to contribute to the frequency of attacks include stress, trauma, infection, menstruation and pregnancy, as well as various medications (such as oestrogen-containing drugs and angiotensin-converting enzyme inhibitors) (Gower 2011).

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

C1INH is a major regulator of the complement, contact and coagulation cascades through inhibition of several different proteases (including plasma kallikrein and coagulation factors XIa and XIIa). Given its role in regulating these systems, a deficiency of C1INH causes uncontrolled activation of these cascades (in the case of HAE, the contact cascade in particular – see Figure 1), resulting in increased vascular permeability and the classic symptoms of HAE (Lumry 2013).

Figure 1. The Role of C1INH in the Control of the Contact Activation Pathways



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

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

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

There have been no changes in the seriousness of the condition since the time of orphan designation. Although many prophylactic treatment options like long-acting plasma kallikrein inhibitors have

become available in recent years that successfully reduce attacks, there is still a need for on-demand treatment of acute attacks.

Most attacks of HAE last 2 to 5 days, resulting in 20 to 100 days of incapacitation per year. Acute episodes of HAE often occur without warning and may often be precipitated by a trigger. In a study of Greek patients, anxiety-related issues were the most dominant from a disease-specific quality of life questionnaire. It was reported that 48% had a fear of possible death from their next laryngeal attack, 47% had problems with their social life and 44% of patients avoided trips away from home. Also, 20% of patients had lost or had to change their employment due to absences. Among children in the study nearly 40% reported frequent absences from school (Psarros 2014). These results are typical of those seen in other studies (Bygum 2017).

While upper airway attacks are less common (1-3%), they are potentially life-threatening. The mortality rate from undiagnosed HAE can be as high as 40% and is primarily attributed to upper airway obstruction. Asphyxiation can occur in patients with no previous history of respiratory symptoms (NORD Guide on Hereditary Angioedema).

Number of people affected or at risk

The sponsor has conducted a literature search for the period 01 January 2022 to 13 November 2024. The publications identified are summarized in Table 1. The sponsor has also added previously referred publications prior to January 2022. All of them only include patients previously diagnosed with Type I and Type II HAE, but do not specifically include Type III HAE (this may be due to the fact that this subgroup has only recently been defined). Although these studies exclude the Type III HAE subgroup, this type is thought to be very rare.

Table 1. Published Prevalence Studies Conducted in the EU

Author	Country	Type of study	Minimum Prevalence Observed
Sandberg 2024	Finland	Patient registry (HAE Type I/II)	2.6 per 100,000
Markocsy 2024	Slovakia	Nationwide survey (HAE Type I/II)	1 per 41,280 (Equivalent to 2.42 per 100,000)
Van der Poorten 2023	Belgium	Nationwide survey (HAE Type I/II)	1.56 per 100,000
Kanepa 2023	Latvia	Nationwide survey (HAE Type I/II)	0.53 per 100,000
Martinez-Saguer 2022	Germany	2-round Delphi expert consensus (HAE Type I/II)	1.62 per 100,000
Previously identified published prevalence studies conducted in the EU (References Previously Supplied)			
Schöffl 2019	Austria	Nationwide survey	1 per 64,396 of the Austrian Population (1.55 per 100,000)
Nordenfelt 2017	Sweden	Nationwide survey	1.54 per 100,000 of the Swedish Population
Zanichelli 2015	Italy	Nationwide survey	1 per 64,935 of the Italian Population (1.54 per 100,000)
Psarros 2014	Greece	Patient Registry	1 per 90,000 of the Greek Population [extrapolated figure]
Bygum 2009	Denmark	Nationwide survey	1.41 per 100,000 of the Danish Population
Roche 2005	Spain	Nationwide survey of HAE physicians	1.09 per 100,000 of Spanish Population
Stray-Pedersen 2000	Norway	Patient Registry of Primary Immunodeficiency Disorders	1.51 per 100,000 of the Norwegian Population

In addition, there were a number of wider global publications that quote a prevalence for HAE (in some cases as a range), with some of the studies quoting secondary and/or tertiary references. These provide additional evidence in support of the prevalence assessment and the figures are in line with the European numbers.

From all the identified EU studies published between 2000 to 2024, the EU prevalence results are within the range of 0.53–2.6 per 100,000.

Many of the reports also acknowledge that, given that HAE is a rare disease and that there is a poor awareness of the condition, there may be many patients with HAE who remain undiagnosed and so were not captured in the survey.

The sponsor proposes a conservative estimate of around 1 in 10,000, which was accepted by the COMP.

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

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

Existing methods

There are two approaches currently used in the management of hereditary angioedema (HAE): acute or 'on-demand' treatment of acute HAE attacks, and prevention of hereditary angioedema attacks with short or long-term prophylactic therapies.

The currently authorized medicinal products in the EU are summarised below:

Table 2. Products authorised for the on-demand treatment of acute HAE attacks.

Date in year	Commercial denomination (INN)	Route of administration	Therapeutic indication	Mechanism of action
2008	FIRAZYR (icatibant)30 mg solution for injection in pre-filled syringe	SC	symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older, with C1-esterase-inhibitor deficiency.	bradykinin type 2 receptor antagonist
2010	RUCONEST conestat alfa 2100 Units powder for solution for injection.	IV	treatment of acute angioedema attacks in adults, adolescents, and children (aged 2 years and above) with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency.	C1 inhibitor
2011	CINRYZE (C1 inhibitor (human) produced from the plasma of human donors) 500 IU powder and solvent for solution for injection	IV	Treatment and pre-procedure prevention of angioedema attacks in adults, adolescents and children (2 years old and above) with hereditary angioedema (HAE).	Plasma derived Human C1-esterase inhibitor
2013	BERINERT (Plasma Human C1-esterase inhibitor) 500 IU powder and solvent for solution for injection/infusion	IV or slow infusion	Hereditary angioedema type I and II (HAE). Treatment and pre-procedure prevention of acute episodes. Children and adults	C1 inhibitor

Table 3. Products authorised for the prophylaxis of acute HAE attacks.

Treatment for routine prevention of recurrent attacks of HAE (long term prophylaxis)					
2011	CINRYZE 500 IU powder and solvent for solution for injection	Plasma Human C1-esterase inhibitor.	IV	Routine prevention of angioedema attacks in adults, adolescents and children (6 years old and above) with severe and recurrent attacks of hereditary angioedema (HAE), who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin
2018	TAKHZYRO 150 or 300 mg solution for injection in pre-filled syringe	lanadelumab	SC	routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 2 years and older.	Inhibitor of plasma kallikrein
2021	ORLADEYO 150 mg hard capsules	berotralstat	Oral	routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older	Inhibitor of plasma kallikrein
2025	ANDEMBRY 200 mg solution for injection	garadacimab	SC	routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older	Inhibitor of plasma kallikrein

As Ekterly is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older, the products approved for on demand treatment of acute attacks (Table 2) were considered satisfactory methods in the context of the significant benefit assessment.

The products authorized for routine prevention (table 3) were not subject to a significant benefit discussion.

Significant benefit

The sponsor is proposed that their product offered a Major Contribution to Patient Care (MCPC) as it is an oral formulation for the treatment of acute attacks in an area where no other oral formulation exists.

Data from the pivotal trial KONFIDENT was submitted to support significant benefit. This was a double-blind, randomized, placebo-controlled, three-way crossover trial that was conducted to evaluate the efficacy and safety of up to two administrations of sebetralstat (300 mg or 600 mg) as compared with placebo for the on-demand treatment of hereditary angioedema attacks. Eligible participants were 12 years of age or older and had a confirmed diagnosis of type 1 or 2 hereditary angioedema, with at least two documented attacks within 3 months before screening or randomization. Participants were randomly assigned in a 1:1:1:1:1:1 ratio to administer sebetralstat at doses of 300 mg and 600 mg and placebo to themselves in one of six sequences. According to the protocol, patients were encouraged to treat as soon as possible after recognition of the start of the attack.

The primary end point was the beginning of symptom relief as assessed in a time-to-event analysis. The beginning of symptom relief was defined as a rating of "a little better" on the 7-point Patient Global Impression of Change (PGI-C) scale (ratings range from "much better" to "much worse") at two or more consecutive time points within 12 hours after the first administration of the trial agent.

Key secondary end points, assessed in a time-to-event analysis, were a reduction in the severity of the attack, defined as an improved rating on the 5-point Patient Global Impression of Severity (PGI-S) scale (ratings range from "none" to "very severe") at two or more consecutive time points within 12 hours after the first administration, and a complete resolution of the attack, defined as a rating of "none" on the PGI-S scale within 24 hours after the first administration.

KVD900-302 is an ongoing, open-label, multicenter extension trial to evaluate the long-term safety of sebetralstat in patients who are 12 years of age or older with HAE Type I or II.

Interim results: As of data cutoff (14 September 2024) a total of 134 patients treated a total of 1706 attacks with 600 mg sebetralstat. The median time to treatment was 10 minutes (IQR 1.0-69.0). The median (95% CI) time to beginning of symptom relief was 2.20 hours (1.93, 2.52). Sebetralstat showed consistent efficacy among patient and attack subgroups. Importantly, for laryngeal attacks (n=32), median time to treatment was 11.5 minutes (IQR 1.0-34.0) and median time to beginning of symptom relief was 1.72 hours (95% CI 1.04, 3.18), respectively. Sebetralstat also demonstrated comparable results over repeated use for multiple attacks; there were no trends observed in time to beginning of symptom relief for the duration of use (i.e. from the first attack treated to the last attack treated).

To establish a major contribution of patients' care (MCPC) the sponsor needed to establish that there is at least equivalent efficacy.

Sponsors claim for Clinically Relevant Advantage

- **Efficacy of Sebetralstat vs Other Approved On-demand Treatments**

Indirect Treatment Comparisons

The sponsor conducted a systematic literature review and identified 15 randomized controlled trials (RCTs), four open-label extension trials, and two non-randomized trials, with a total of 68 reports regarding the satisfactory methods. Of those, 13 were randomized placebo controlled, and twelve of the 13 were excluded from the ITC due to differences in trial design, such as variations in definitions and measurement of the time to beginning of symptom relief endpoint, use of rescue medication,

censoring and AE reporting, in addition to the inclusion criteria of moderate to severe attacks. Summary of key reasons for exclusion:

- **pdC1INH**: The phase 3 randomized, double-blind, placebo-controlled study of 125 patients with pasteurized C1 esterase inhibitor concentrate at intravenous doses of 10 or 20 U/kg body weight and placebo (IMPACT trial) was described in Craig et al 2009 (IMPACT 1). The IMPACT 1 trial was conducted between August 2005 and December 2007. Patients who were at least 6 years of age with a presentation of an acute moderate to severe abdominal or facial attack within 5 hours of the attack attaining moderate intensity were eligible for treatment with pdC1INH at a center. For each patient, only a single abdominal attack (gastrointestinal colic, not cutaneous) or facial attack (not laryngeal) was treated and evaluated. The primary endpoint of time to onset of symptom relief was evaluated using a Wilcoxon 1-sided 2-sample test, as determined by patient responses to a standard question posed at appropriate time intervals for as long as 24 hours after the start of treatment. However, a description of the standard question for measuring this outcome was completely lacking in the publication. Similarly, the two phase 3 trials of nanofiltered pdC1INH (Farkas 2012) didn't use a primary endpoint measure comparable with the PGI-C scale used in the KONFIDENT trial and the patients were asked to present onsite for treatment within 4 hours after onset of acute attack.
- **Icatibant**: There were phase 3 trials for icatibant: FAST-1, FAST-2 and FAST-3. FAST-2 did not have a placebo arm (an oral tranexamic acid was the comparator) and therefore cannot be compared to other trials via placebo in an anchored analysis. FAST-1 and FAST-3 had placebo arms, however, there was a substantial difference in median survival time for symptom relief endpoint for placebo arms in these two studies: 19.8 hours in FAST-3 vs 7 hours in FAST-1, suggesting differences in study populations. Moreover, while hazard ratios for sebetralstat vs placebo were available from KONFIDENT, no hazard ratios nor Kaplan-Meier curves were reported in either FAST-1 nor FAST-3 publications, making a MAIC infeasible was it relies on a method for estimating a hazard ratio from the median.

  Of note, although longer time to treatment has been associated with suboptimal clinical outcomes, in FAST-3, study treatment was administered "no later than 6 hours after an attack became at least moderate in severity (investigator Global Assessment using a validated 100 mm visual analog scale (VAS) with at least 1 VAS score >30 mm)." (Lumry 2011) The median time from attack onset to treatment with icatibant was 6.5 hours.(Otani 2017). Given all attacks were moderate to very severe (mean VAS 43 mm), in combination with a long attack duration, this would have resulted in significant attack morbidity for participants in this trial.
- **Ruconest (rhC1INH):** Zuraw et al 2010 reported pooled results for C1-1304-01 and C1-1205-01 trials, however the results were based on VAS and TEQ was not reported.

However, the only trial with comparable data to enable an ITC to the Phase 3 clinical trial data generated on sebetralstat was the phase 3 randomized placebo-controlled trial for the intravenously administered recombinant human C1 esterase inhibitor, Ruconest.

Indirect comparison versus Ruconest (rhC1INH)

The primary endpoint in the pivotal trial for Ruconest was "time to beginning of symptom relief" and used a Treatment Effect Questionnaire (TEQ) which included a 7-point response (ratings ranged from "much better" to "much worse") at two or more consecutive time points.

This is aligned to the primary endpoint in the pivotal trial for sebetralstat (KONFIDENT), "time to beginning of symptom relief", defined as a rating of "a little better" on the 7-point Patient Global

Impression of Change (PGI-C) scale (ratings ranged from "much better" to "much worse") at two or more consecutive time points within 12 hours after first administration.

A Bayesian fixed-effects network meta-analysis (NMA) was conducted to indirectly compare the results from the primary endpoint of "time to beginning of symptom relief" for sebetralstat in KVD900-301 and the Ruconest trial and found no statistical difference (hazard ratio 95% CrI] 0.96 [0.42, 2.15] to 1.19 [0.58, 2.45], where a hazard ratio >1 favours sebetralstat) (Figure 2).

A random-effects model was also run as sensitivity analysis and returned similar results.

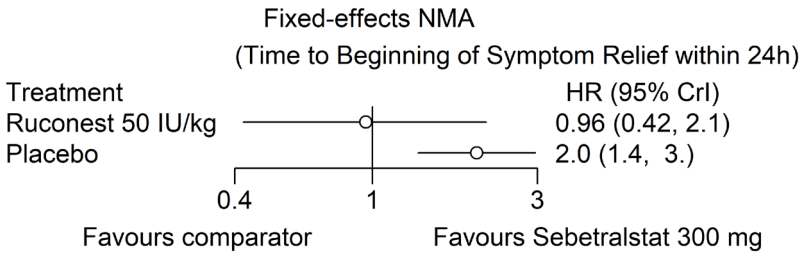
One of the key differences between the KONFIDENT trial and previous on-demand trials was that it was designed with the aim to adhere more closely to HAE treatment guidelines that patient should treat attacks early at the recognition of onset to arrest the progression of swelling (Busse 2021; Maurer 2022). In contrast, previous studies with Ruconest and the other products for on-demand treatment of HAE attacks, instructed patients to hold off treatment until attack severity was at least moderate to severe.

The network meta-analyses (NMA) found no significant differences in the primary endpoints ("time to beginning of symptom relief") between sebetralstat 300 mg and Ruconest 50 IU/kg. Two hazard ratios were reported for Ruconest, one for region and the other for sex.

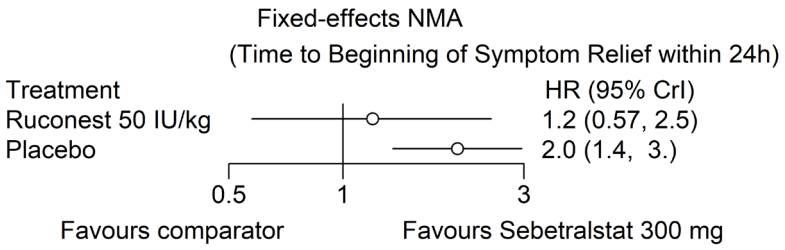
The results of the comparisons are summarised in Table 4. The hazard ratio (HR) in all cases is close to or >1, indicating sebetralstat being favourable to Ruconest.

Figure 2. Fixed-Effects Network Meta-Analysis for Time to Beginning of Symptom Relief

(a) Using Hazard Ratio for Region



(b) Using Hazard Ratio for Gender



In addition, a matching-adjusted indirect comparison (MAIC) was conducted after adjusting for baseline severity and matching demographics (age, sex, race). The results of the comparisons are summarised in Table 4. After adjusting for baseline attack severity, the MAIC also showed numerically favourable results with sebetralstat vs Ruconest, regardless of whether baseline demographics (age, sex, race) variables were matched. All sensitivity analyses returned consistent results.

Table 4. Matching-Adjusted Indirect Comparison Results of Sebetralstat with Ruconest Using "time to symptom relief"

HR stratification	**MAIC KVD900-301 vs Ruconest phIII trial C1 1310 (NCT01188564), Riedl et al. 2014**	**HR (95% CI) for time to symptoms relief, sebetralstat 300 mg vs Ruconest 50 IU/kg***
MA for region	Scenario 1 - adjusting only for attack severity	1.27 (0.48, 3.35)
	Scenario 2 - adjusting for attack severity and demographics~~)~~	1.24 (0.46, 3.31)
MA for sex	Scenario 1 - adjusting only for attack severity (using VAS)	1.59 (0.65, 3.92)
	Scenario 2 - adjusting for attack severity and demographics	1.56 (0.63, 3.88)

*Hazard Ratio (HR) >1 favours sebetralstat

The network meta-analysis (NMA) found no significant differences in the primary endpoints ("time to beginning of symptom relief") between sebetralstat 300 mg and Ruconest 50 IU/kg.

After adjusting for baseline attack severity, the MAIC also showed numerically favourable results with sebetralstat vs Ruconest, regardless of whether baseline demographics (age, sex, race) variables were matched. All sensitivity analyses returned consistent results.

The performance of the MAICs were evaluated by assessing the distribution of the MAIC weights from matching the KONFIDENT patients to the patient characteristics in the Riedl 2014 study, also by assessing the resulting effective sample size (ESS) of the weighted KONFIDENT population (Phillippo 2018). Figure 3 and Figure 4 below presents the distribution of MAIC weights for patients in KONFIDENT matched to the Riedl 2014 study, using only baseline severity for matching (Figure 3), or using baseline severity and demographics (age, sex and race) for matching (Figure 4).

Figure 3. Distribution of MAIC Weights from Matching Patients in KONFIDENT Trial to those in the Riedl et al 2014 Study, only baseline severity is matched

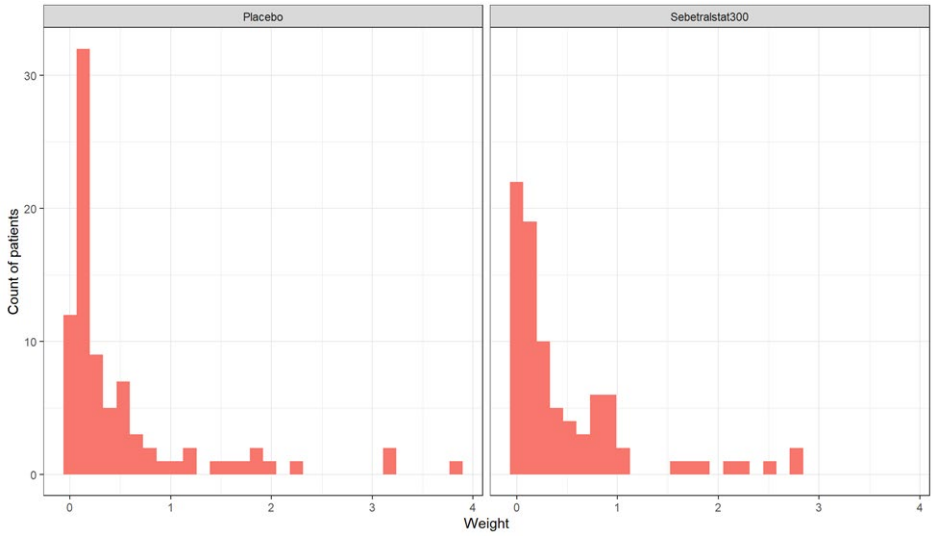
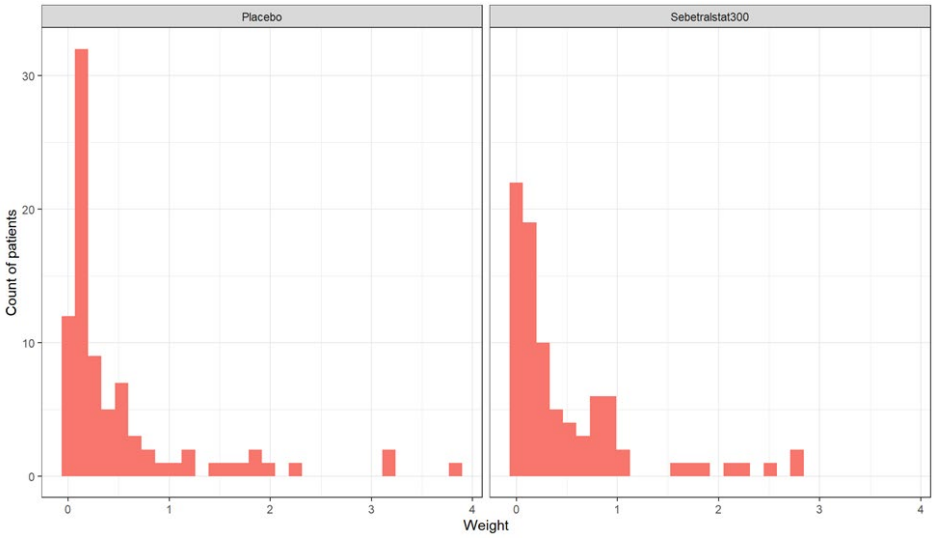


Figure 4. Distribution of MAIC Weights from Matching Patients in KONFIDENT Trial to those in the Riedl et al 2014 Study, baseline severity and demographics are matched



Comparison of baseline characteristics of the KONFIDENT trial before and after matching, together with the resulting ESS are shown in Table 5.

Table 5. Comparison of Baseline Characteristics Pre- and Post-Matching

	N/ESS	Age (yrs)	% Female	% White	Baseline VAS
KONFIDENT	169	37.49	63.3	85.2	46.57
Riedl et al 2014 patient characteristics (pooled rhC1-INH 50 IU/kg and Placebo)	75	40.23	63.3	95.8	75.07
Matching for baseline VAS					
Weighted KONFIDENT	**62***	-	-	-	75.07
Matching for baseline VAS and demographics					
Weighted KONFIDENT	**58***	40.23	63.3	95.8	75.07

* Numbers shown are the effective sample size

The Sponsor considered that the MAIC weights were well distributed, weighted KONFIDENT populations matched the population included in the Riedl 2014 study, and ESSs were reduced after matching compared to the original sample size but still sufficiently high. These three criteria underscored the excellent performance of the MAICs conducted.

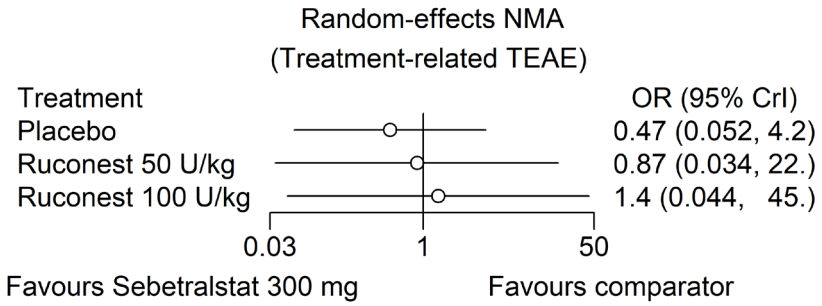
It is important to note that time to treatment, an important driver for severity and a critical component of attack duration, was not reported in the Ruconest trials, which hampers to draw conclusions based on these indirect comparisons.

Safety of Sebetralstat vs Other On-demand Treatments

Based on randomised trials, sebetralstat has demonstrated a positive safety profile, comparable to placebo. The only TEAE reported by ≥2% of patients in any treatment group was headache (1 patient [1.2%] who received 300 mg, 7 patients [4.6%] who received 600 mg, and 4 patients [2.9%] who received placebo). For the event of headache, the risk difference (95% CI) for 300 mg or 600 mg versus placebo was -1.2% (-4.5, 2.0) and 1.8% (-2.6, 6.1), respectively. The primary safety conclusion from the KONFIDENT manuscript in NEJM was: "The observed safety profile of sebetralstat was no different from that of placebo." (Riedl 2014).

Given their similarities with regard to efficacy (benefit) after treatment, the sponsor used the aforementioned Bayesian random-effects network meta-analysis (NMA) using data from KVD900-301 together with two published studies of Ruconest (Zuraw 2010; Riedl 2014) to compare risk. The results are shown in 5.

Figure 5. Bayesian random-effects network meta-analysis of TEAEs



Overall, for sebetralstat 300 mg there was no significant difference in rates of treatment-related TEAEs vs. Placebo with either Ruconest 50 U/kg or 100 U/kg. One limitation with this type of approach was that it only covers a numerical comparison of treatment-related adverse events; it does not account for the severity of the adverse events.

With respect to **Clinically Relevant Advantage**, the sponsor concluded that:

- The available evidence demonstrated that sebetralstat is non-inferior with regard to efficacy to intravenous rhC1INH, which would represent the fastest possible route of administration. No other indirect treatment comparisons (i.e. pdC1INH, icatibant) were given their lack of alignment with current treatment guidelines and related differences in trial design.
- The available evidence demonstrated that sebetralstat is non-inferior with regard to safety from rhC1INH. However, as an oral on-demand treatment for HAE, sebetralstat eliminates treatment-limiting injection-site reactions and injection-related anxiety which represent clinically relevant advantages.

COMP discussion

The Sponsor argued that indirect comparisons with 3 out of the 4 available "satisfactory methods" cannot be made, as in these studies only patients with moderate-severe attacks were included, after a delay of maximal 5-8 hrs after onset of the attack. In the KONFIDENT trial on the other hand, patients were encouraged to take their study drugs as soon as the attack emerged, in accordance with current treatment guidelines. The pivotal studies for Ruconest, Firazyr, Cinrye and Berinert were performed in an earlier era, before the knowledge that immediate intervention leads to better outcomes were available.

Although indirect comparisons are therefore challenging, more efforts were made to establish that efficacy would be at least similar to authorised treatments, e.g. by exploring comparisons with subgroups of moderate-severe attacks from the KONFIDENT trial. Published experience from the real world was explored for the indirect comparisons. Additionally, subgroup analyses of patients who did not respond satisfactorily and did not tolerate icatibant, or other approved on demand HAE products, was provided, if the reasons for prior intolerance/irresponsiveness were well-documented for the KONFIDENT trial.

Concerning the methodology of the indirect comparisons between Ekterly and Ruconest several clarifications were needed:

a) Specifically for the Bayesian analyses, please report the choice of priors, a justification why a fixed/random effect(s) model was chosen, and present a sensitivity analyses. For the Network Meta-Analysis, please report the estimates of all direct and indirect comparisons in addition to considerations on homogeneity and inconsistency.

b) Given the KONFIDENT trial had a cross-over design and patients were exposed to multiple treatments, please comment on how this was accounted for in the indirect comparison analyses. What were the assumptions for the indirect comparison? Were all assumptions met? If not, what are the violations and what is the impact of the violations?

c) For the MAIC: Please comment to what extent conclusions can be drawn regarding the comparability of efficacy versus Ruconest, given that the matching for baseline features led to a considerable reduction of the ESS by approximately 65%. Please clarify whether rescaled weights are shown in Figures 3 and 4. Furthermore, please clarify the sample size of the KONFIDENT trial reports 169 patients, but Riedl et al. (2024) report only 136 patients included in the trial, of which

110 were randomised). A justification of the choice of variables that were used in the indirect comparisons and clarify which variables were used for matching, stratification and adjustment.

The sponsor should present a table to compare the distributions of all relevant baseline variables (used and not used for weighting) between (i) the unadjusted trial 1, (ii) the adjusted trial (iii) and the comparator trial 2, see template table 6 below:

Table 6.

Baseline Variables							
Variable 1 (continuous)	Yes	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Variable 2 (categorical) Category 1 Category 2	Yes	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)
Variable 3	Yes	…	…	…	…	…	…
Variable 4	Yes						
Variable 5	No						
Variable 6	No						
Variable 7	No						
Variable 8	no						

Sponsor's claim for Major Contribution to Patient Care

The sponsor proposed that oral sebetralstat offered significant benefit over existing parenteral on-demand treatments for the following reasons:

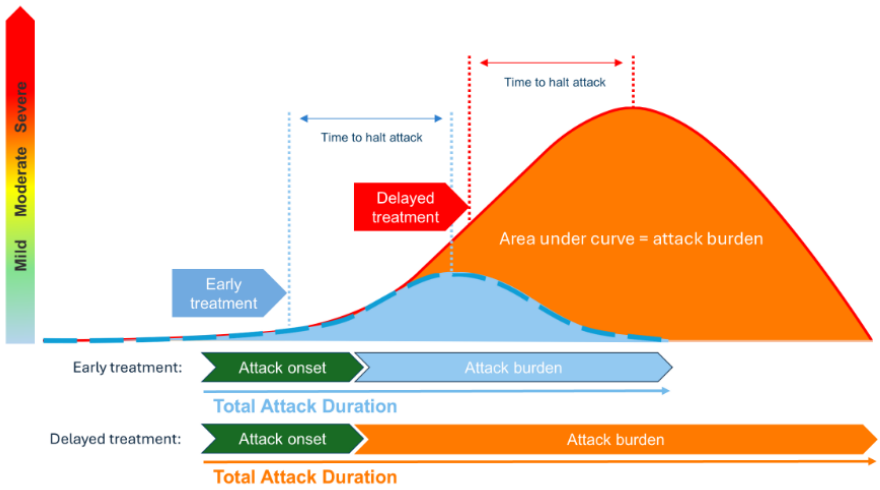
- **Reduces attack morbidity:** By treating soon after onset when attacks are most likely to be mild, sebetralstat halts progression at an early stage resulting in reduced attack severity and anxiety, and earlier time to complete attack resolution. HAE attack morbidity comprises symptom and psychological burden from onset to complete attack resolution. By enabling early treatment, sebetralstat reduces HAE morbidity when compared to injectable on-demand treatments, with no reduction in efficacy or safety. A reduction in morbidity, especially over repeated attacks, can improve a patient's quality of life.
- **Enables compliance with current treatment guidelines:** By reducing or eliminating treatment barriers, sebetralstat allows treatment as early as possible, prior to progression; considering the **treatment of all attacks** regardless of location or severity; carrying adequate medication to treat at least 2 attacks).
- **Reduces or eliminates barriers to on-demand treatment:** Increases ease of administration, enhances portability, eliminates need to train patients and caregivers on storage, preparation, and administration of intravenous or subcutaneous on-demand therapies; eliminates the need for

patients and caregivers to find a discreet, hygienic location to infuse or inject parenteral therapy; eliminates treatment-limiting injection-site reactions and injection-related anxiety.

The impacts of the above points were considered one by one in the following sections, followed by an assessment of the potential of sebetralstat to address each of these points and therefore make a major contribution to patient care over current on-demand treatments based on a reduction in HAE morbidity comprised by reduced attack severity, psychological burden and attack duration, without any diminution of efficacy, safety or tolerability.

Figure 6 shows the correlation between start of treatment and attack severity/duration.

Figure 6. Early Initiation of On-demand Therapy Reduces HAE Morbidity



HAE, hereditary angioedema.
Figure used and adapted under the terms of the Creative Commons CC BY license from: Cohn D et al. *Clin Transl Allergy*. 2023. doi:10.1002/clt2.12288.
1. Maurer M et al. *PLoS One*. 2013. doi:10.1371/journal.pone.0053773. 2. Banta E et al. *Allergy Asthma Proc*. 2011. doi:10.2500/aap.2011.32.3440. 3. Craig T et al. *Ann Allergy Asthma Immunol*. 2013. doi:10.1016/j.anai.2013.06.021. 4. Zanichelli A et al. *Allergy*. 2015. doi:10.1111/all.12731. 5. Cohn T et al. *Clin Transl Allergy*. 2023. doi:10.1002/clt2.12288.

Approved on-demand treatments: Delays to treatment, reasons and impact

One of the key points the sponsor considered important from a major contribution to patient care aspect is early start to treatment by the patient and its link to morbidity and mortality. In essence the sponsor made a claim of patient preference to start treatment early as the basis of a major contribution to patient care versus IV formulations. To establish the basis the sponsor submitted data from patient surveys and then compared the data from their clinical trials.

In order to better understand the treatment of HAE attacks, KalVista, HAE experts and the US Hereditary Angioedema Association conducted an online survey in 2023 among patients who had treated ≥1 attack in the prior 3 months with an FDA-approved OD treatment. Respondents included 80 adults and 14 adolescents, 54% of whom were receiving LTP at the time of their most recent treated attack. For the patients last treated attack, mean reported time from attack onset to on-demand treatment was 3.8 hours, with only 19% treating in <1 hour. The longest treatment delays were in adolescents, mean 7.7 hours. The mean time to treatment for attacks involving the throat/tongue was 2.5 hours (Christiansen 2024).

The most common barriers to early treatment were:

- uncertainty whether the attack was real (53%),
- hope that the attack was going to remain mild (39%),
- desire to save on-demand treatment for a severe attack (32%),
- not having on-demand treatment with them (20%), and
- desire to avoid injection pain/stinging/burning (19%).

Impact of earlier time to treatment with sebetralstat

In the sebetralstat Phase 2 and 3 clinical trials, the median time from onset of attack to IMP administration was 30 minutes in the Phase 2 trial (KVD900-201) and 41 minutes in the Phase 3 trial KVD900301. In the ongoing open label extension study (interim data based on 640 treated attacks) the median time from onset of attack to IMP administration was just 9 minutes and, importantly, only 3 minutes for attacks treated by adolescents and 8 minutes for attacks involving the larynx. In comparison, the only reported time to treatment from a phase 3 trial with a currently approved on-demand treatment was from FAST-3. The median time from attack onset to treatment with icatibant was 6.5 hours. (Otani 2017; Maurer 2014).

By removing the barriers to early treatment, the time to treatment with sebetralstat is significantly reduced compared with the much longer times taken to administer the currently available injectable, on-demand treatments as outlined previously. Participants did not hesitate related to the potential for treatment-limiting adverse reactions such as pain or injection-site reactions, or delay treatment until attacks were severe. Indeed, in the phase 3 pivotal trial KVD900-301, 42.8% of attacks were treated by participants when they were still mild, prior to progression. The closest comparison would be the previously referenced 11.6% of attacks treated with icatibant when still mild/very mild in the Icatibant Outcomes Survey (Guilarte 2021); 45.8% of attacks had already progressed to severe or very severe at the time of treatment, reflecting significantly greater morbidity.

The sponsor conducted a post hoc analysis to examine time to end of attack progression following treatment with sebetralstat in KONFIDENT-S (interim analysis September 14, 2021, 1706 attacks) and KONFIDENT. End of progression was defined as the time at which the worst attack severity was recorded using the 5-point Patient Global Impression of Severity (PGI-S) scale (from very severe to none). Attacks with no post-baseline assessment were excluded. Analysis included 1591 attacks (37% mild, 42% moderate, 17% severe, 4% very severe) treated with 600mg sebetralstat from KONFIDENT-S and 84 attacks (43% mild, 39% moderate, 14% severe, 2% very severe) treated with 300mg sebetralstat and 88 attacks (46% mild, 34% moderate, 18% severe, 2% very severe) treated with 600mg sebetralstat from KONFIDENT. The median (interquartile range) time to end of progression was 19.8 minutes (16.2-42.6) for attacks treated with 600 mg sebetralstat in KONFIDENT-S, which was similar to 19.8 minutes (16.8-97.2) and 19.2 minutes (16.8-46.2) for attacks treated with 300 mg and 600 mg sebetralstat in KONFIDENT.

In KONFIDENT-S, 90.3% of attacks treated with sebetralstat reached the end of progression within 4 hours. In KONFIDENT, 82.1% of attacks were treated with 300 mg sebetralstat and 89.81% treated with 600 mg sebetralstat, reaching the end of progression within 4 hours. Based on this post hoc analysis, treatment with sebetralstat 600mg ended progression of HAE attacks early, with a median of 19.8 minutes in KONFIDENT-S, which was consistent with results from the KONFIDENT trial (medians of 19.8 and 19.2 minutes for 300 mg and 600 mg sebetralstat, respectively).

Reduction in attack-severity related anxiety

In KVD900-301, prior to administering study medication and for 24 hours after, participants self-reported anxiety using a Modified Generalized Anxiety Numeric Rating Scale (GA-NRS) from 0 (not at all anxious) to 10 (extremely anxious). Pearson correlation was used to determine the coefficients between GA-NRS and baseline demographics and attack characteristics. Cumulative GA-NRS was calculated as the area under the curve over 12 hours (AUC_{0-12}) or 24 hours (AUC_{0-24}) from administration. Least squares mean (LSM) changes in GA-NRS from baseline through 12 hours post-baseline were calculated.

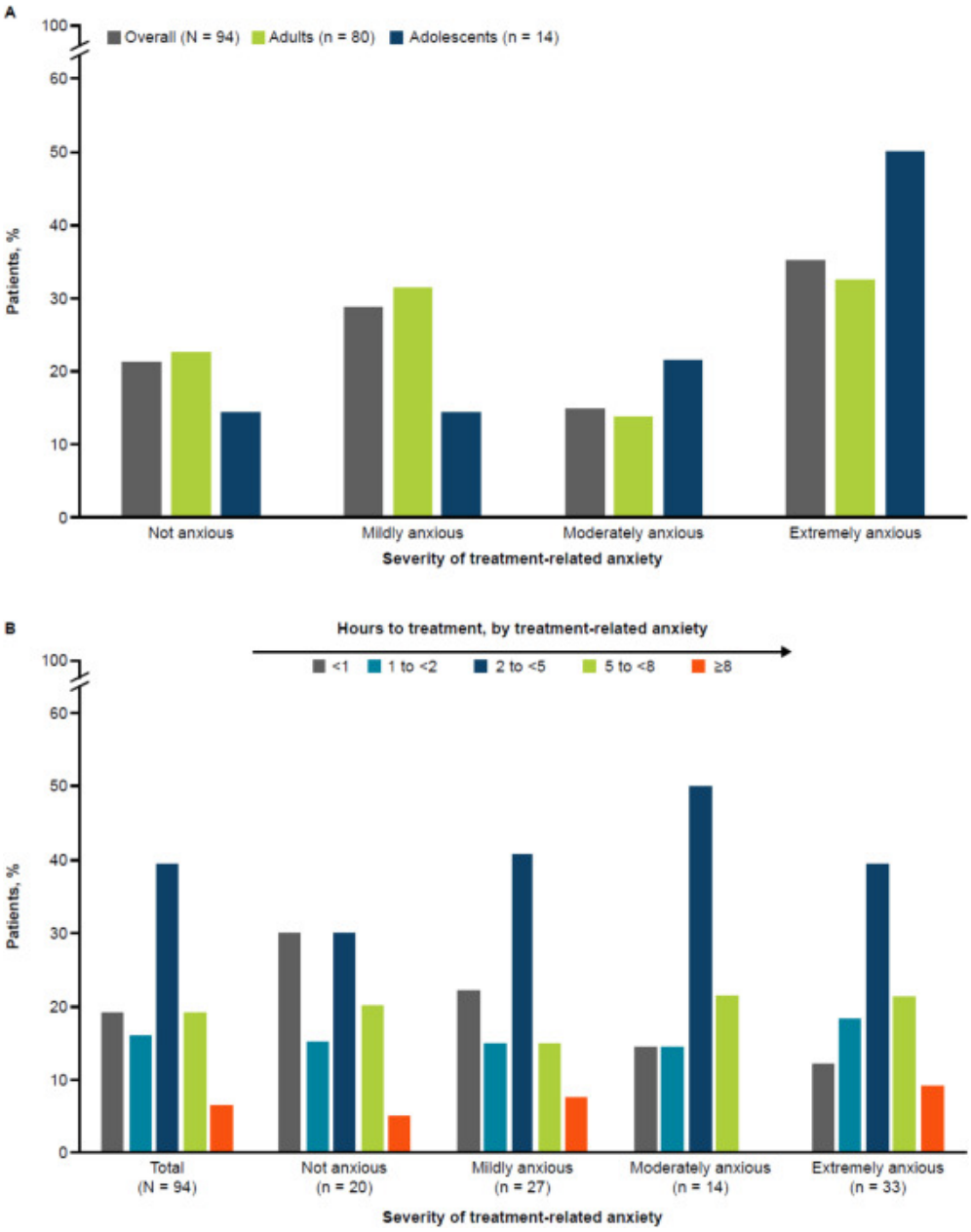
Of 264 treated attacks, 250 (sebetralstat 300 mg: 83; sebetralstat 600 mg: 87; placebo: 80) included GA-NRS records through 24 hours. Median baseline GA-NRS was 3.0. Among baseline variables, Patient Global Impression of Severity ("Very Severe" to "None") demonstrated the strongest correlation with GA-NRS reflecting the idea that severity was the most significant determinant of the remnant anxiety. The relatively low anxiety score is likely the result of treating attacks early, when attacks are most likely to be mild, prior to progression.

AUC_{0-12} and AUC_{0-24} were reduced with sebetralstat 300 mg (P=0.004 and P=0.022, respectively) and 600 mg (P=0.0008 and P=0.0012) versus placebo. For participants with moderate-to-extreme anxiety (4-10; median 5.0 for 300 mg and 6.0 for 600 mg and placebo), LSM change from baseline (95% CI) at 4 hours was −2.8 (−3.6, −1.9) for each sebetralstat group and −1.3 (−2.2, −0.4) for placebo and at 12 hours was −3.5 (−4.3, −2.6) with sebetralstat 300 mg, −4.3 (−5.2, −3.5) with 600 mg, and −1.7 (−2.6, −0.8) with placebo. Overall, in the absence of injectable on-demand treatment, attack severity at the time of treatment drove overall anxiety. Compared with placebo, sebetralstat significantly reduced anxiety, including in participants with moderate-to-extreme anxiety (Maurer 2024).

Thus, sebetralstat doesn't only have the potential to eliminate anxiety, often severe, associated with injectable on-demand treatments, but also reduces the remnant anxiety driven by attack severity.

Figure 7. Treatment-Related Anxiety Among Adults and Adolescents. B, Relationship Between Treatment-Related Anxiety and Time to Treatment

Treatment-Related Anxiety and Time to Treatment



Patient reported outcomes.

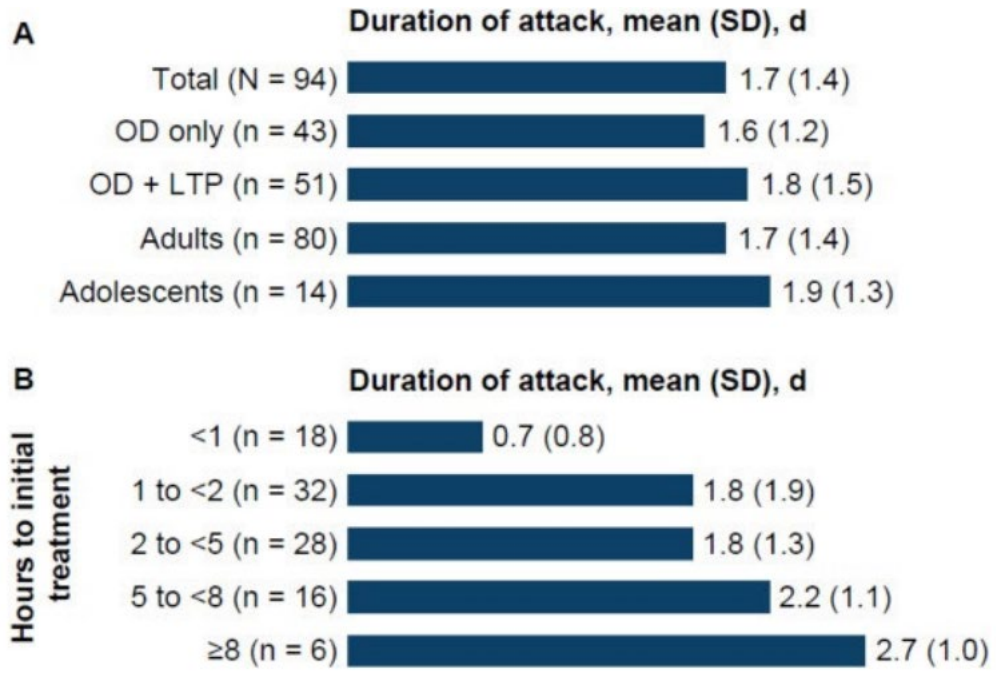
Health-related quality of life and work productivity is substantially impacted by HAE attacks (O'Connor 2025). IV formulations have been associated with time to on-demand treatment increase, the proportion of patients with more severe attacks increased, and Health-Related Quality of Life and Work Productivity and Activity during treated attacks decreased. Early treatment of attacks (less than 1 hour) was also associated with less negative impact on energy, sleep, activity, and social outcomes. (Busse 2024). EQ-5D-5L index scores and EQ-5D-5L VAS (General Health) generally worsened with increasing treatment delays (Christiansen 2024). Among patients who treated attacks late (5 to <8 hours after onset), mean EQ-5D-5L and EQ VAS scores "During the last treated attack" were 0.568 and 56.4. In the 7 days following attack onset, the average rates of absenteeism (work missed due to HAE), presenteeism, and overall work impairment was 20%, 33%, and 38% among patients who treated late (O'Connor 2025).

In a cohort of 20 adult respondents (mean age 38.5 years, 75% female, 80.0% with HAE type I), who reported not treating their last attack, 45.0% (9 of 20) of the attacks progressed in severity and 25.0% (5/20) spread to other locations, including 1 to the larynx and 1 to the face (Christiansen 2024). Of respondents who described their last untreated attack as mild, 50.0% had their attack progress to moderate or severe (Christiansen 2024)

Despite attacks being of milder severity than the treated attacks, declines in HRQoL (mean EQ-5D-5L and EQ VAS scores "During the last treated attack": 0.661 and 73.0, respectively) and impairments in work productivity (mean level of absenteeism, presenteeism, and overall work impairment: 12%, 32%, and 36%, respectively) were also observed when attacks were not treated (O'Connor 2025).

A case of non-treatment that was reported by a Physician. A patient with HAE experienced an attack involving the face and lips. The patient had access to on-demand treatment (plasma-derived C1INH) at home but did not want to treat the attack. The patient was found unconscious and even though an ambulance arrived within 10 minutes, resuscitation was unsuccessful. Time from symptom onset to fatality was approximately 1.5 hours. A complete autopsy was performed within 8 hours of death and demonstrated evidence of asphyxiation secondary to laryngeal oedema. Similarly, in a previously reported case series, laryngeal attacks were noted to be lethal in as little as 10 minutes after onset (Bork 2012). In the US patient survey, the mean time to treatment for attacks involving the throat/tongue was 2.5 hours; 25% of respondents reported waiting 5 hours of more (Christiansen 2024).

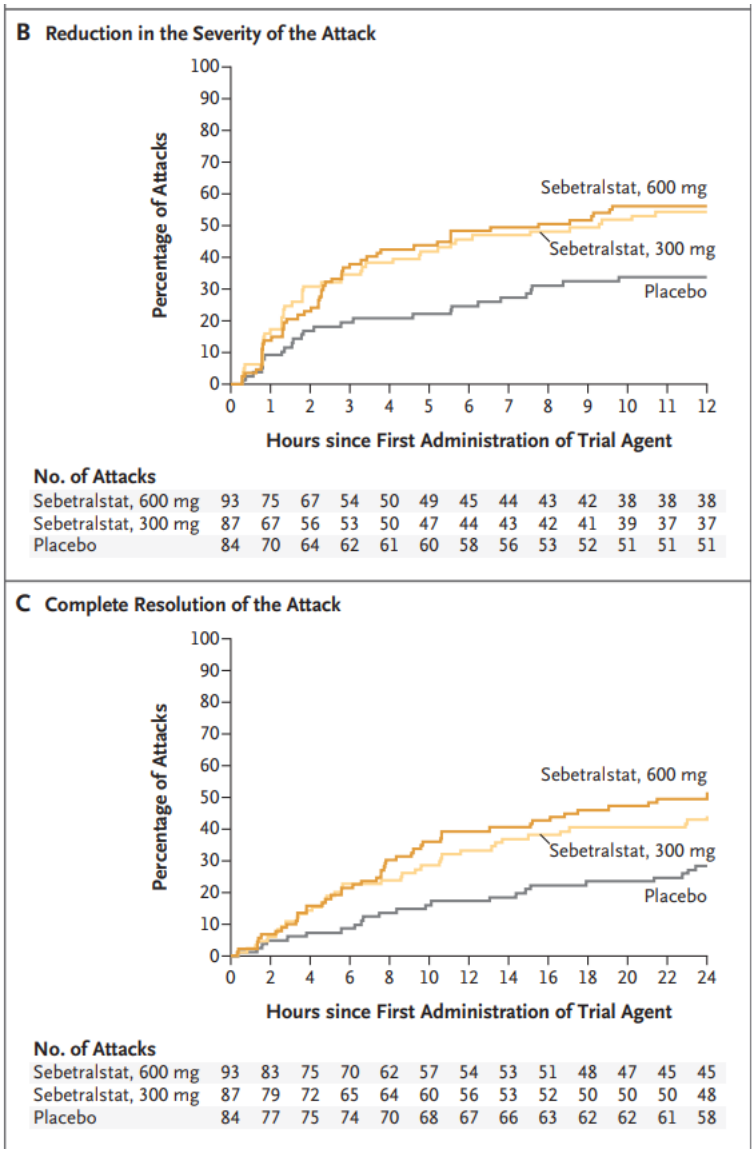
Figure 8. A, Mean Duration of Last Attack._B, Mean Duration of Attack by Time to Treatment



Impact to Time of Treatment on Attack Duration

The key secondary end points, assessed in a time-to-event analysis: a reduction in the severity of the attack, defined as an improved rating on the 5-point Patient Global Impression of Severity (PGI-S) scale (ratings range from "none" to "very severe") at two or more consecutive time points within 12 hours after the first administration (Panel B); and a complete resolution of the attack, defined as a rating of "none" on the PGI-S scale within 24 hours after the first administration.

Figure 9.



The sponsor provided a naïve indirect comparison between on demand IV formulations and their oral formulation to measure the impact on the severity of the attack associated with patient perceptions. According to this data, the oral formulation offers a better outcome regarding severity and resolution of the attack versus outcome with IV formulations.

Always carrying treatment for at least two attacks

The sebetralstat film-coated tablet was designed to provide patients with a formulation that can be discreetly carried at all times and can be quickly and easily administered, with little to no training required. The very short time to treatment in KVD900-302 reflects the impact of improved portability without the need for a discreet or hygienic location to administer treatment. Particularly demonstrative was the time to treatment for adolescents (median 3 minutes), who from the US survey and other direct feedback highlighted that they delayed treatment due to not having their intravenous treatment with them. Attacks often occur outside the home but even having ready access at the bedside (vs. in the refrigerator) is of great value, especially in the setting of a laryngeal attack which may start while a patient is sleeping.

Although not measured directly, the sponsor observed that sebetralstat increased ease of administration and portability, attributes which facilitate early treatment and compliance with treatment guidelines.

The sponsor has submitted interim data from the KVD900-302 study showing that the time to treatment was short with sebetralstat and that the severity and duration of the attacks was shorter than expected with SC or IV treatments. This might in part be associated with the reduced anxiety associated with the oral formulation as opposed to the subcutaneous injection with icatibant.

Comparison to sub-cutaneous formulation Icatibant (Firazyr)

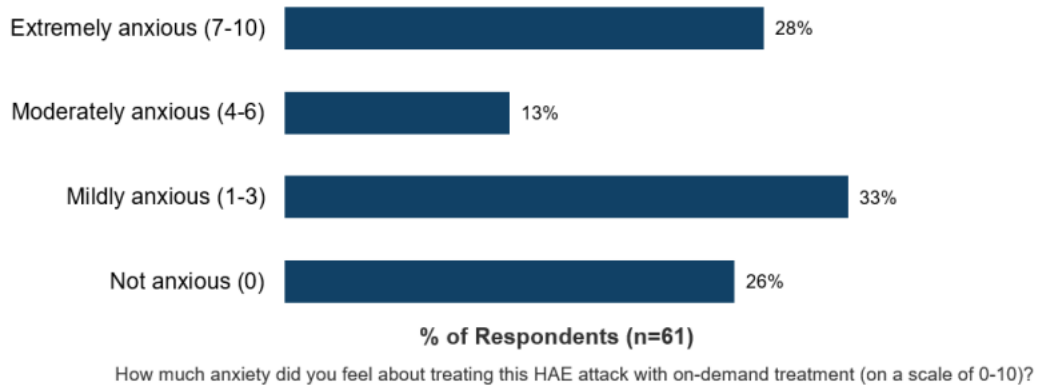
The Icatibant Outcome Survey (IOS), a large-scale international prospective observational study that assessed the real-world use of icatibant (Firazyr; n=481), found that there were often significant delays between the onset of the attack and the treatment administration. The delay was considerably longer in patients who did not self-administer their medication; some attacks were treated as long as 10-14 hours after symptom onset. Whilst the delay was shorter with self-administration, one in 5 attacks were treated in 5 hours or more (Caballero 2017).

Although the proportion of patients who self-administered on-demand treatment subcutaneously increased over time, observational studies of on-demand treatment patterns across European countries reported substantial delays to administration of icatibant that varied between regions (Hernández Fernandez de Rojas 2015; Wang 2015; Burton 2023). In the KalVista patient survey investigating real-world timing, potential barriers, and impact of delaying on-demand treatment of HAE attacks, 74% (45/61) of US patients who treated their last attack with SC on-demand therapy reported treating attacks in ≥1 hour (mean [SD] 2.9 [3.6] hours) (Honda 2024, data on file).

In the Italian patient cohort, 89.1% (49/55) treated their attacks with SC in ≥1 hour (mean 2.6 [2.4] hours) (data on file). In France, 84.2% (32/38) treated attacks with SC in ≥1 hour (mean 2.0 [1.9] hours) (data on file). In the UK patient cohort, 82.6% (19/23) treated their attacks with SC in ≥1 hour (mean 2.6 [3.0] hours) (Savic 2024, data on file). In the US patient survey (Christiansen 2024), 95.2% (60/63) of patients in this study self-administered their SC on-demand treatment. When asked "What prevented you from treating this HAE attack sooner with on-demand treatment?", the most common barriers noted by respondents treating attacks with SC on-demand therapy (n=55) included uncertainty whether the attack was real (47.3%), desire to save on-demand treatment for a severe attack (38.2%), belief the attack was going to be mild (34.5%), desire to avoid injection pain/stinging/burning (23.6%), and not having on-demand treatment with them (21.8%). Similar reasons for delay were reported by patients from Italy (data on file), France (data on file), and the UK (Savic 2024) treating with SC on-demand treatment. Italian patients (n=45) reported delaying treatment due to thinking the attack would be mild, wanting to save treatment for a severe attack, and uncertainty the attack was real (data on file). French patients (n=34) reported delaying treatment due to uncertainty as to whether the attack was real, and thinking the attack would be mild (data on file). UK patients (n=20) reported delaying treatment due to thinking the attack would be mild, wanting to save treatment for a severe attack, and wanting to avoid burning, stinging or pain (data on file). Most (74%) respondents from the US reported experiencing mild to extreme anxiety about treating their attack with SC icatibant (28% extreme, 13% moderate, 33% mild, 26% none; Figure 10) (Honda 2024). Most respondents from Europe reported experiencing mild to extreme anxiety about treating their attack with SC on-demand therapy (Italy: 21.8% extreme, 20.0% moderate, 23.6% mild, 34.5% none; France: 18.4% extreme, 21.1% moderate, 26.3% mild, 34.2% none; UK: 17.4% extreme, 17.4% moderate, 34.8% mild, 30.4% none).

Among those respondents in the US who reported experiencing anxiety related to SC on-demand treatment, the most common reasons were concerns about running out of treatment (46.8%), desire not to waste treatment if the attack was less severe than thought (46.8%), uncertainty about how long the treatment would take to begin working (29.8%). Respondents noted factors contributing to treatment-related anxiety included anticipating burning/pain (25.5%) or other side effects associated with the SC injection (10.6%). This analysis of respondents utilizing SC on-demand therapy further supported that most patients encounter barriers to early treatment and experience anxiety about using SC administered on-demand therapy. Most respondents in Europe reported similar reasons for anxiety.

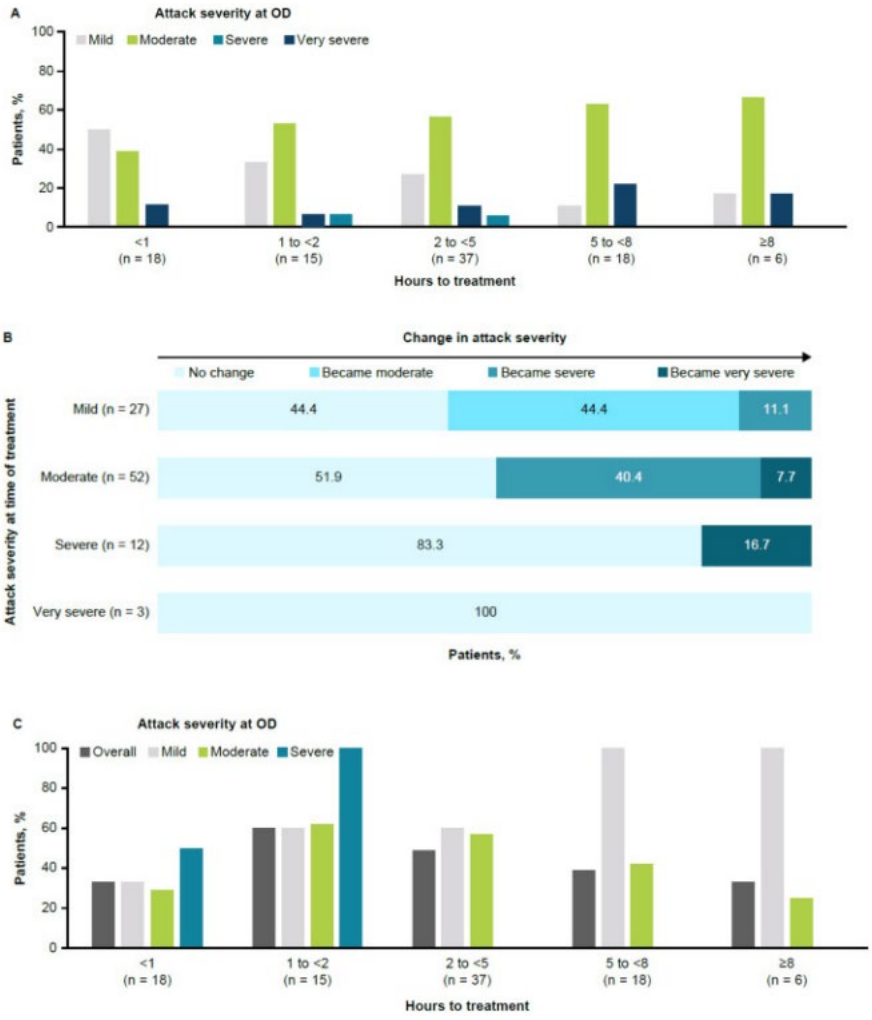
Figure 10. Subcutaneous icatibant treatment-related anxiety among patients with HAE participating in the KalVista US survey (n=61)



In this same survey it was found that there were often significant delays between the onset of the attack and the treatment administration. The delay was considerably longer in patients who did not self-administer their medication; some attacks were treated as long as 10-14 hours after the onset of symptoms. Whilst the delay was shorter with self-administration, one in 5 attacks were treated in 5 hours or more (Caballero 2017).

Results from the same study noted that delaying treatment increased attack duration (Maurer 2013). In a follow-up analysis of this study comparing German patients to those from other countries, German patients, who treated their attacks significantly earlier, had fewer severe attacks than those from other countries who treated later (38.7% vs. 57.5% $p<0.001$) (Maurer 2019). Guilarte and colleagues noted that only 11.6% of attacks were still mild at the time of treatment (33.1% had progressed to severe and 12.7% to very severe), which highlights the increased morbidity associated with delayed treatment. (Guilarte 2021)

Figure 11. Relationship Between Time to Treatment and Attack Severity. A, Relationship between Time to Treatment and Attack Severity. B, Change in Attack Severity and Progression after Treatment. C, Change in Attack Severity by Time to Treatment Note: Values less than 5% are not labeled. OD, on-demand treatment (Christiansen 2024)



COMP discussion on MCPC:

The COMP noted that in the online survey (Christiansen et al), the most common reason mentioned why (adult) patients delayed the use of SC injections, was not knowing for sure whether the attack would evolve to be serious and wanting to save their OD medication for severe attacks, also because of concerns of the cost. In contrast, in the Icatibant Outcome Survey in 6 EU countries, (Caballero, 2017), showed that overall, in the EU, there was less delay in self-administration of the SC injection product as compared to the US survey, leading to better treatment outcomes. Particularly in Germany and the UK, time to self-administration was short, which may indicate local differences in treatment policies. In Germany, Austria and the UK, the short time to self-administration were associated with better treatment outcomes. These RWE data illustrate that also for icatibant self-administration, patients can be successfully guided to timely/early administration in practice.

Since the Icatibant Outcome Survey, recent international treatment guidelines further stress the importance of early intervention with on demand treatments, and a change in treatment paradigm has occurred in the field, also in the EU. Furthermore, it is noted that generics of icatibant have entered the EU market, supporting availability and access.

As the online study was in the US, with has a different care systems and reimbursement policies, it is questioned whether these data are directly extrapolatable to the EU. In another US survey by Katelaris (HAEi Regional Conference Americas - March 15-17, 2024), 43% of the respondents applied early injection, which is much more than reported by Cristiansen (19%). Furthermore, it remains challenging to compare the RWE data to clinical trial data of Ekterly in selected patients, who were encouraged to take their treatment as soon as the attack emerged.

The MCPC versus the SC injection with icatibant requires further justification. Technically speaking, the preparation time for an SC injection with icatibant is short and it is questioned if this can lead to hours of delay.

Finally, regarding the risk of injection related reactions, no specific warnings regarding severe site reactions are included in the SmPC section 4.4 of icatibant products.

The COMP considered additional explanation, and justification were needed to establish if a clinically relevant advantage could be shown and that a major contribution to patient care could be justified.

4. COMP list of issues

Significant benefit

1. More attempts should be made to make comparisons with all the satisfactory methods (Cinryze, Berinert, Ruconest, Orladeyo and Firazyr), e.g. by comparing the subset of patients with moderate-severe symptoms from the KONFIDENT trial with the historic trials. Published experience from the real world could be explored for the indirect comparisons. Additionally, subgroup analyses of patients who did not respond satisfactorily and did not tolerate icatibant, or other approved on demand HAE products, may be provided, if the reasons for prior intolerance/irresponsiveness were well-documented for the KONFIDENT trial.
2. A detailed description of the statistical methods and models used for the indirect comparisons versus Ruconest should be provided (see report for details).
3. The sponsor is asked to discuss the relevance of the responses to the US Hereditary Angioedema Association online survey for the EU patient population. Overall shorter time-to-treatment intervals were reported for icatibant in the literature.
4. The Major Contribution to Patient Care versus the SC injection with icatibant, based on delayed use, requires further justification. Technically spoken, the preparation time for an SC injection with icatibant is short and this cannot be a reason for hours of delay. The sponsor is asked to explain how and when a patient identifies the severity of an attack.

Comments on sponsor's response to the COMP list of issues

The sponsor provided a written response and an oral explanation addressing the questions raised by the COMP.

In response to Question 1. the Sponsor did not provide additional matched analyses with the severe attack subgroup form the KONFIDENT trial as comparator to historic data for trials that were primarily performed in severe attacks. A declaration was made that the responses to Ekterly for the moderate-severe attacks in pivotal trial KONFIDENT were consistent with the overall response for the total study population. Neither subgroup analyses could be provided of patients from the KONFIDENT trial who did not tolerate or were irresponsive to one or more of the authorised on-demand treatments, as this was not clearly documented at inclusion.

In response, the Sponsor explored RWE data as control group and refers to a US study that used the same instrument (by mobile app) among existing on-demand treatments as applied in the KONFIDENT trial (Mendivil 2023). Median time to beginning of symptom relief was defined in the same way as in KONFIDENT, with a rating of "a little better" on PGI-C at two consecutive timepoints. A total of 35 participants recorded at least one treated attack. The study sample included 30 (85.7%) type 1 HAE, 1 (2.9%) type 2 and 4 (11.4%) type 3. A total of 133 HAE attacks were recorded, of which 98 were non-laryngeal. Of the 98 non-laryngeal attacks, 59 (60.2%) were treated with icatibant (branded or generic), 22 (22.5%) with plasma-derived C1-INH concentrate, 9 (9.2%) with recombinant C1-INH concentrate, and 9 (9.2%) with other medications. The median time to achieving symptom relief based on the PGI-C "a little better" definition was 2.147 (95% confidence interval [CI] 1.518, 3.017) hours. In comparison, in the KONFIDENT study, the median (95% CI) time to achieving symptom relief was 1.61 (1.28, 2.27) hours for the sebetralstat 300 mg arm and 1.79 (1.33, 2.27) hours for the sebetralstat 600 mg arm. Numerically, the median time favoured sebetralstat vs. comparator, however the 95% CIs overlap suggests no statistically significant difference. Demographic characteristics between the two studies were largely similar (Table 7 below). The Sponsor concludeds that this data supports the claim that the efficacy of sebetralstat is at least equivalent to the authorised treatments studied in the comparator study. During the oral explanation it was discussed that the study by Mendivil (2023) include type III patients (with normal C1-INH), which were excluded from the KONFIDENT trial. Details are lacking in the public domain to what extent this subset had influenced the Mendivil study outcomes, and matching is therefore not possible. Neither is it clear from the Mendivil study when the treatments were taken after the first symptoms of the attack, making it difficult to draw firm conclusions on the equivalence of treatment with sebetralstat versus standard care based on this study alone.

Table 7. Demographic characteristics in Riedl et al 2024 (KONFIDENT) and Mendivil et al 2023

	Riedl et al 2024 (KONFIDENT) (N=110)	Mendivil et al 2023 (N=35)
Age (years), mean (min, max)	37.7 (13, 74)	40.3 (16, 70)
Sex, female, n (%)	66 (60.0)	26 (74.3)
Race, White, n (%)	92 (83.6)	30 (85.7)
Age at diagnosis (years), mean (min, max)	22.8 (0, 73.6)	24.6 (1, 65)
Type of HAE, n (%)		
Type 1	101 (91.8)	30 (85.7)
Type 1	9 (8.2)	1 (2.9)
HAE with normal C1-INH	0	4 (11.4)

The COMP acknowledged that the sponsor could not address any further the points raised in question 1 and 2 on the methodology of the indirect comparisons. The differences in inclusion criteria, design and endpoints of the historic trials hamper the conclusions and robustness of indirect comparisons. This is because the KONFIDENT trial is the first randomised study performed in an early treatment setting, where patients were encouraged to take their study treatments as soon as possible at emerging first symptoms of an attack. The COMP also acknowledged the importance and benefits of early intervention of attacks with on-demand treatments including Ekterly, as shown in the model where early intervention leads to better less severe attacks of shorter duration (see figure 6 above). This correlation was also established in the KONFIDENT trial for sebetralstat. Early intervention is also strongly recommended in current international treatment guidelines on HAE.

In response to Question 3, the sponsor provided further data regarding the European setting when compared to the US setting. Although some references from earlier days indicated that patients actually used SC icatibant immediately (Cabellero 2017, Maurer, 2019), more recent data indicate that also in the EU the actual onset of use of on-demand treatments is delayed to the same extent as in the US.

Reference was made to KalVista International Patient Surveys from European and US patients treating attacks with icatibant indicated similar delays were reported when compared to the US patients.

Time to treatment (icatibant only):

- US: mean 2.9 hours (SD 3.6)
- EU (Italy, France, UK, Germany): mean 3.6 hours (SD 5.3)

Given that the main reasons for delay in treatment of attacks are:

- not being certain that the attack was real,
- thinking that an attack would be mild,
- wanting to save the on-demand treatment for a severe attack.

In response to Question 4, it is important to understand how the patients identify attack severity. Patient perception of symptom improvement and attack severity has been consistently used for patient-reported outcomes (PROs) in on-demand HAE clinical trials and observational studies to assess drug responsiveness and define the severity of an attack at symptom recognition. The secondary endpoint in the KONFIDENT study was assessed using the patient global impression of severity (PGI-S) which is based on patient perception of how severe their attack was at different points in time allowing assessment of drug effect on attack progression and reduction of severity (see Appendix 2, Figure 1 for overview of PGI-S scale).

The Sponsor conducted a qualitative study to describe patient and caregiver experience with existing HAE on-demand treatments in the US and UK (Yong 2025(a), Kiani 2025). Respondents (N=25; 16 US, 9 UK) included 12 adult patients, 5 adolescent patients and 8 caregivers. Firazyr/icatibant was the most used on-demand therapy in the US and UK samples. Even though it offers better portability and accessibility than IV infusion-based therapies, most participants (89%, 8 out of 9) would treat at home only, and one out of nine would treat at home or away from home. Most participants did not carry their on-demand treatment with them outside the home on a daily basis. Instead, almost all participants described preferring to return home to administer treatment when attacks occurred despite noting the disruption to daily activities this sometimes caused. Patients reported that they would sometimes decide not to treat to avoid the pain of the injection/medicine, despite recommendation for early as made in the treatment guidelines.

Data provided from the sponsor's KONFIDENT trial showed that earlier treatment with the oral formulation was possible and that this led to less severe crisis as treatment was started within the first half hour of the appearance of symptoms, than later intervention.

Evidence that patients tend to use oral on-demand treatment earlier than the conventional SC/IV treatment options comes from the long-term extension trial. In this study, patients could choose freely between Ekterly 300 mg and SoC IV/SC treatments. The vast majority chose Ekterly (84% vs 13%, 3% no treatment) and used this within a much shorter time frame (median 10 min versus 78 minutes).

The COMP accepted the basis of this argumentation

The COMP concluded they could recommend maintaining the orphan designation.

5. COMP position adopted on 30 July 2025

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of hereditary angioedema (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to recurrent attacks of oedema in various parts of the body that may cause airway obstruction leading to asphyxia;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the claim that Ekterly is of significant benefit to those affected by the orphan condition still holds. The sponsor demonstrated that an oral tablet formulation induces earlier treatment by the patient of an emerging attack than the authorised parenteral on demand treatments, thereby further reducing the risk of a severe crisis as there is a recognised difficulty in effectively treating these patients. The Committee considers this constitutes a clinically relevant advantage and a major contribution to patient care.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Ekterly, sebetralstat for treatment of hereditary angioedema (EU/3/22/2625) is not removed from the Community Register of Orphan Medicinal Products.