Single Technology Appraisal

Sebetralstat for treating acute attacks of hereditary angioedema in people 12 years and over [ID6284]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Sebetralstat for treating acute attacks of hereditary angioedema in people 12 years and over [ID6284]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from KalVista Pharmaceuticals:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Hereditary Angioedema UK – authored by patient expert, Angela Metcalfe, and endorsed by patient expert, Timothy Crouch
   b. British Society for Allergy & Clinical Immunology
   c. BSI Clinical Immunology Professional Network (BSI-CIPN) – co-authored by clinical expert, Patrick Yong
   d. Royal College of Pathologists – authored by clinical expert, Patrick Yong
   e. NHS England

4. **Expert personal perspectives** from:
   a. Patrick Yong – clinical expert, nominated by KalVista Pharmaceuticals, British Society for Allergy and Clinical Immunology, British Society for Immunology, Royal College of Pathologists, & Takeda
   b. Sinisa Savic – clinical expert, nominated by KalVista Pharmaceuticals
   c. Angela Metcalfe – patient expert, nominated by Hereditary Angioedema UK
   d. Timothy Crouch – patient expert, nominated by Hereditary Angioedema UK

5. **External Assessment Report** prepared by Kleijnen Systematic Reviews

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over [ID6284]

Company evidence submission

May 2025

File name	Version	Contains confidential information	Date
ID6284 Sebetralstat KalVista_Main submission_Updated 16.9.25	**Final**	**Yes**	**Updated: 16th September 2025**

Contents

Tables and figures

Tables

Figures

Abbreviations

Acronym	Definition
A&E	Accident and Emergency
AA	Attenuated androgens
ACAAI	European Academy of Allergy and Clinical Immunology
ACE	Angiotensin-converting enzyme
ADL	Activity of daily living
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AWTTC	All Wales Therapeutics and Toxicology Centre
AUC	Area Under the Curve
BK	Bradykinin
BL	Baseline
BMI	Bod-mass index
BNF	British National Formulary
BR2	Bradykinin receptor 2
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effective plane
CI	Confidence Interval
CL/F	Apparent oral clearance
Cmax	Maximum concentration
COVID-19	Coronavirus Disease 2019
CrI	Credible Interval
cSTM	cohort State-Transition Model
CSS	Composite symptoms score
CSR	Clinical Study Report
CYP3A4	cytochrome P450 3A4
C1-INH or C1INH	C1-esterase inhibitor
DCE	Discrete choice experiment or Discrete choice elicitation
EAMS	Early Access to Medicines Scheme
EDC	Electronic Data Capture
EMBASE	Excerpta Medica database
EQ-5D	EuroQoL 5-Dimensions
EU	European Union
FAS	Full analysis set
FAST	For Angioedema Subcutaneous Treatment
FDA	Food and Drug Administration
GA-NRS	General Anxiety–Numeric Rating Scale
GI	Gastro-intestinal

GIM	Global improvement measure
GP	General Practitioners
HAE	Hereditary angioedema
HAE-C1-INH	Hereditary angioedema due to C1 inhibitor deficiency
HAE-n-C1-INH	Hereditary anioedema with normal C1-esterase inhibitor (Type III HAE)
HCP	Health care professional
HK	High molecular weight kininogen
HR	Hazard Ratio
HRQoL	Health-related quality of life
HRU	Healthcare resource utilisation
HSUV	Health state utility value
HTA	Health technology assessment
IMP	Investigational medicinal product
INR	International Normalized Ratio
ICER	Incremental cost-effectiveness ratio
IOS	Icatibant Outcomes Survey
IQR	Interquartile range
IS	Investigator Score
ITC	Indirect treatment comparison
IU	International units
IV	Intravenous
Kg	Kilograms
KKS	Kallikrien-kinin system
LAR	Legally authorised representative
LOCF	Last observation carried forward
LTP	Long-term prophylaxis/ prophylactic
LYG	Life years gained
MAIC	Matching-adjusted indirect comparisons
Max	Maximum
MEDLINE	Medical Literature Analysis and Retrieval System Online
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
Min	Minimum
MRHD	Maximum recommended human dose
MSCS	Mean symptom complex severity score
MXL	Mixed Logit
N/A	Not applicable
NE	Not evaluable
nf	Nano-filtered
NHB	Net Health Benefit

NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NMA	Network Meta Analysis
NR	Not reported
OATP	Organic Anion Transporting Polypeptide
OD	On demand
OLE	Open-label extension
ONS	Office for National Statistics
OR	Odds Ratio
PAS	Patient Access Scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PBO	Placebo
pdC1-INH	Plasma-derived C1-esterase inhibitor
PGI	Patient Global Impression
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PICO	Population Intervention Comparator Outcome
PKa	Plasma Kallikrein inhibitor
PPS	Per-protocol set
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred Term
Pt	Patient
QALYs	Quality-adjusted life years
QoL or QOL	Quality of life
OWSA	One-way sensitivity analysis
Q1	25th percentile
Q3	75th percentile
RCT	Randomised controlled trial
rh	Recombinant
rhC1INH	Recombinant human C1-esterase inhibitor
RUT	Random Utility Theory
SAE	Serious adverse event
SAF	Safety set
SC	Subcutaneous injection
SD	Standard deviation
SE	Standard Error

SERPING1	Serpin Family G Member 1
SLR	Systematic Literature Review
SMC	Scottish Medicines Consortium
SmPc	Summary of Product Characteristics
SOC or SoC	Standard of Care
STA	Single Technology Appraisal
STP	Short-term prophylactic
SUAC	Severe Upper Airway Compromise
TEQ	Treatment effect questionnaire
TEAEs	Treatment-emergent adverse events
Tmax	Time to peak drug concentration
TOS	Treatment Outcome Score
TRAE	Treatment related adverse event
TTA	Time to treatment administration
TTAR	Time to attack resolution
TTO	Time trade-off
TXA	Tranexamic acid
ULN	Upper Limit Normal
UK	United Kingdom
US	United States
VAS	Visual Analogue Scale
VAT	Value Added Tax
VBA	Visual Basic Applications
Vz/F	Volume of distribution
WOA	World Allergy Organization
WTP	Willingness-to-pay threshold

1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

Please see Table 1 below for a summary of the decision problem.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People 12 years and over with hereditary angioedema having an acute attack	Same as scope	N/A
Intervention	Sebetralstat	Same as scope	N/A
Comparator(s)	Established clinical management for the treatment of acute attacks of hereditary angioedema which may include: • C1-esterase inhibitors (this includes Cinryze, Berinert and Ruconest) • Icatibant	Same as scope	N/A
Outcomes	The outcome measures to be considered include: • severity of angioedema attacks • duration of angioedema attacks • time to beginning of symptom relief • reduction in symptoms of angioedema attacks • mortality • use of rescue medication • frequency and duration of hospitalisation • adverse effects of treatment • health-related quality of life (for patients and carers).	Same as scope	N/A

1.2 Description of the technology being evaluated

Table 2 Technology being evaluated

UK approved name and brand name	Sebetralstat (brand name: Ekterly®)
Mechanism of action	Sebetralstat is an oral plasma kallikrein inhibitor that works by targeting the kallikrein-kinin system, specifically inhibiting plasma kallikrein (PKa) and its activity, which is overactive in hereditary angioedema (HAE). The inhibition of PKa leads to reduction in bradykinin production which is a potent inflammatory mediator of HAE attacks. The decrease in bradykinin levels leads to reduction in the swelling and pain associated with HAE attacks.
Marketing authorisation/CE mark status	Regulatory approval for sebetralstat by the UK Medicines and Healthcare products Regulatory Agency (MHRA) was granted on 15th July 2025 for the "treatment of hereditary angioedema (HAE) attacks in adult and adolescents aged 12 years and older." EU regulatory approval is still underway. The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on 24th July 2025, with approval anticipated in [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The planned indication for sebetralstat is for the "*treatment of hereditary angioedema (HAE) attacks in adult and adolescents aged 12 years and older*."
Method of administration and dosage	The recommended dose of sebetralstat is a 1 x 300 mg tablet to be taken orally by patients at the earliest recognition of a HAE attack. An additional dose may be taken if needed.(1)
Additional tests or investigations	N/A
List price and average cost of a course of treatment	List price of £12,000 for a pack of 6 x 300 mg tablets including VAT. This equates to a list price of £2,000 per 300 mg tablet.
Patient access scheme (if applicable)	A simple discount PAS has been submitted based on a [redacted] discount resulting in a net price of [redacted]

1.3 Health condition and position of the technology in the treatment pathway

Overview of HAE

Hereditary angioedema (HAE) is a rare and potentially life-threatening inherited disorder. HAE is characterised by repeated, unpredictable, painful, and potentially life-threatening episodes of swelling (attacks) that vary on location.(2) There are two main subtypes of HAE, Type I and Type II. Type I HAE accounts for approximately 85% of HAE cases and is caused by a deficiency in C1-esterase inhibitor (C1-INH) protein. Type II HAE accounts for approximately 15% of HAE cases and is caused by dysfunction in C1-INH.(3) Yong *et al.* (2023) estimated that 1 in 59,000 people in the UK suffer from HAE Type I or II.(4)

A third much rarer subtype of HAE exists and presents with normal C1-INH (HAE-nC1-INH; previously classified as HAE type III), in which patients have HAE attacks despite normal C1-INH levels and function. HAE-nC1-INH is understood to be caused by a variety of genetic mutations for example in factor XII (5), angiopoietin-1 (6), plasminogen (7), and kininogen genes.(8)

HAE affects all aspects of a patient's life, causing significant social, education and work disability. The impact of HAE on health-related quality of life (HRQoL) is profound and has been extensively studied.(9-12)

Pathophysiology

The pathophysiology in HAE Type I and II is caused by autosomal dominant mutations in the Serpin Family G Member 1 (SERPING1) gene which causes a deficiency (Type I HAE) or reduced function (Type II HAE) in C1-INH levels.(4) C1-INH function to inhibit the activity of plasma kallikrein which regulates the production of bradykinin. Elevated bradykinin levels promotes vascular permeability, vasodilation and smooth muscle contraction which results in capillary leakage into tissues and the swelling characteristic of HAE.(4)

The swelling in HAE is the result of capillary leakage into the tissues caused by inappropriately elevated bradykinin levels, which promote increased vascular permeability, vasodilatation, and smooth muscle contraction.(4, 13)

Clinical presentation & diagnosis

HAE attacks predominantly manifest as painful swellings of the subcutaneous tissue or mucous membranes.(14) Whilst these attacks can affect any part of the body, they most frequently involve subcutaneous tissue, resulting in swelling of the limbs, face, trunk or genitals as well as the mucous membranes of the gastrointestinal (GI) tract. Episodes affecting the oral mucous membranes are less common (occurring in less than 10% of cases), and even rarer are instances of angioedema in the brain, joints, and abdominal viscera.(15)

Patients may experience simultaneous swellings at more than one site, with symptoms varying depending on attack location. Swelling within the GI tract can be extremely painful and disruptive, causing symptoms such as nausea, vomiting, diarrhoea and abdominal pain.(16) Laryngeal swellings occur in up to 50% of HAE patients and are potentially life threatening since they can lead to the obstruction of airways, loss of consciousness and death due to asphyxiation.(17, 18) However, with proper treatment and management, the life expectancy of people with HAE is the same as the general population.(19) Diagnosis is particularly important with Bork, Hardt *et al.,* (2012) reporting “mortality by asphyxiation was higher in patients with undiagnosed hereditary angioedema due to C1 inhibitor deficiency (HAE-C1-INH) (63 cases) than in patients with diagnosed HAE-C1-INH (7cases)”.(18)

Early symptoms at the initial phase of attack are frequently reported and can warn a patient of an upcoming swelling. One study reported almost 40% of HAE patients across the UK and Spain noticed early symptoms within 2 hours before the attack progressed.(20) Common early symptoms include tiredness/fatigue, pressure, tightness or tingling in the skin, abdominal pressure, rash and muscle aches as well as anxiety.(20-22)

Classifying the severity of HAE is challenging due to several factors including the fluctuating nature of disease activity over time, the impact of treatment effects and the

subjective nature of patient-reported outcomes used to measure severity. Severity perception varies widely between individuals, with symptoms such as hand swelling impacting patients differently. One common way to assess disease severity is by measuring the frequency of attacks.(23) Importantly, all HAE patients face the risk of potentially fatal laryngeal attacks, regardless of their previous symptom history.(23)

Epidemiology and risk factors

HAE (Type I and Type II) is an autosomal dominant condition caused by one of more than 700 known genetic mutations in the SERPING1 gene, which codes for the C1-INH protein. The C1-INH protein is the major inhibitor of complement proteases and contact-system proteases (plasma kallikrein and coagulation factor XIIa), as well as a minor inhibitor of the fibrinolytic protease plasmin. (24) SERPING1 mutations and resulting C1-INH dysfunction or deficiency promote the vascular permeability, vasodilatation, and smooth muscle contraction underpinning a HAE attack.(4, 13)

According to the British Society for Immunology, HAE affects approximately 1 in 50,000 of the population and does not show ethnic variation in frequency.(25) This is fairly consistent with a large and recent UK-based study by Yong *et al.* (2024) which estimated a minimum UK prevalence of HAE Type I or II as 1 in 59,000 people, noting the true UK prevalence may likely be higher as some HAE treatment centres were not included in the analysis.(20) Similar to previous studies, there were a higher number of females recorded with HAE in the UK (58%).(4) Observational study data suggest that women have more frequent attacks and have more severe symptoms during an attack than men. These differences are believed to be due to fluctuations in female sex hormones, with many women reporting that disease worsened during puberty or while taking oestrogen-containing oral contraceptives.(26)

HAE symptoms can manifest at any age. The mean age at first symptom onset is between eight and twelve years, with the development of laryngeal attacks usually occurring after the age of three years, with an increased frequency observed after puberty.(15, 27)

Various factors can trigger HAE attacks, including physical trauma, mental stress, infections, surgical or dental procedures, hormonal changes (menstruation,

pregnancy), and certain medications. Disease activity fluctuates due to changes in exposure to these triggers and in response to treatment. Additionally, environmental factors such as weather changes may also play a role.(28) During times of physical or emotional stress, people with HAE lack enough functional C1-inhibitor to properly control inflammatory responses, leading to localised swellings.(15)

Furthermore, attack location appears to be influenced by trigger. Zotter *et al.*, (2014) followed 92 patients with HAE type 1 over a seven-year long observation period and found 65% of attacks were subcutaneous and 36% were submucosal (consisting of 29% abdominal and 7% upper airway attacks).(28) Furthermore, physical exertion was most commonly associated with the onset of subcutaneous swelling, while psychological or mental stress was the primary trigger for abdominal episodes. For upper airway oedema both infection and menstruation were the leading triggers.(28)

Whilst genetic predisposition is the primary risk factor, the frequency and severity of attacks can be influenced by lifestyle factors and the specific trigger as discussed. Effective management strategies are crucial to reduce the disease severity.

Burden of HAE

The lifelong persistence of HAE, combined with the sudden, unpredictable and debilitating attacks experienced by patients throughout their lifetime cause substantial personal, economic, and health care costs.(29)

Clinical burden

People living with HAE experience unpredictable, painful and debilitating attacks of tissue swelling at various locations of the body that can be life-threatening depending on the location(s) affected. Attacks typically involve the face, extremities, trunk, genitalia, upper airways and/or the gastrointestinal tract.(30)

Severe pain is a major symptom of HAE attacks, specifically those affecting the abdomen. A study by Bork *et al.*, (2006) reported that up to 87% of HAE patients describe the pain during abdominal attacks as excruciating or severely painful, often leading them to seek medical attention.(9)

UK clinical experts interviewed as part of submission development consistently reported that roughly 5-10% of patients have an accident and emergency (A&E) visit per year.(31)

Humanistic burden

HAE patients report significantly worse HRQoL outcomes compared to healthy individuals, including increased rates of depression and depression.(10, 22) A recent study reported that 45.6% HAE patients had moderate to extreme anxiety associated with the treatment of their most recent attack.(32) Similarly, analysis from the Phase 3 KONFIDENT study show that [redacted] ([redacted]%) treated HAE attacks were scored as inducing moderate to extreme anxiety in patients.(22) Due to the unpredictable nature of HAE, patients' everyday life choices are significantly affected, meaning individuals often avoid travelling, specific hobbies or social engagements.(12) Furthermore, a considerable percentage of patients with HAE reported the disease affected their relationships and decisions, such as whether to have children.(33-36)

Symptoms of HAE attacks, including spasms, pain, vomiting, diarrhoea, and disfigurement cause patients to frequently struggle with daily life.(12) A US-based patient survey by Banerji *et al.,* (2020) found 24.8% of patients rated their general health status as "poor" or "fair," and 34.2% indicated their physical or emotional health issues limited their participation in social activities at least some of the time during the previous week.(37) On an annual basis, it is estimated that HAE-C1-INH patients miss between 20 and 100 days of social activities.(38, 39)

According to a study by Zotter *et al.* (2014), patients reported the most common trigger of HAE attacks as emotional stress.(28) One patient said "*I go to bed every night and at the back of my mind is the thought I might wake up with a swelling – or not wake up*".(40) Continuous stress exacerbated by the presence of an attack can result in a vicious cycle of further debilitating episodes.(37, 41) Feelings of anxiety and depression are also often intensified by the fear of laryngeal oedema, which can be potentially life-threatening if not treated promptly.(36, 42) Furthermore, some patients experience additional anxiety and worry over self-administering injectable treatments, feeling they lack the confidence and proper technique to adminster treatment effectively.(43) This further increases the chances of an attack, with UK clinical experts

reporting that delaying treatment increases severity of attacks and that once an attack is established, the longer the attack will last (31), which is in line with World Allergy Organization (WAO) and the European Academy of Allergy and Clinical Immunology (EAACI) (WAO/EAACI) guidelines for the management of HAE.

HAE patients have also reported experiencing judgement from others with one patient expressing to KalVista that "*I had to leave, go back to inject… you can't just carry all these boxes with you, you certainly can't get them out on a table in a restaurant or, and start mixing vials of powder and water and dealing with needles and .. people would just, nobody would understand, you know?"* (UK Adult with HAE)(44)

Please see Unmet Need section further below for additional aspects related to patient impact living with HAE, treatment-related anxiety and challenge meeting the treatment goal to achieve total control of the disease and normalise patients' lives whilst adhering to treatment guidelines with injectable treatments.

Economic burden

"Having this disease has taken my life; my education, my prospect of a career, having a family" (UK HAE patient).(40)

HAE significantly impacts patients' ability to maintain normal levels of functionality and productivity due to the severe physical and emotional effects of attacks. Research has shown that some untreated HAE attacks can last a median of 48 hours, with UK patients experiencing an average of 13.5 attacks annually – more than one per month.(45) This means patients spend a considerable portion of their time dealing with HAE symptoms, which substantially interferes with work and daily activities. A European study on the socioeconomic burden of HAE found that over half (56%) of patients reported missing school or work during their most recent attack, highlighting the disorder's disruptive nature on education and employment.(46) Furthermore, a US-based study found survey respondents reported that HAE had substantial impact on their ability to work and their productivity when at work. When participants were asked to estimate their potential achievement without having HAE, over half (57.7%) of the indirect costs – equivalent to $30,344 – were attributed to higher labour force involvement and increased productivity.(47) These findings underscore the pervasive

impact of HAE on patients' personal and professional lives, emphasising the need for effective management strategies to mitigate these disruptions.(46)

In addition to personal economic impacts through absenteeism, HAE results in a significant wider economic burden on patients and the healthcare system. A cross-sectional, retrospective study of HAE (type I and II) burden in England and Scotland estimated the total annual cost of secondary care in England was £3,227,149 – corresponding to £2,749 per HAE patient.(48) Furthermore, over a 2-year period 1,174 HAE patients were admitted to hospitals in England, for any reason, with a mean length of stay of 2.8 days, including day cases.(48)

Caregiver burden

There is a significant caregiver burden identified for HAE patients. To manage HAE attacks, patients may urgently require the administration of on-demand treatments, often via subcutaneous injection (SC). Caregivers regularly support patients (particularly children) during these debilitating attacks and with treatment management, often receiving training for the urgent administration and usage of on-demand treatments.(12, 49) A cross-sectional study of HAE patients in Spain, Germany, and Denmark indicated that 86 (52%) had received assistance from a caregiver (primarily family members) during their previous attack.(46) This study also showed caregivers of HAE patients with severe pain lost more time (2.1 days) during the last attack than those caring for patients with mild or no pain (1.2 days) and caregiver absenteeism increased as pain severity rose.(46)

Caregivers offer both physical and emotional support to HAE patients and share anxiety over attacks.(46) Many caregivers experience stress and anxiety, often as a result of their responsibilities in disease management, which includes locating suitable veins and timely administration of on-demand treatments.(49) Emotionally, caregivers highlight the psychological impact of witnessing the individual they care for in pain or distress following an attack. Qualitative findings from a time trade-off (TTO) study by Lo *et al.* (2022) signified throat and abdominal attacks to be the most emotionally impactful.(50) Furthermore, Lo *et al.* (2022) showed the TTO scores indicated that the caregiver state has a lower utility than the attack-free patient state, supporting the burden described by caregivers during the qualitative interviews.(50)

In a recently accepted abstract, Kiani-Alikhan *et al.* (2025) found that 20% (n=2) of adults surveyed in their study, who used icatibant and 100% adolescents (n=5) required caregiver or healthcare provider support to administer their on-demand treatment. Caregivers also reported experiencing emotional distress, including anxiety (n=6) and stress (n=8), due to witnessing the pain or discomfort the person they care for endures during on-demand and injectable administration.(51)

A carer also shared the following quote with KalVista relating to the impact on their quality of life: *"I had to leave work...and I would have to go home and give him an injection so that definitely was sort of you know, as you never know when it .. will happen, it could be any day, you know? Any time of the day, it could be at night."* (UK Caregiver to child with HAE)(44)

Clinical pathway of care

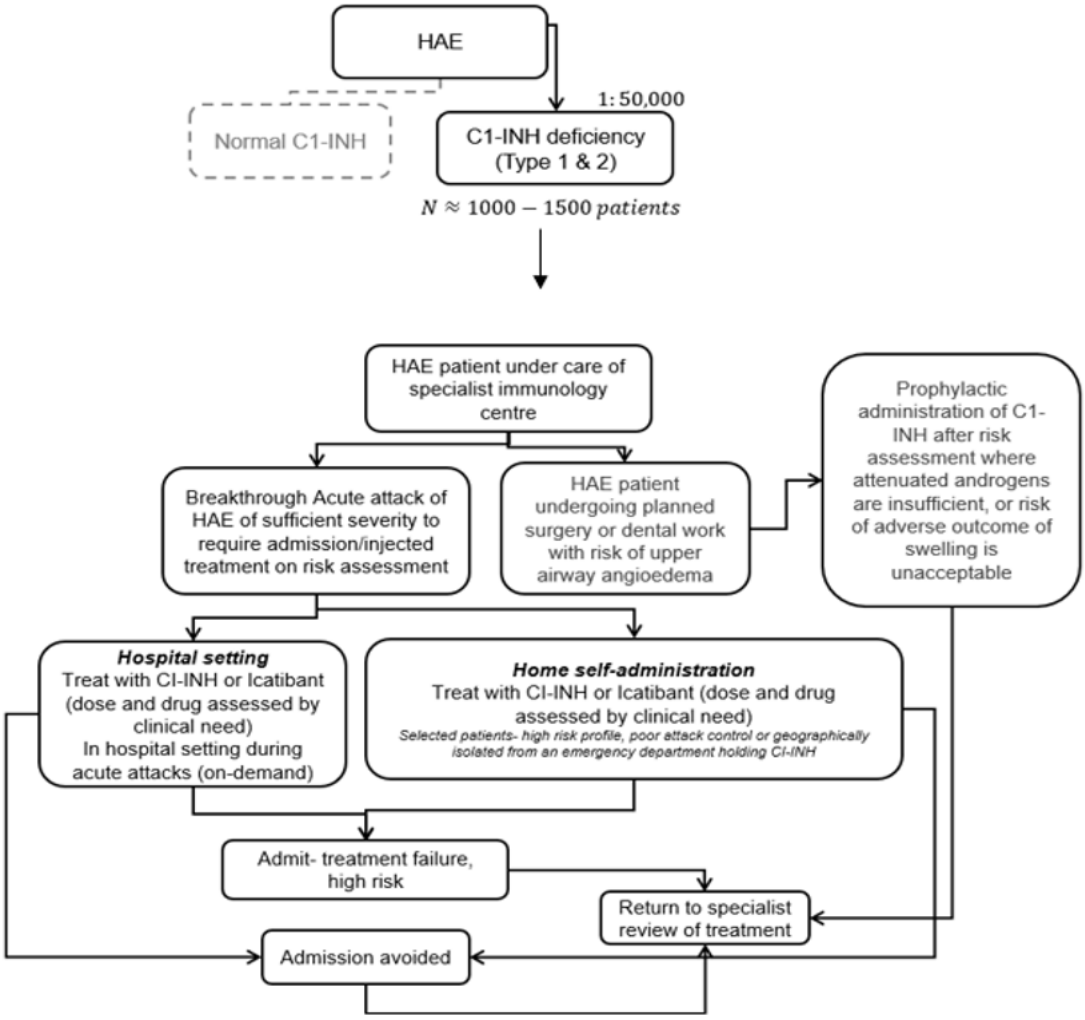
Diagnosis of HAE usually begins with clinical suspicion (patients displaying recurrent episodes of swelling, recurrent episodes of abdominal pain and vomiting or laryngeal oedema) or a positive family history of angioedema as a strong indicator of hereditary angioedema.(52) Laboratory tests for HAE involve testing for a C1 esterase inhibitor deficiency, which results in abnormally high bradykinin levels. HAE can also be diagnosed through low C4, C1-INH protein, and C1-INH functional levels.(53)

In the UK, the majority of diagnosis referrals would be via General Practitioners (GPs) to secondary care and then onwards to Specialist Immunology Centres where specialist physicians direct the appropriate treatment.(15) A range of additional healthcare professions could also involved in HAE care including specialist nurses (54), gastroenterologists and A&E specialists (16).

Treatment of HAE takes the form of three distinct methodologies: treatment of acute attacks, short-term prophylactic (STP) treatments, and long-term prophylactic (LTP) treatments. According to the large UK-based study by Yong, Couter *et al.* (2023), on-demand treatment provided to patients was largely icatibant (n = 565; 45%) and C1-INH (n= 713; 56%), with a minority provided with attenuated androgens (n = 52; 4%) and tranexamic acid (n = 73; 6%). Yong *et al.* (2023) also found that "adults in the UK

were more likely to be on LTP compared with adolescents, who were more likely to be on LTP compared with children under 12 years".(4)

Figure 1 HAE UK Treatment Pathway



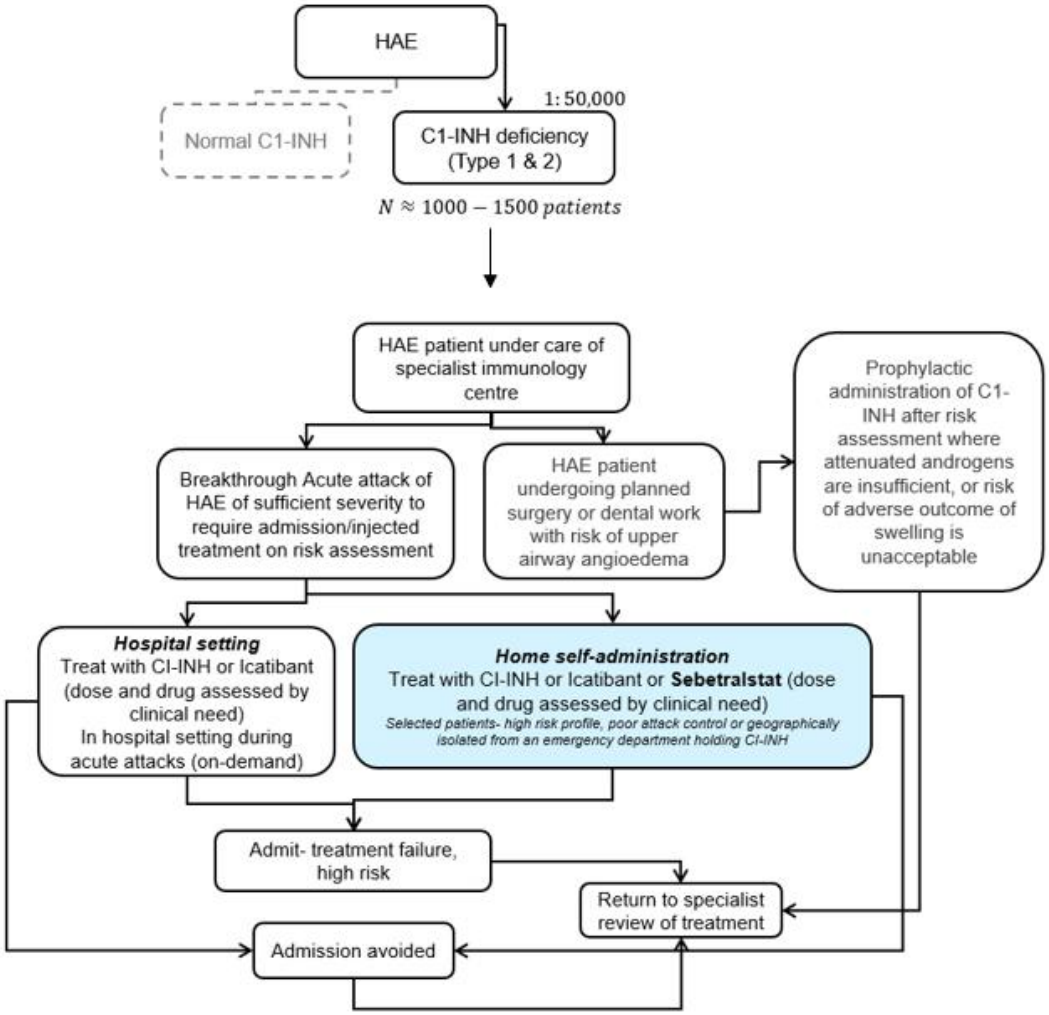
Source: Adapted from NHS commissioning Board Policy report (2013)(15)
Abbreviations: C1-INH:C1-esterase inhibitor, HAE: hereditary angioedema

Sebetralstat position in the treatment pathway

Sebetralstat is being investigated as the first oral on-demand treatment for acute HAE attacks via self-administration. Sebetralstat works by targeting the kallikrein-kinin system (KKS) cascade, selectively inhibiting plasma kallikrein and its uncontrolled activity that drive HAE attacks. Sebetralstat is designed to offer people living with HAE with a medication that can be taken as a discreet oral dose to readily treat HAE attacks

on-demand, including at the earliest signs before the attack fully develops- thereby lowering the severity of the attack burden.

Figure 2 Positioning of Sebetralstat in the HAE UK Treatment Pathway



Source: Adapted from NHS commissioning Board Policy report (15)
Abbreviations: C1-INH:C1-esterase inhibitor, HAE: hereditary angioedema

Acute (on-demand) treatment

Acute treatment of HAE attacks aims to reduce symptoms and shorten attack duration. In the UK, several approved treatments are available for acute HAE management. These include: intravenous (IV) plasma-derived C1-INHs (Berinert & Cinryze), recombinant Human C1-INH (Ruconest) and subcutaneous bradykinin-receptor antagonist icatibant (Firazyr).(15)

These therapies are administered via injection, either by healthcare professionals at specialised centres or through self-administration at home after proper training. (15) The latter option empowers patients and caregivers to manage attacks promptly, which is crucial for effective treatment. Additionally, self-administration would alleviate requirement for healthcare resource use to administer on-demand treatment.

C1-INH on-demand treatment is only licensed to be delivered by IV in the UK. Additionally, a recent online clinician survey (conducted by KalVista) involving 12 UK clinicians found that half of patients self-administer their C1-INH on-demand treatment, 13% require carer administration, and over one-third require administration by healthcare professionals (38%) within the secondary care setting. (31)

The WOA/EAACI HAE 2021 guidelines recommend all attacks (irrespective of location or severity) are considered for on-demand treatment of HAE (type I and type II) and treatment should begin as early as possible to arrest progression. Earlier administration of on-demand treatment provides a better treatment response, with shorter time to symptom relief and attack resolution. (24)

The guidelines also note all patients should have sufficient medication for on-demand treatment of two attacks and carry on-demand medication at all times. Furthermore, as early treatment is facilitated by self-administration, guideline recommend all patients with HAE type I and type II should be considered for home therapy and self-administration training.(24)

In the UK, icatibant is the more commonly prescribed on-demand treatment. Clinicians consulted as part of this submission reported that they observe relatively high redosing rates in patients using icatibant, with approximately 18-25% patients requiring an icatibant re-dose per attack. Moreover, some clinicians also stated that icatibant generally requires patients to use rescue therapy more often, which can be largely due to delays in icatibant treatment administration as it is a painful injection with fear of needles also impacting. (31)

Pain from injectable on-demand treatments such as icatibant has been linked to the needle puncture, as well as the painful sensation caused by the medication itself, and also reactions at the injection site. Every participant in a recently accepted abstract by

Kiani-Alikhan *et al.* 2025 qualitative study, reported that the pain and discomfort from these injections contributed to overall dissatisfaction with their current injectable treatment. This study involved 25 respondents (16 US, 9 UK) included 12 adult patients (mean age 42.4 years, 83% on non-androgen long term prophylaxis [LTP]), 5 adolescent patients (mean age 13.8 years, 60% on LTP) and 8 caregivers (mean age 42.8 years).(51) Yong *et al.* are reporting further findings from this qualitative study during the 14th C1-INH 2025 workshop in Budapest. The Yong *et al.* analysis report that all respondents reported delaying or forgoing on-demand treatment for attacks, and many respondents (n=10) associated increased severity and duration of attacks with treatment delays as a result. Respondents commonly reported that lack of portability (n=13), painful administration (n=19), and logistical barriers restricting use away from home (n=19), led to dissatisfaction with their current on-demand treatment. For some participants these characteristics of injectable treatments contributed to poor HRQoL, negative psychological impacts, and activity disruptions or limitations. Respondents indicated that if they had oral on-demand treatment available, they would be willing to treat more attacks (n=4) and treat them earlier (n=8).(55)

Further findings are being reported by Cancian *et al.* at the 14th C1-INH 2025 workshop in Budapest, whereby an online survey involving 284 respondents across the US, UK, France and Italy found that nearly one third of survey respondents experienced moderate to extreme anxiety due to anticipated use of parenteral on-demand treatment, particularly adolescents and those receiving IV therapy. During the last treated attack, the mean anxiety rating regarding on-demand treatment was 3.7 (0-10 scale), with 29% of respondents feeling extremely anxious (anxiety 7-10), 17% moderately anxious (anxiety 4-6), 28% mildly anxious (anxiety 1-3), and 26% not anxious (anxiety 0).(56)

Of note, greater levels of anxiety were associated with longer on-demand treatment delays. For respondents treating in <1hr, the mean anxiety was 3.0. Anxiety increased with increased time to treatment, with mean ratings of 3.6, 3.7, 3.9, and 4.3 when treating within 1 to <2hrs, 2 to <5hrs, 5 to <8hrs, and ≥8hrs, respectively. The most common reasons for anxiety in participants receiving IV treatment were related to injection and treatment administration (76%). For participants receiving subcutaneous

treatment, the most common reasons for anxiety were related to concerns about treatment efficacy (67%).(56)

Clinicians reported that delay behaviour to icatibant was experienced by 29% of their patients. One clinician also noted that treatment delay could also be due to patients not wanting to waste their medication supply.(31)

This appraisal for sebetralstat is specifically as an on-demand treatment of HAE attacks. However, we will provide a short overview of short-term prophylactic and long-term prophylactic treatments of HAE attacks for completeness of the condition.

Short-term prophylaxis

Short-term prophylaxis (STP) in HAE management aims to prevent acute attacks when patients are exposed to known triggers. This preventive approach is particularly crucial before certain medical interventions or stressful events that may precipitate HAE attacks. Medical procedure such as dental work, local anaesthetic injections and major surgeries requiring intubation have been identified as common triggers for HAE attacks. Consequently, healthcare providers often prescribe STP treatments to mitigate the risk of attacks during these procedures.(24, 52)

Beyond medical interventions, WAO/EAACI guidelines also recommend STP may be considered when anticipating exposure to stressful life events. (24) This proactive approach helps manage the increased risk of attacks associated with heightened stress levels. The primary medications used for STP in HAE include: C1-INHs, attenuated androgens or antifibrinolytics.(24)

Tranexamic acid (TXA) is a blood clotting agent and the most commonly used anti-fibrinolytic in STP HAE treatment.

Long-term prophylaxis

Long-term prophylaxis (LTP) treatments are used to help prevent acute attacks. While HAE cannot be cured, individuals who remain attack-free can lead similar lives to those of healthy individuals. LTP treatments available in the UK for patients with HAE, include attenuated androgens, lanadelumab, berotralstat, C1-INHs, and anti-fibrinolytics. (4, 15, 20, 57, 58)

A Yong *et al.* (2024) UK study reported that whilst modern prophylactic treatments such as lanadelumab and berotralstat are available in the UK, access is restricted by HAE attack frequency, with only those experiencing extremely frequent HAE attacks eligible for treatment, leaving a cohort of patients who may benefit from LTP at a disadvantage. (20)

Whilst there might be a perception that LTP enables attack-free lives, patients on LTP still have attacks and still face challenges in managing and recovering from HAE attacks similar to those using on-demand therapy only. (59)

Attenuated androgens

Attenuated androgens (AAs) such as danazol and oxandrolone are steroid hormones used off-label in UK clinical practice for STP and LTP management of HAE. AAs such as danazol, stanozolol and oxandrolone, have not been studied in large, randomised, placebo-controlled trials, and available data are from limited numbers of patients. (60-63)

The use of AAs is decreasing as more effective and better-tolerated targeted therapies are being approved. Consequently, discontinuation of AAs is becoming increasingly common due to side effects, contraindications, and patient or physician preferences.(60)

Recent LTPs: Lanadelumab and berotralstat

Lanadelumab (TA606, October 2019) and berotralstat (TA738, October 2021) have been appraised by NICE.

Lanadelumab is a monoclonal antibody inhibitor of plasma kallikrein delivered by subcutaneous injection, recommended by NICE as a LTP treatment of attacks in HAE patients aged 12 and older only if they are eligible for C1-INH treatments; that is, patients having 2 or more clinically significant attacks per week over 8 weeks despite oral preventative therapy, or oral therapy is contraindicated or not tolerated. (57)

UK HAE clinical experts reported patients on lanadelumab experience hardly any attacks but patients on lanadelumab comprise roughly <10% of LTP + on-demand

patients due to its restrictions (data on file). Thus, a limited number of patients are eligible for lanadelumab treatment.

Berotralstat is an oral small-molecule inhibitor of plasma kallikrein approved by NICE in 2021 for the prevention of recurrent attacks in HAE in people 12 years and older only if they have at least 2 attacks per month. (58) Furthermore, treatment must be stopped if the number of attacks per month does not reduce by at least 50% after 3 months.(58) The restrictions to berotralstat's use mean that there is a cohort of patients that should be given prophylaxis but are unable to access it and this was supported by recent findings from a UK delphi panel of clinical experts in HAE.(20)

C1-INHs

In the UK, Cinryze IV (C1-INH) is indicated both as an on-demand treatment for HAE attacks and as LTP. Subcutaneous Berinert is also approved for LTP in the UK. In practice, a very restricted proportion of the UK HAE population are eligible to receive C1-INHs due to current NHS commissioning criteria stipulating the use of C1-INHs *"for individuals who fail or are intolerant of oral prophylaxis and who experience two or more clinically significant attacks per week, despite oral prophylaxis, over a period of at least 56 days requiring treatment with C1-INHs or Icatibant". Or for "Individuals in whom oral prophylaxis is contraindicated for example pregnant women".(64)*

Unmet need

The management of HAE faces significant challenges despite the existence of clear international guidelines. The WAO/EAACI guidelines for HAE management recommends the goals of treatment are to achieve total control of the disease and to normalise patients' lives.(24) However, these objectives remain largely unmet, with 96% patients on prophylaxis and on-demand treatment reporting they do not feel 100% themselves all the time.(65)

A major issue in current HAE management is the undertreatment of attacks. Despite guidelines recommending all attacks are considered for on-demand treatment (24), 69% of people living with HAE report not treating all attacks (66) and 44% people living with HAE prefer to avoid attack triggers rather than carry on-demand treatment with

them.(67) In a recent study, Lumry *et al. (*2025) surveyed US HAE patients and found 65.7% patients taking prophylaxis + on-demand treatment and 78.8% patients using on-demand only treatments would prefer to treat at home and cited this as a key reason why they do not carry on-demand treatment when away from home. (59) Furthermore, 75% of patients report delaying their on-demand treatment, which increases both the severity and recovery time of attacks.(68) On average, patients wait 3.8 hours before treating attacks with on-demand treatment.(69, 70)

The importance of earlier treatment is shared with KalVista by a patient: the *"Sooner you take it, the more effective it is, um, and less likely to relapse and have attacks again and also less likely that actually at the offset of the pain and sometimes I've been, delayed it too long and I've been injecting and the pain's come and it's really horrible, so try and inject yourself and go through the pain is pretty bad but you're kind of thinking 'it's gonna get worse if I don't do this,' so you've just got to get through it"*. (UK adult with HAE)(44)

Furthermore, a KalVista supported survey involving 107 respondents, found that approximately 2 out of 3 HAE patients (64%) do not always carry their on-demand treatment, with some travelling an average of 3.5 hours away from home without it.(67) This is in clear opposition to treatment guidelines which advise patients to carry sufficient medication for on-demand treatment (24) of at least 2 attacks and carry on-demand medication at all times. The delay or failure to treat and non-adherence to treatment guidelines is often due to the nature of current on-demand treatments, which are administered either intravenously or subcutaneously. Patients report issues such as pain (24%), lack of privacy for administration (23%), and fear of needles (11%) as core reasons preventing them from treating as recommended with current on-demand medication.(68) In a more recent study, Lumry *et al.* (2025) found "the injection needle" was a reason for anxiety when anticipating on-demand treatment (among those reporting having anxiety) in 41.9% HAE patients sampled taking on-demand only treatment.(59) Furthermore, Betschel et al. (2024) showed 49% of prophylaxis patients experienced moderate-to-high levels of anxiety when anticipating on-demand treatment administration.(71)

Thus, there remains a considerable proportion of people living with HAE who do not have total control of their disease and are unable to use their on-demand treatment as recommended. Prophylaxis treatment does not guarantee elimination of attacks and access to LTP such as lanadelumab and berotralstat is largely restricted in the UK, whilst the use of AAs is associated with safety and tolerability concerns. Consequently, there is a significant unmet need for new effective on-demand therapies, particularly for an oral on-demand therapy.

Sebetralstat would be the first orally administered therapy for the on-demand treatment of HAE and would make strides towards achieve the WAO/EAACI treatment guideline recommendation for all attacks (irrespective of location or severity) to be considered for on-demand treatment, and for on-demand treatment to be carried at all time to enable treatment to begin as early as possible to arrest attack progression. Furthermore, sebetralstat also supports the guideline recommendation for all patients with HAE type I and type II to be considered for home therapy and self-administration, with the added benefit of not requiring treatment-administration training.

Unlike current injectable on-demand therapies, sebetralstat tablets offer simple and easy self-administration at home or whilst travelling, without the need for specialist training. The ease of use that sebetralstat can offer would reduce burden on both patients and the healthcare system. The Valerieva *et al.* (2024) survey, supported by KalVista, showed 95% HAE patients questioned would carry an oral on-demand treatment, 89% would treat their attack with this medication, 76% would treat their attack earlier and 80% stated they would be less anxious.(72) A time to treatment analysis from the KONFIDENT study showed that attacks that were treated earlier were more likely to be mild (than attacks treated later) and attack resolution was also reached faster.(73)

Furthermore, all UK clinicians consulted as part of this submission confirmed that oral treatment would reduce patient concerns regarding treatment administration with one clinician noting that they had already observed lower anxiety in one patient enrolled in the ongoing open-label extension sebetralstat study. This is an important consideration since worry around treatment administration can contribute to the

anxiety patients feel, and anxiety is a well reported trigger of HAE attacks as mentioned previously.(37, 41, 68)

Sebetralstat is currently being offered to patients with high unmet need as part of an Early Access to Medicines Scheme (EAMS) that was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) in March 2025.(74) Currently [redacted] are actively engaged in dialogue to take part in the EAMS programme.

Overall, a safe and effective oral on-demand therapy such as sebetralstat can help ease the burden of treatment people living with HAE are currently experiencing. Furthermore, oral administration can help increase the likelihood of carrying treatment at all times, thereby encouraging treatment of all attacks at the onset, leading to a better sense of control over the disease and better clinical outcomes.(72) The introduction of sebetralstat would help to meet the treatment guidelines for HAE allowing patients to achieve total control of their disease and to normalise their lives.

1.4 Equality considerations

Not applicable

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

See appendix B for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

- In appendix B we have described the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

2.2 List of relevant clinical effectiveness evidence

There are no randomised controlled trials (RCTs) that directly compare sebetralstat with other on-demand treatments for HAE. Relevant evidence for the clinical effectiveness of sebetralstat comes from placebo trials. The efficacy and safety of sebetralstat has been demonstrated in a phase 2 trial (KVD900-201; NCT04208412), phase 3 KONFIDENT trial (KVD900-301; NCT05259917), and an ongoing open-label KONFIDENT-S extension study (KVD900-302; NCT05505916).

Only sebetralstat data from the phase 3 KONFIDENT study and the open-label KONFIDENT-S study are used in the economic model, however, for background a summary write up of the Phase 2 study is provided in Appendix J.

- Topline details regarding these three sebetralstat studies (including study identifier numbers) are as follows and summarised in Table 3:
    - **Phase II: [KVD900-201 study] NCT04208412**: A Phase II, Cross-over Clinical Trial Evaluating the Efficacy and Safety of sebetralstat in the On-demand Treatment of Angioedema Attacks in Adult Subjects With Hereditary Angioedema Type I or II. (75, 76) [See Appendix J for summary write up].
    - **Phase III: KONFIDENT [KVD900-301 study] NCT05259917**. The pivotal KONFIDENT [KVD900-301] study is a randomised, double-blind, placebo-controlled, phase 3, three-way crossover trial that evaluates the efficacy and safety of two dose levels of sebetralstat (300 mg and 600 mg), an oral plasma kallikrein inhibitor, for on-demand treatment of

angioedema attacks in adolescent and adult patients with hereditary angioedema type I or II. (77-81) [KONFIDENT study presented in Sections 2.2–2.11].

- Open-label extension (multicenter): KONFIDENT-S [KVD900-302 study] NCT05505916**.** (82-84). [See section 2.12 'Ongoing studies'].

Table 3 Clinical effectiveness evidence for sebetralstat

Study	**KVD900-201**	**KONFIDENT**	**KONFIDENT-S**
Study design	A randomised, double-blind, placebo-controlled, phase 2, cross-over trial evaluating the efficacy and safety of sebetralstat	A phase 3 double-blind, randomised, placebo-controlled, three-way crossover trial	Multicentre, open-label extension trial
Population	Adults (≥18 years) with HAE type I or II with at least 3 documented HAE attacks in the past 93 days, as supported by medical history.	Adolescents and adults (≥12 years) with a confirmed diagnosis of HAE type I or II and at least 2 documented attacks within 3 months before screening or randomisation and access to conventional on-demand therapy.	Adolescent and Adult Patients (≥12 years) with Hereditary Angioedema Type I or II. Rollover patients are patients who were randomised in the KONFIDENT phase 3 trial. Non-rollover patients include patients who were randomised in the KVD900-201 trial (Phase 2) or sebetralstat naïve patients.
Intervention(s)	Sebetralstat 600 mg	Sebetralstat 300 mg and 600 mg	Sebetralstat 600 mg (Note the study dose was switched to 300 mg Sebetralstat at the beginning of 2025)
Comparator(s)	Placebo	Placebo	N/A
Indicate if study supports application for marketing authorisation	Yes	Yes	Yes

Study	KVD900-201	KONFIDENT	KONFIDENT-S
Indicate if study used in the economic model	No	Yes	Yes
Rationale if study not used in model	Phase 3 study data available	-	
Reported outcomes specified in the decision problem [**bold** if used in the model]	N/A not used in the model	• **severity of angioedema attacks** • **duration of angioedema attacks** • **time to beginning of symptom relief** • **reduction in symptoms of angioedema attacks** • **mortality** • **use of rescue medication** • **adverse effects of treatment** • **health-related quality of life.**	Only the following data from the KONFIDENT-S study are used in the model • **Additional dosing rates** • **Rescue medication**

Comparator studies

Please note that in the absence of direct trials comparing sebetralstat with active on-demand treatments for HAE, an indirect comparison was considered by the company. However, due to heterogeneity between trials (patient populations and definition of outcomes) an ITC was not feasible. [See section 2.10 'Indirect and mixed treatment comparison' for more details] Furthermore, an active comparator study was not feasible due to the interaction of Icatibant with receptors in the skin resulting in injection-site reactions which cannot be mimicked with placebo.(85)

The cost-effectiveness model does use data from the comparator studies listed in Table 4. A summary write up of these trials is available in Appendix K:

Table 4 List of comparator studies in the model

Comparator	Study	Type of study	Source
Icatibant	IOS study	Real-world study, international prospective observational disease registry	Longhurst *et al.* 2018 (86)
Icatibant	FAST1 / NCT00097695 & FAST2 / NCT00500656	RCTs	Cicardi *et al.* 2010 (85)
Berinert	SABHA	Real-world observational, monocentre, prospective study	Zanichelli *et al.* 2018 (87)
Berinert	IMPACT 2	Open-label extension study to IMPACT 1 (Berinert RCT)	Craig *et al.* 2011 (88)
Berinert & Ruconest	(no particular name)	Real-world, monocentre, prospective observational study	Zanichelli *et al.* 2015 (89)
Ruconest	C1-1205-01 / NCT00225147 & C1-1304-01/ NCT00262301	Randomised, saline-controlled, double-blind studies	Zuraw, Cicardi, Levy *et al.* 2010 (90)

Comparator	Study	Type of study	Source
Ruconest	NCT00225147 [C1–1205] NCT00262301 [C1–1304] NCT01188564 [C1–1310]	A pooled analysis of data from three independent clinical trials with open-label extensions	Riedl *et al.* 2017 (91)
Cinryze	LEVP-2005-1 (Part A) / NCT00289211 LEVP-2006-1/ NCT00438815 (OLE)	RCT OLE	Zuraw, Busse, White *et al.* 2010 (92)

RCT: randomised controlled trial

A summary write up of these comparator studies is available in Appendix K.

2.3 Summary of methodology of the relevant clinical effectiveness evidence

KONFIDENT Phase 3

- The KONFIDENT trial is the first randomised controlled phase 3 trial that includes patients receiving stable, long-term, prophylactic therapy and does not include attack severity as an eligibility criterion for enrollment.
- KONFIDENT is the first phase 3 HAE trial to use the Patient Global Impression of Change (PGI-C) scale to measure the primary endpoint: time to beginning of symptom relief; Interviewed HAE patients agreed that this endpoint was meaningful to them and that the PGI-C rating scale best captured the gradual change in symptoms experienced during an HAE attack.
- The secondary endpoint in KONFIDENT evaluated the time to the first incidence of decrease from baseline for 2 time points in a row on Patient Global Impression of Severity (PGI-S) within 12 hours of the first investigational medicinal product (IMP) administration (i.e., time to reduction in severity). More attacks achieved the time to reduction in severity in the 300 mg sebetralstat (44 [50.6%] attacks) and 600 mg sebetralstat groups (49 [52.7%] attacks) than placebo group (26 [31.0%] attacks).
- In KONFIDENT, the median time from attack onset to the first administration of sebetralstat or placebo was 41 minutes, with 25% of trial participants treating their HAE attack within 6 minutes. Moreover, complete resolution of the attack was also reached faster with the 300 mg dose and the 600 mg dose than with placebo. The percentage of attacks with complete resolution within 24 hours after the first administration was 42.5% with the 300 mg dose of sebetralstat, 49.5% with the 600 mg dose, and 27.4% with placebo.
- Earlier treatment with sebetralstat is associated with improved HAE outcomes. Recent analysis of the KONFIDENT phase 3 trial by Craig *et al.* at ACAAI 2024 showed that complete attack resolution was achieved faster in attacks which were treated earlier (1st quartile) compared with those treated later (4th quartile). A further post-hoc analysis by Lumry *et al.* (presented at ACAAI 2024) found that sebetralstat (300 mg and 600 mg) provides a faster, more significant reduction in symptom burden for HAE attacks compared to placebo.

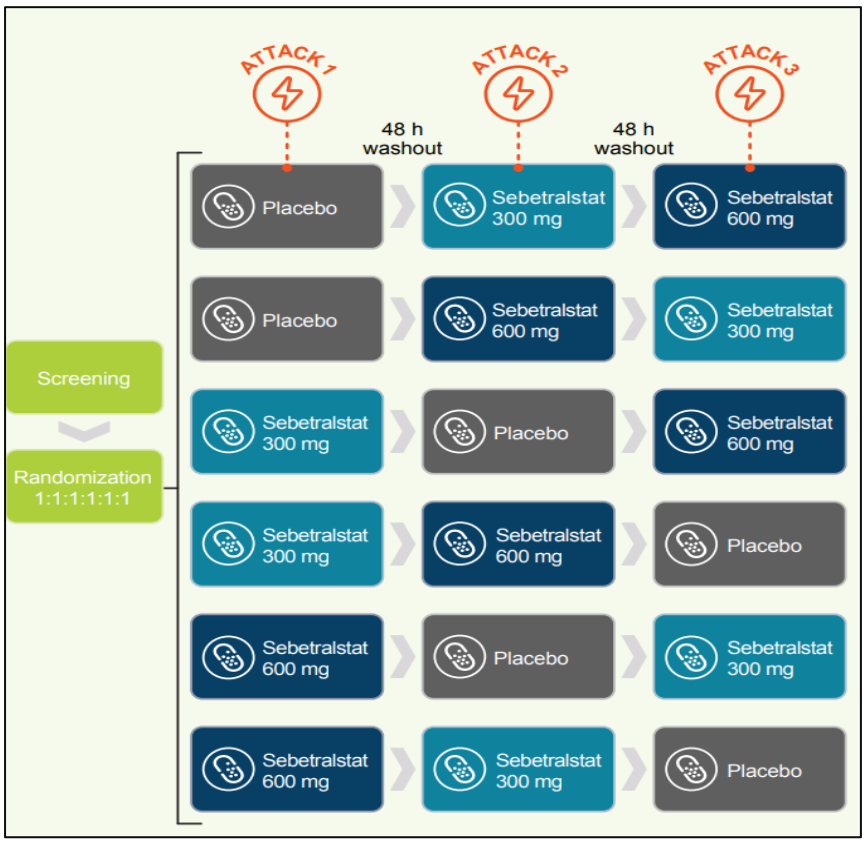
- Whilst patients in the KONFIDENT study were permitted to take a further dose of sebetralstat, as determined by the patient themselves, ad hoc efficacy analyses show that the majority of patients go onto achieve HAE attack resolution without the need of a second dose of sebetralstat.

KONFIDENT methods and trial design

KONFIDENT was a phase 3 double-blind, randomised, 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 HAE attacks.

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 (Figure 3).

Figure 3 KONFIDENT Phase 3 Trial Design



h, hour.
Patients will be randomised to treat 3 eligible attacks with sebetralstat 300 mg, sebetralstat 600 mg, or placebo in a 3-way crossover design using 1 of 6 treatment sequences
Source: Lumry et al. (2022)(93)

Randomisation was stratified according to the use of long-term prophylaxis at enrollment. Eligible attacks were those considered by the participant to meet the following criteria: the start of the attack could be identified, at least 48 hours had elapsed since the trial agent or conventional treatment was taken for a previous attack, the participant had the ability to enter attack information in an electronic diary during the initial 4 hours after first taking the trial agent, and the attack involved any location and severity at baseline, excluding laryngeal attacks that were considered by the participant to be severe.

Patients were asked to self-administer a single dose of 300 mg sebetralstat (1 × 300 mg sebetralstat tablet plus 1 placebo tablet), 600 mg sebetralstat (2 × 300 mg sebetralstat tablets), or 2 matching placebo tablets in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours a second dose of IMP may have been administered for each attack. The second dose of IMP matched the initial dose administered.

Table 5 KONFIDENT Phase 3 trial design

Trial number (acronym)	**NCT05259917 (KONFIDENT) (80, 81)**
Location	US, Australia, Bulgaria, Canada, France, Germany, Greece, Hungary, Israel, Italy, Japan, Netherlands, New Zealand, North Macedonia, Poland, Portugal, Puerto Rico, Romania, Slovakia, Spain, United Kingdom. (Included 5 UK sites*)
Trial design	A Randomised, Double-Blind, Placebo-Controlled, Phase 3, Three-way Crossover Trial to Evaluate the Efficacy and Safety of Two Dose Levels of sebetralstat, an Oral Plasma Kallikrein Inhibitor, for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients With Hereditary Angioedema Type I or II.
Eligibility criteria for participants	**Inclusion Criteria:** • Male or female patients 12 years of age and older. • Confirmed diagnosis of HAE type I or II at any time in the medical history. • Patient has access to and ability to use conventional on-demand treatment for HAE attacks (plasma-derived or recombinant C1 inhibitor, icatibant, or ecallantide). • If a patient is receiving long-term prophylactic treatment with one of the protocol-allowed therapies (intravenous or subcutaneous plasma-derived C1 inhibitor protein, lanadelumab, or berotralstat), they must be on a stable dose and regimen for at least 3 months immediately before and during the trial. Patient

	must be willing to remain on a stable dose and regimen for the duration of the trial.
	• Patient's last dose of attenuated androgens other than danazol was at least 28 days prior to randomization.
	• Patient:
	  ○ has had at least 2 documented HAE attacks within 3 months prior to screening or randomisation; or
	  ○ is a completer of the KVD824-201 trial within 3 months prior to randomisation and meets all other entry criteria to enroll in KVD900-301 KONFIDENT phase 3 study
	• Patients must meet the contraception requirements.
	• Patients must be able to swallow trial tablets whole.
	• Patients, as assessed by the Investigator, must be able to appropriately receive and store IMP, and be able to read, understand, and complete the electronic diary (eDiary).
	• Investigator believes that the patient is willing and able to adhere to all protocol requirements.
	• Patient provides signed informed consent or assent (when applicable). A parent or legally authorised representative (LAR) must also provide signed informed consent when required

Eligibility criteria for participants	**Exclusion Criteria:** • Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1-inhibitor deficiency, HAE with normal C1-INH (previously known as HAE type III), idiopathic angioedema, or angioedema associated with urticaria. • Attenuated androgens, antifibrinolytic agents, and other investigational long-term prophylactic agents were not permitted in most countries. Exclusion of attenuated androgens was due to safety concerns related to their mixed use across the countries included in KONFIDENT, with only danazol approved in the United States and a wide range of others used across other regions, many of which are not approved for use in hereditary angioedema. Similarly, exclusion of tranexamic acid was due to its variable approval status across the countries included in KONFIDENT. • A clinically significant history of poor response to bradykinin receptor 2 (BR2) blocker, C1-INH therapy or plasma kallikrein inhibitor therapy for the management of HAE, in the opinion of the Investigator. • Use of angiotensin-converting enzyme (ACE) inhibitors after the Screening Visit or within 7 days prior to randomization. • Any oestrogen containing medications with systemic absorption (such as oral contraceptives including ethinylestradiol or

	hormonal replacement therapy) within 7 days prior to the screening visit or during the trial. • Patients who require sustained use of strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers. • Inadequate organ function, including but not limited to: 1. Alanine aminotransferase (ALT) >2x upper limit of normal (ULN) 2. Aspartate aminotransferase (AST) >2x ULN 3. Bilirubin direct >1.25x ULN 4. International normalized ratio (INR) >1.2 5. Clinically significant hepatic impairment defined as a Child-Pugh B or C • Any clinically significant comorbidity or systemic dysfunction, which in the opinion of the Investigator, would jeopardize the safety of the patient by participating in the trial. • History of substance abuse or dependence that would interfere with the completion of the trial, as determined by the Investigator. • Known hypersensitivity to sebetralstat or placebo or to any of the excipients. • Prior participation in trial KVD900-201. • Participation in any gene therapy treatment or trial for HAE. • Participation in any interventional investigational clinical trial (with the exception of KVD824-201), including an investigational COVID-19 vaccine trial, within 4 weeks of the last dosing of investigational drug prior to screening. • Any pregnant or breastfeeding patient.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	Participants were randomly assigned in a ratio of 1:1:1:1:1:1 to one of six sequences. In each sequence, one or two doses of the first trial agent in the sequence was administered by the participant for the first eligible hereditary angioedema attack, one or two doses of the second trial agent in the sequence was administered for the second eligible attack, and one or two doses of the third trial agent in the sequence was administered for the third eligible attack, see Figure 3 above. Prior medications (including conventional HAE medications) are defined as those medications taken within 4 weeks prior to the Screening Visit up to the first dose of IMP. Concomitant medications are defined as those medications (including conventional HAE medications) ongoing at or started after the first dose of IMP.
Primary outcomes (including scoring methods and timings of assessments)	• Evaluation of Efficacy • PGI-C: Time to beginning of symptom relief defined as at least “a little better” (2 time points in a row) within 12 hours of the first IMP administration.

Other outcomes used in the economic model/specified in the scope	Key secondary outcomes • PGI-S: Time to first incidence of decrease from baseline (2 time points in a row) within 12 hours of the first IMP administration. • PGI-S: Time to HAE attack resolution defined as "none" within 24 hours of the first IMP administration. Secondary endpoints: • PGI-C: Proportion of attacks with beginning of symptom relief defined as at least "a little better" (2 time points in a row) within 4 hours and within 12 hours of the first IMP administration. • PGI-C: Time to at least "better" (2 time points in a row) within 12 hours of the first IMP administration. • PGI-S: Time to first incidence of decrease from baseline (2 time points in a row) within 24 hours of the first IMP administration. • Composite VAS: Time to at least a 50% decrease from baseline (3 time points in a row) within 12 hours and within 24 hours of the first IMP administration. Exploratory Endpoints • General Anxiety–Numeric Rating Scale (GA-NRS): Cumulative GA-NRS expressed as area under the curve over 12 and 24 hours of the first IMP administration. Outcomes modelled that are in the NICE scope • Severity of angioedema attacks • Reduction in symptoms of angioedema attacks • Mortality • Use of rescue medication • Adverse effects of treatment • Health-related quality of life.
Pre-planned subgroups	Prespecified subgroup analyses of the primary and key secondary end points were performed according to: • Age group • Use of long-term prophylaxis (yes or no), • Baseline attack location and severity • Number of administrations of the trial agent (1 or 2) • Geographic region.

* the 5 UK sites and the associated number of subjects enrolled, include: Royal London Hospital, London (1 subject); Frimley Park Hospital, Surrey (2 subjects); St James University Hospital, Leeds (4 subjects); University Hospital Birmingham (1 subject); Immunodeficiency Centre for Wales, Cardiff (0 subjects).

The study baseline characteristics are summarised in Table 6. Of the 110 participants who received at least one dose of double-blind treatment, 66 were female (60.0%), and 101 (91.8%) had HAE type 1. The median age was 39.5 years, and 30 participants (27.3%) were adolescents between 12 and 17 years of age(94), with [redacted] adolescent patients evaluable for the primary analysis.(78) Race was self-reported as White in the majority of participants (83.6%), followed by Asian (9.1%), Black/African American (0.9%), and other (0.9%). Additionally, the median time since the diagnosis of

hereditary angioedema was 12 years (interquartile range, 7 to 22).(94) Only on-demand therapy at enrollment was received by 86 participants (78.2%) of the overall study population. Twenty-four participants (21.8%) of the overall population were receiving long-term prophylaxis. Of these 24 receiving LTP, proportions were as follows: berotralstat in 9 (37.5%), lanadelumab in 8 (33.3%), C1 inhibitor in 6 (25.0%), and both berotralstat and C1 inhibitor replacement in 1 (4.2%).(80)

Table 6 KONFIDENT Phase 3 Study Baseline Characteristics (full analysis population)

Characteristic	Sebetralstat 300 mg (N=87)	Sebetralstat 600 mg (N=93)	Placebo (N=84)	Overall (N=110, treating 264 attacks)
Age, years				
Median (IQR)	37.0 (25.0-49.0)	39.0 (25.0-49.0)	38.0 (25.0–49.0)	39.5 (25.0–49.0)
Sex, n (%)				
Male	33 (37.9)	37 (39.8)	29 (34.5)	44 (40.0)
Geographic region, n (%)				
Europe United States Asia-Pacific region	44 (50.6) 27 (31.0) 16 (18.4)	49 (52.7) 28 (30.1) 16 (17.2)	48 (57.1) 23 (27.4) 13 (15.5)	58 (52.7) 34 (30.9) 18 (16.9)
HAE-C1INH type — n (%)				
Type I	79 (90.8)	87 (93.5)	79 (94.0)	101 (91.8)
Type II	8 (9.2)	6 (6.5)	5 (6.0)	9 (8.2)
Current treatment regimen — no. (%)				
On-demand treatment only	68 (78.2)	72 (77.4)	66 (78.6)	86 (78.2)
Prophylaxis plus on-demand treatment	19 (21.8)	21 (22.6)	18 (21.4)	24 (21.8)
Race – no. (%)†				
White Asian Black Other Not reported	73 (83.9) 9 (10.3) 1 (1.1) 0 4 (4.6)	80 (86.0) 8 (8.6) 0 1 (1.1) 4 (4.3)	73 (86.9) 7 (8.3) 0 1 (1.2) 3 (3.6)	92 (83.6) 10 (9.1) 1 (0.9) 1 (0.9) 6 (5.5)
Median BMI (IQR)	26.3 (22.8–31.2)	26.2 (22.9–30.9)	26.2 (22.9–30.8)	26.2 (22.8–31.6)

The full analysis population comprised participants who administered sebetralstat or placebo to themselves for at least one angioedema attack. Participants may be represented in multiple columns. Percentages may not total 100% because of rounding. HAE-C1INH denotes hereditary angioedema due to C1 inhibitor deficiency and IQR interquartile range.
IMP: investigational medicinal product
† Race was reported by the participant
Source: Riedl *et al.* (2024) (80)

Attack characteristics

The trial participants administered at least one dose of sebetralstat or placebo for 264 attacks. The distribution of the attack severity at baseline was consistent across the trial agents and according to the use of long-term prophylaxis.(80) The majority of treated attacks were of mild (or moderate ( ) severity on the PGI-S at the time of treatment. attacks were severe and were very severe at the time of treatment.(78)

The median time from the onset of the attack to the first administration of sebetralstat or placebo was 41 minutes (interquartile range, 6 to 140).(80) (Table 7)

The majority of primary pooled attack locations were and . The laryngeal swelling occurred in of the attacks.(78)

An optional second administration of the trial agent was used for 34 attacks (39.1%) in the 300 mg group, 37 attacks (39.8%) in the 600 mg group, and 47 attacks (56.0%) in the placebo group.(80, 94) Information about most of the attacks was thoroughly recorded in the electronic diary, whereas information about a small percentage of the attacks was insufficient for the assessment of the endpoints; this percentage was relatively low and balanced across the trial agents. Conventional treatment was used within 12 hours after first taking sebetralstat or placebo for 12 attacks (13.8%) in the 300 mg group, 8 attacks (8.6%) in the 600 mg group, and 21 attacks (25.0%) in the placebo group.(80)

Table 7 Summary of additional baseline characteristics including attack characteristics (Full analysis set)

Characteristic	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo	Overall
Number of HAE attacks	87	93	84	264
Baseline PGI-S score[a]				
N Mean (SD) Min, max				
Baseline PGI-S category, n (%) [a]				
None Mild Moderate Severe				

Very severe				
Missing				
Baseline GA-NRS score				
N				
Mean (SD)				
Min, max				
Baseline GA-NRS category [b], n (%)				
Not at all anxious (0)				
Mildly anxious (1-3)				
Moderately anxious (4-6)				
Extremely anxious (7-10)				
Baseline Composite VAS score[c]				
N				
Mean (SD)				
Min, max				
Time from onset of the first attack to the first IMP administration (min)				
N				263
Median				41.0
Q1, Q3				6.0, 140.0
Time from onset of the first attack to the first IMP administration category, n (%)				
<30 mins				
≥30-60 mins				
≥60 mins				
Missing				
Baseline primary attack locations[d], n (%)				
Head/face/neck				
Torso				
Arms/hands				
Genitals				
Legs/feet				
Abdomen				
Larynx/throat				
Baseline primary pooled attack locations 1[e], n (%)				
Laryngeal				
Abdominal only				
Subcutaneous only				
Abdominal and Subcutaneous				
Missing				
Baseline primary pooled attack locations 2[f] n (%)				
Neck and above				
Abdominal				
Other				
Missing				

Notes: Number of HAE attacks is number of IMP-treated HAE attacks. The number of IMP-treated HAE attacks is equivalent to the number of patients in each group.

[a] The PGI-S score was transformed into numeric values: 0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe

[b] GA-NRS score was categorised into intervals: 0=not at all anxious, 1-3=mildly anxious, 4-6=moderately anxious, and 7-10=extremely anxious.

[c] The composite VAS score was derived as the average score across the 3 symptoms (abdominal pain, skin pain, and skin swelling).

[d] One patient could be summarised in several attack locations.

[e] Baseline primary pooled attack locations 1 are using locations: laryngeal, an attack involving at least 1 laryngeal location, including the larynx/throat, regardless of other locations involved; abdominal only, an attack with abdomen location only; subcutaneous only, an attack with arms/hands, genitals, legs/feet, head/face/neck, or torso

location(s) only; and abdominal and subcutaneous, an attack with at least 1 abdominal location and at least 1 subcutaneous location
[f] Baseline primary pooled attack locations 2 were using locations: neck and above, an attack involving larynx/throat or head/face/neck location(s), regardless of other locations involved; abdominal, an attack involving abdomen location and not involving larynx/throat or head/face/neck locations, regardless of other locations involved; and other, an attack involving arms/hands, genitals, legs/feet, or torso location(s) only
Sourced from Table 5-4 of the KONFIDENT CSR report (78)

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.4.1. Primary hypothesis and sample size calculations

In the phase 3 KONFIDENT study, the primary hypothesis was that each sebetralstat treatment group would be more effective than placebo for the on-demand treatment of HAE attacks based on a difference in survival distribution of the time to beginning of symptom relief defined by the PGI-C as at least “a little better” for 2 time points in a row within 12 hours of the first IMP (investigational medicinal product) administration versus the null hypothesis that the survival distributions are not different (for each of the sebetralstat treatment groups versus placebo).

Phase 3 KONFIDENT sample size and primary endpoint

A total sample size of approximately 114 patients were to be randomised to ensure approximately 84 patients completed the trial to ensure approximately 84 attacks were treated with placebo, 300 mg sebetralstat, and 600 mg sebetralstat. The trial population comprised 2 subsets: (1) patients who entered the trial taking only conventional on-demand treatment; and (2) patients who entered the trial on a stable dose and regimen of long-term prophylactic treatment. Following screening, 136 patients underwent enrolment in KONFIDENT.(78)

Based on results from the Phase 2 trial (KVD900-201), a sample size of 66 patients completing the trial would provide 90% power for testing each pairwise comparison (sebetralstat versus placebo) at the 2.5% alpha level (2-sided) for the primary endpoint of time to beginning of symptom relief of the HAE attack as defined by PGI-C as at least “a little better” for 2 time points in a row within 12 hours of the first IMP administration.(78)

This sample size was derived using the assumption that median time to symptom relief of the HAE attack is 1.6 hours in active dose arm and 9 hours in placebo arm from the Phase 2 KVD900-201 trial. It was assumed that patients begin the trial together and will be followed for the same period of time, 49% of patients in control group and 17% of patients in sebetralstat treatment group were assumed to be lost-to-follow-up (right-censored). (94)Using conservative approach and simulation-based procedure for power calculations for a parallel group design, the two-sided two-group survival comparison Gehan-Wilcoxon test had approximately 90% power to detect a median time ratio of 5.6 (9/1.6) with a target 2-sided significance level of 2.5% for 66 patients in each treatment group.(78)

Multiplicity Adjustment: Two pairwise comparisons were performed: 300 mg sebetralstat versus placebo and 600 mg sebetralstat versus placebo. All statistical tests were 2-sided with an overall alpha of 0.05. The primary efficacy endpoint analysis and key secondary endpoints had Bonferroni multiplicity adjustment for multiple dose levels with a loop-back feature to allow two-way alpha passing. Within each pairwise comparison, fixed sequence closed testing procedure was followed. The fixed testing procedure was employed first on the primary and then on the key secondary endpoints 1 and 2, separately for each dose comparison to placebo. Specifically, key secondary endpoint 1 was tested only if the test on the primary endpoint was statistically significant. Key secondary endpoint 2 was tested only if the test on the primary and key secondary endpoint 1 were statistically significant. The loop-back feature allowed for retesting of unrejected hypotheses at 0.05 alpha level if all hypotheses were rejected within the other pairwise comparison.(78)

Analysis sets in the KONFIDENT study included:(78)

- **Safety Set:** The Safety Set included all patients who received at least one dose of trial medication. If one or more patient(s) received the incorrect trial medication, data summarised using the Safety Set were presented according to the actual treatment received. The Safety Set was the population for safety analyses.

- **Full Analysis Set**: The FAS included all randomised patients who received trial medication from at least one period for the respective qualifying HAE attack. If

one or more patient(s) received the incorrect trial medication, data summarised using the FAS were presented according to the randomised treatment. The FAS was the population for efficacy analyses.

- **Per-Protocol Set:** The PPS included all randomised patients who received trial medication from at least one period for the respective qualifying HAE attack and who did not have major protocol deviations that could affect the primary efficacy endpoint.

- **On-Demand Full Analysis Set:** The on-demand FAS included FAS patients who entered the trial taking only conventional on-demand treatment.

- **Prophylaxis Full Analysis Set:** The prophylaxis-FAS included FAS patients who entered the trial on a stable dose and regimen of long-term prophylactic treatment.

Final analyses: All efficacy data were summarised by randomised treatment. All efficacy analysis was performed using the FAS and primary and key secondary endpoints analysis was repeated using the PPS. Statistical tests were 2-sided with an overall alpha of 0.05 unless otherwise specified. Treatment comparisons of interest were pairwise comparisons of 300 mg sebetralstat versus placebo and 600 mg sebetralstat versus placebo.

Analysis of Primary Efficacy Endpoint: As mentioned above, the null hypothesis was that there is no difference in survival distribution of the time to beginning of symptom relief defined by the PGI-C as at least “a little better” for 2 time points in a row within 12 hours of the first IMP administration (no difference between each dose of sebetralstat group versus placebo) versus the alternative hypothesis that the survival distributions are different (each of the sebetralstat treatment groups versus placebo).(78)

Analysis of Key Secondary Efficacy Endpoints

The key secondary endpoints in KONFIDENT were tested according to the fixed sequence closed testing procedure.(78)

- **Time to First Incidence of Decrease Within 12 Hours:** Time to first incidence of decrease from baseline on PGI-S for 2 time points in a row (hours) = Date/time of first incidence of decrease of symptom intensity from baseline for 2 time points in a row (with possible missing values in between) – Date/time of first IMP administration. Note: this reflects the time to reduction in severity.

- **Time to HAE attack resolution within 24 hours:** Time to HAE attack resolution (hours) = Date/time of first PGI-S rating of "None"– Date/time of first IMP administration.

Both primary and key secondary endpoints were analysed using Gehan score transformation test. Least-squares means and standard errors were presented by treatment. P-values were calculated for the comparison of each sebetralstat dose group versus placebo, along with the least-square mean treatment difference and corresponding 95% CI were presented. Additionally, adjusted p-values for each pairwise comparison was also presented with Bonferroni adjustment allowing alpha loop-back. The number and percentage of attacks that met both endpoints and the number censored were presented by treatment. Kaplan-Meier estimates of the 25th percentile (Q1), the median, and the 75th percentile (Q3) and corresponding 95% CI were presented by treatment. Kaplan-Meier survival curves were presented by treatment.

Secondary endpoints (non-key)

A list of non-key secondary endpoints in the KONFIDENT study (their measurements and timepoints) include:

- PGI-C: Number and percentage of attacks with beginning of symptom relief defined as at least "a little better" (2 time points in a row) within 2, 4, 6, 8, 10, 12, 24, and 48 hours of the first IMP administration.

- PGI-C: Time to at least "better" (2 time points in a row) within 12 and 24 hours of the first IMP administration.

- Time to either (1) first incidence of PGI-C being rated ‘a little worse’ or lower for two time points in a row, or (2) use of conventional attack treatment, whichever comes first within 12 hours and 24 hours. Time to conventional attack treatment use (h) = Date/time of first conventional attack treatment use – Date/time of IMP administration.

- PGI-S: Time to first incidence of decrease from baseline (2 time points in a row) within 24 hours of the first IMP administration.

- Time to either (1) first incidence of worsening in attack severity on the PGI-S by one level or more from baseline for two time points in a row, or (2) use of conventional attack treatment, whichever comes first within 12 hours and 24 hours.

- PGI-S: Time to HAE attack resolution defined as “none” within 48 hours.

- Time to first incidence of conventional attack treatment use within 12 hours and 24 hours. Time to first incidence of conventional attack treatment use (hours) = Date/time of first incidence of conventional attack treatment use – Date/time of first IMP administration.

- Time to the second IMP administration within 12 hours and 24 hours. Time to the second IMP administration (hours) = Date/time of the second IMP administration – Date/time of first IMP administration.

- Number and percentage of attacks receiving second IMP administration within 4, 8, 12, 24, and 48 hours of the first IMP administration.

- Composite VAS: Time to at least a 50% decrease from baseline (3 time points in a row) within 12 hours and within 24 hours of IMP administration. The Gehan scores transformation statistics and p-value were provided for exploratory purposes for these endpoints. Kaplan-Meier estimates of the 25th percentile (Q1), the median, and the 75th percentile (Q3) and corresponding 95% CI were presented by treatment. Kaplan-Meier survival curves were presented by treatment.

Subgroup Analyses: Subgroup analyses of the primary and key secondary efficacy endpoints were performed by sex (if provided), race, age group, prophylactic treatment status, region, type of HAE, baseline primary attack location, attack severity at baseline based on PGI-S, number of doses received, and time from onset of attack to the first IMP administration. Frequencies and survival estimates were presented for each subgroup. P-values were added for exploratory purposes. The examination of primary and key secondary endpoints, utilising both the on-demand FAS and the prophylaxis-FAS, is the same as the subgroup analyses comparing the 'On-Demand' subgroup with the 'On Prophylactic Treatment' subgroup.

2.5 Critical appraisal of the relevant clinical effectiveness evidence

A clinical systematic literature review (SLR) was conducted to identify studies (sebetralstat and comparator studies) relevant to this appraisal. An overview of the methodology, search strategies, included studies identified and excluded studies is available in Appendix B. In the absence of direct trials comparing sebetralstat with the comparators in this decision problem, an ITC was considered by the company. However, due to heterogeneity between trials (patient populations and definition of outcomes) an ITC was not feasible for utilisation in the cost-effectiveness model. Of note, an ITC was conducted by the company. [Please see section 2.10 ‘Indirect and mixed treatment comparison’ for more details]

Table 8 shows a summary of the quality assessment results for the sebetralstat studies (KONFIDENT Phase 3 study and KONFIDENT-S open-label study), that are used in the economic model. Fuller details of the complete quality assessment are provided in Appendix B.

Table 8 Quality assessment results for sebetralstat trials used in the model

Trial number (acronym)	**KONFIDENT [Phase 3 KVD900-301 study; NCT05259917]**	**KONFIDENT-S [KVD900-302 open-label extension study; NCT05505916]**
Was randomisation carried out appropriately?	Y	Y
Was the concealment of treatment allocation adequate?	Y	Y

Trial number (acronym)	KONFIDENT [Phase 3 KVD900-301 study; NCT05259917]	KONFIDENT-S [KVD900-302 open-label extension study; NCT05505916]
Were the groups similar at the outset of the study in terms of prognostic factors?	Y	Y
Were the care providers, participants and outcome assessors blind to treatment allocation?	Y	N
Were there any unexpected imbalances in drop-outs between groups?	N	N
Is there any evidence to suggest that the authors measured more outcomes than they reported?	N	N
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Y	Y

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

KONFIDENT Phase 3 study limitations

Limitations of the KONFIDENT study include the potential effect of increasingly extended intervals between assessments after the first 4 hours of data collection for each attack, which may have led to the delayed capture of data on participant-reported outcomes. Investigational agents that have shown efficacy as long-term prophylaxis in patients with HAE were excluded.(80)

Approximately 19% of the participants who underwent randomisation were not included in the safety or efficacy analyses because they did not have an eligible attack during the trial. However, an intention-to-treat analysis that used imputed data for these excluded participants showed results similar to those for the full analysis population.(80)

2.6 Clinical effectiveness results of the relevant studies

Phase 3 KONFIDENT – Primary Efficacy Results

The analysis of time to the beginning of symptom relief defined as at least "a little better" (2 time points in a row) on the PGI-C within 12 hours of the first IMP treatment administration using the Gehan score transformation test for the FAS population set is presented in Table 9.

There was a statistically significant improvement in the time to the beginning of symptom relief between 300 mg sebetralstat (adjusted p<0.0001) versus placebo group and between 600 mg sebetralstat (adjusted P=0.0013) versus placebo group. The median (95% CI) time to the beginning of symptom relief was 1.61 hours (95% CI: 1.28, 2.27) for 300 mg sebetralstat group, 1.79 hours (95% CI: 1.33, 2.27) for 600 mg sebetralstat group, and 6.72 hours (95% CI: 2.33, not evaluable) for placebo group.(80)

More attacks reached beginning of symptom relief within 12 hours of first IMP administration in the sebetralstat treatment groups than placebo group (300 mg sebetralstat group: 66 [75.9%] attacks and 600 mg sebetralstat group: 71 [76.3%] attacks versus placebo group: 41 [48.8%] attacks).(94)

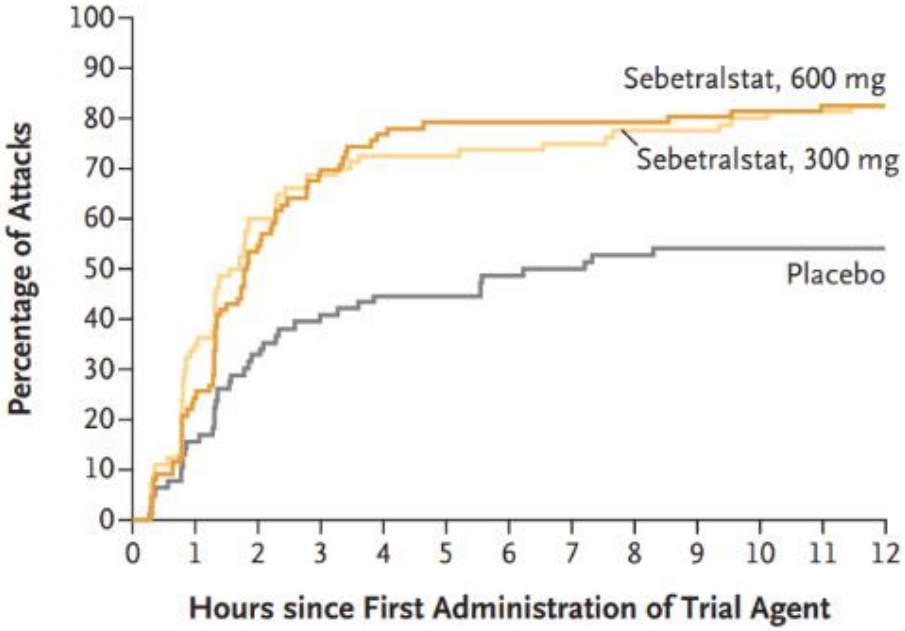
Table 9 KONFIDENT Phase 3 - Primary endpoint results

	Sebetralstat 300 mg (N = 87)	**Sebetralstat 600 mg (N = 93)**	**Placebo (N = 84)**
Time to beginning of symptom relief within 12 hours (primary)*			
Participants: no. (%)			
Events	66 (75.9)	71 (76.3)	41 (48.8)
Censored	21 (24.1)	22 (23.7)	43 (51.2)
Censored at hour 0 due to underivable end point	7 (8.0)	7 (7.5)	8 (9.5) –
Adjusted P value compared with placebo	<0.001	0.001	6.72 (1.34->12)
Median (IQR)	1.61 (0.78-7.04)	1.79 (1.02-3.79)	

IQR denotes interquartile range.
*Defined as a rating of at least “A Little Better” on the Patient Global Impression of Change scale for two or more consecutive time points.
Source: Riedl *et al.* (2024) (Table S4 of the supplementary appendix)(94)

The Kaplan-Meier plot for the time to beginning of symptom relief on PGI-C within 12 hours is presented in Figure 4 below. More attacks reached the beginning of symptom relief in the 300 mg sebetralstat and 600 mg sebetralstat treatment groups than placebo group.

Figure 4 Primary endpoint. Kaplan-Meier plot for Time to Beginning of Symptom Relief Within 12 Hours (Full Analysis Set)



No. of Attacks													
Sebetralstat, 600 mg	93	65	39	26	20	18	18	18	18	17	16	15	15
Sebetralstat, 300 mg	87	52	32	25	22	22	21	20	18	18	16	15	14
Placebo	84	64	51	45	42	42	39	38	36	35	35	35	35

Time to beginning of symptom relief (primary end point) 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 scale (ratings range from “much better” to “much worse”) at two or more consecutive time points within 12 hours after the first ad-ministration of sebetralstat or placebo.
Source: Riedl *et al.* (2024)(80)

Key Secondary Efficacy Results

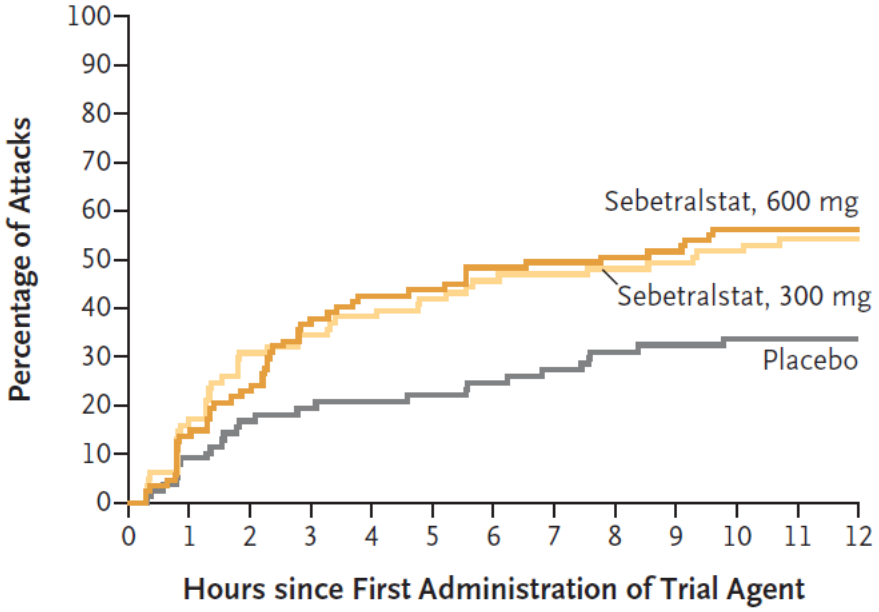
KONFIDENT Phase 3 – key secondary efficacy results

Time to the first incidence of decrease from baseline for 2 time points in a row on PGI-S within 12 hours of the first IMP administration (i.e. time to reduction in severity) for FAS is presented in Table 10 below and in Figure 5. A reduction in attack severity (within 12 hours after the first administration) was reached faster than placebo with the 300 mg dose (P=0.004) and the 600 mg sebetralstat dose (P=0.003). Furthermore,

the median time to a reduction in severity with the 300 mg dose was 9.27 hours (interquartile range, 1.53 to >12), 7.75 hours (2.19 to >12) with the 600 mg dose, and over 12 hours (6.23 to >12) with placebo. (80)

More attacks achieved the time to reduction in severity within 12 hours in the 300 mg sebetralstat (44 [50.6%] attacks) and 600 mg sebetralstat groups (49 [52.7%] attacks) than placebo group (26 [31.0%] attacks).(94) The baseline PGI-S score ($p<0.0001$), which was controlled for in the mixed model showed significant impact on time to first incidence of decrease on PGI-S (i.e. time to reduction in severity) (Table 10).(80, 94)

Figure 5 KONFIDENT Phase 2 key secondary endpoint results: Reduction in severity of attack



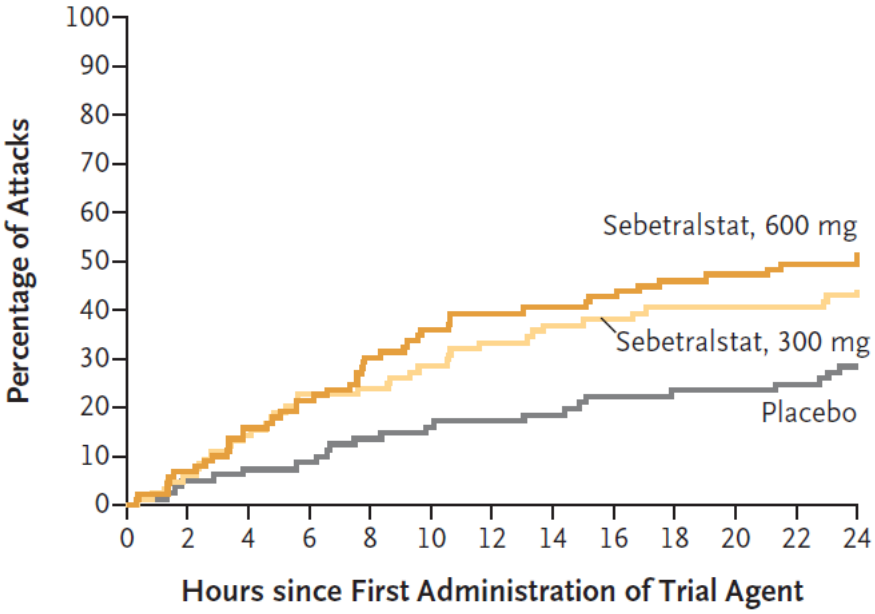
No. of Attacks													
Sebetralstat, 600 mg	93	75	67	54	50	49	45	44	43	42	38	38	38
Sebetralstat, 300 mg	87	67	56	53	50	47	44	43	42	41	39	37	37
Placebo	84	70	64	62	61	60	58	56	53	52	51	51	51

Key secondary end point assessment 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
Source: Riedl *et al.* (2024)(80)

Complete resolution of the attack was also reached faster with the 300 mg dose and the 600 mg dose than with placebo (P=0.002 and P<0.001, respectively) (Figure 6). Furthermore, complete resolution of attacks within 24 hours of the first administration

occurred in 42.5% of attacks for the 300 mg sebetralstat group, 49.5% of attacks for the 600 mg group, and 27.4% of attacks for those receiving placebo.(80)

Figure 6 KONFIDENT Phase 3 key secondary endpoint: Complete resolution of the attack



No. of Attacks													
Sebetralstat, 600 mg	93	83	75	70	62	57	54	53	51	48	47	45	45
Sebetralstat, 300 mg	87	79	72	65	64	60	56	53	52	50	50	50	48
Placebo	84	77	75	74	70	68	67	66	63	62	62	61	58

Key secondary end point assessment for complete resolution of the attack, defined as a rating of “none” on the PGI-S scale within 24 hours after the first administration
Source: Riedl *et al.* (2024)(80)

Table 10 KONFIDENT Phase 3 – Key secondary endpoint results

	Sebetralstat 300 mg (N = 87)	**Sebetralstat 600 mg (N = 93)**	**Placebo (N = 84)**
Time to reduction in the severity of attack within 12 hours (key secondary)†			
Participants: no. (%)			
Events	44 (50.6)	49 (52.7)	26 (31.0)
Censored	43 (49.4)	44 (47.3)	58 (69.0)
Censored at hour 0 due to underivable end point	6 (6.9)	6 (6.5)	7 (8.3) –
Adjusted P value compared with placebo	0.004	0.003	
Median (IQR)	9.27 (1.53->12)	7.75 (2.19->12)	>12 (6.23->12)
Time to complete resolution of the attack within 24 hours (key secondary)‡			
Participants: no. (%)			
Events	37 (42.5)	46 (49.5)	23 (27.4)
Censored	50 (57.5)	47 (50.5)	61 (72.6)
Censored at hour 0 due to underivable end point	3 (3.4)	4 (4.3)	3 (3.6) –
Adjusted P value compared with placebo	0.002	<0.001	
Median (IQR)	>24 (8.58->24)	24.00 (7.54->24)	>24 (22.78->24)

IQR denotes interquartile range.
†Defined as an improved rating from baseline in Patient Global Impression of Severity for two or more consecutive time points.
‡Defined as a Patient Global Impression of Severity rating of “None”.
Source: Riedl *et al.* (2024) (Table S4 of the supplementary appendix)(94)

Other secondary endpoints results (non-key secondary endpoints)

As stated in Section 2.4, the KONFIDENT study comprised additional (non-key) secondary endpoints. These secondary endpoint results also demonstrating improvement across a range of endpoints for patients treated with sebetralstat compared to placebo. These secondary endpoint findings are summarised in Table 11 below.

There was a statistically significant difference in the time to at least “better” on PGI-C between 300 mg sebetralstat (nominal P<0.0001) versus placebo group and 600 mg sebetralstat (nominal P<0.0001) versus placebo group. The median (95% CI) time to at least "better" was [redacted] hours (95% CI: [redacted]) for 300 mg sebetralstat group, [redacted] hours (95% CI: [redacted]) for 600 mg sebetralstat group, and [redacted] for placebo within 12 hours and [redacted] hours (95% CI: [redacted]) for 300 mg sebetralstat group, [redacted] hours (95% CI: [redacted]) for 600 mg sebetralstat group, and not evaluable (95% CI: [redacted]) for placebo group within 24 hours. More attacks reached time to at least "better" on the PGI-C within 12 and 24 hours of first IMP administration in the sebetralstat 300 mg and 600 mg sebetralstat treatment groups than placebo group.(78)

Regarding time to first incidence of PGI-C being rated “a little worse” or lower or use of conventional attack treatment within 12 and 24 hours for FAS, Time to worsening was reached slower with 300 mg sebetralstat (nominal P=[redacted] [12 hours], nominal [redacted] [24 hours]) and 600 mg KVD900 (nominal [redacted] [12 and 24 hours]) groups than placebo group. The median time to worsening was not evaluable for 300 mg sebetralstat and 600 mg sebetralstat treatment groups within 12 and 24 hours, and not evaluable (95% CI[redacted]) within 12 hours and not evaluable (95% CI[redacted]) within 24 hours for placebo group. More attacks in the placebo group experienced worsening within 12 and 24 hours of first IMP administration than 300 or 600 mg sebetralstat treatment groups.(78)

There was statistically significant difference in time to reduction in severity between 300 mg sebetralstat (nominal [redacted] versus placebo group, and 600 mg sebetralstat (nominal [redacted]) group versus placebo group when reviewing the PGI-S results relating to time to first incidence of decrease from baseline at 2 time points

in a row within 24 hours of the first IMP administration. The median (95% CI) time to reduction in severity was [redacted] hours (95% CI: [redacted]) for 300 mg sebetralstat group, [redacted] hours (95% CI: [redacted]) for 600 mg sebetralstat group, and [redacted] (95% CI: [redacted]) for placebo group. More attacks achieved the time to reduction in severity within 24 hours in the 300 mg sebetralstat ([redacted]%] attacks) and 600 mg sebetralstat groups ([redacted] attacks) than placebo group ([redacted]%] attacks).(78)

For PGI-S, time to HAE attack resolution defined as “none” within 48 hours of the first IMP administration, there was a statistically significant difference in the time to complete attack resolution between 300 mg sebetralstat (nominal [redacted] versus placebo group, and 600 mg sebetralstat (nominal [redacted]) groups versus placebo group. The median (95% CI) time to complete HAE attack resolution was [redacted] (95%CI: [redacted]) for 300 mg sebetralstat group, [redacted] hours (95% CI: [redacted]) for 600 mg sebetralstat group, and [redacted] (95% CI: [redacted]) for placebo group. More attacks reached complete attack resolution within 48 hours in the 300 mg sebetralstat ([redacted] [redacted]%] attacks) and 600 mg sebetralstat groups ([redacted]%] attacks) than placebo group ([redacted] [redacted]%] attacks).(78)

Regarding time to the first incidence of worsening in attack severity on the PGI-S or use of conventional attack treatment within 12 and 24 hours for FAS, this was reached more slowly with 300 mg sebetralstat (nominal p=[redacted] [12 hours], nominal [redacted] [24 hours]) and 600 mg sebetralstat (nominal p<[redacted] [12 hours] and nominal p<[redacted] [24 hours]) groups than placebo group. The median time to the first incidence of worsening on PGI-S or use of conventional attack treatment was [redacted] for the 300 mg sebetralstat and 600 mg sebetralstat treatment groups; and [redacted](95% CI: [redacted]) within 12 hours and [redacted](95% CI: [redacted]) within 24 hours for placebo group. The proportion of attacks reaching first incidence of worsening in attack severity on the PGI- S or use of conventional attack treatment within 12 and 24 hours was [redacted] in the 300 mg sebetralstat group ([redacted] [redacted]%] attacks within 12 hours and [redacted] attacks within 24 hours) and 600 mg Sebetralstat group ([redacted]%] attacks within 12 hours and [redacted]%] attacks within 24 hours) than placebo group ([redacted] attacks within 12 hours and [redacted]%] attacks within 24 hours).(78)

The number of attacks with first incidence of conventional attack treatment use within 12 and 24 hours was lower in the 300 mg sebetralstat group ([redacted]%] patients within 12 hours and [redacted]%] patients within 24 hours) and 600 mg sebetralstat group ([redacted]%] patients within 12 hours and [redacted]%] patients within 24 hours) than placebo group ([redacted]%] patients within 12 hours and [redacted]%] patients within 24 hours).(78)

Regarding time to the second IMP administration within 12 and 24 hours for FAS, the number of attacks with first incidence of second IMP administration within 12 and 24 hours was lower in the 300 mg sebetralstat group ([redacted]%] patients within 12 hours and [redacted]%] patients within 24 hours) and 600 mg sebetralstat group ([redacted]%] patients within 12 hours and [redacted]%] patients within 24 hours) compared to placebo ([redacted]%] patients within 12 hours and [redacted] patients within 24 hours).(78)

Finally, for the composite VAS endpoint, there was a statistically significant difference in the time to at least a 50% decrease on the composite VAS from baseline between 300 mg sebetralstat (nominal P=[redacted] [12 hours], nominal P=[redacted] [24 hours]) versus placebo group and 600 mg sebetralstat (nominal p=[redacted] [12 hours], nominal [redacted] [24 hours]) groups versus placebo group. The median time (95% CI) to at least a 50% decrease on composite VAS from baseline was [redacted] hours ([redacted]) within 12 hours and [redacted] hours [redacted] within 24 hours for 300 mg sebetralstat group, [redacted] hours ([redacted]) within 12 hours and [redacted] hours ([redacted]) within 24 hours for 600 mg sebetralstat group and [redacted] for placebo group. The number of attacks with time to at least a 50% decrease on composite VAS from baseline within 12 and 24 hours was higher in the 300 mg sebetralstat group ([redacted] [redacted]%] attacks within 12 hours and [redacted] [redacted]%] attacks within 24 hours) and 600 mg sebetralstat group ([redacted] [redacted]%] attacks within 12 hours and [redacted] [redacted]%] attacks within 24 hours) than placebo group ([redacted] [redacted]%] attacks within 12 hours and [redacted] [redacted]%] attacks within 24 hours).(78)

Table 11 Linear Mixed Model of Gehan score and Kaplan-Meier estimates for other secondary endpoints within 12 and 24 hours (Full analysis set)

		300 mg sebetralstat			600 mg sebetralstat			Placebo
Endpoint	Number of patient Events[a]	Median (95% CI)	Nominal p-value (sebetralstat	Number of patients Events[a]	Median (95% CI)	Nominal p-value (sebetralstat versus	Number of patients Events[a]	Median (95% CI)

			versus placebo)			placebo)		
n	87			93			84	
Time to at Least "better" on PGI-C Within 12 and 24 hours								
Within 12 hours	[redacted]							
Within 24 hours	[redacted]							
Time to First Incidence of PGI-C Being Rated 'a Little Worse' or Lower or Use of Conventional Attack Treatment Within 12 and 24 hours								
Within 12 hours	[redacted]							
Within 24 hours	[redacted]							
Time to First Incidence of Decrease on PGI-S Within 24 hours								
Within 24 hours	[redacted]							
Time to HAE Attack Resolution on PGI-S Within 48 hours								
Within 48 hours	[redacted]							
Time to First Incidence of Worsening in Attack Severity on the PGI-S or Use of Conventional Attack Treatment Within 12 and 24 hours								
Within 12 hours	[redacted]							
Within 24 hours	[redacted]							

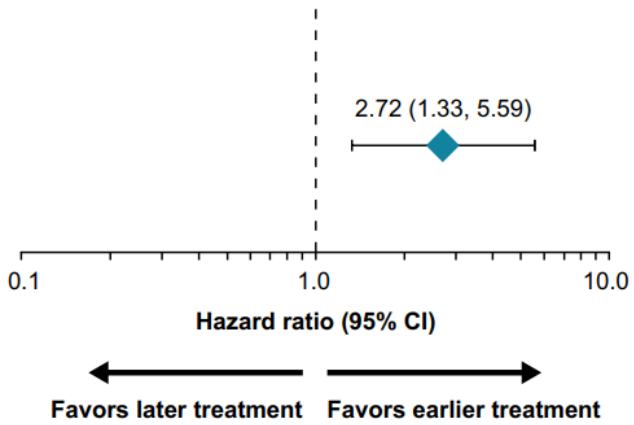
Notes: n is number of IMP-treated HAE attacks. The number of IMP-treated HAE attacks is equivalent to the number of patients in each group. Time to at least better at 2 time points in a row (hours) = date/time of first rating of "better" or higher immediately followed by another rating of "better" or higher (with possible missing values in between) – date/time of first IMP administration.
Time to first incidence of symptom decrease from baseline at 2 consecutive time points (hours) = date/time of first incidence of decrease from baseline for 2 time points in a row (with possible missing values in between) – date/time of first IMP administration.
Time to HAE attack resolution (hours) = date/time of first rating of "none"– date/time of first IMP administration.
Time to first incidence of worsening in attack severity by 1 level or more from baseline on the PGI-S for 2 time points in a row (hours) = date/time of first incidence of increase from baseline on the PGI-S for 2 time points in a row (with possible missing values in between) – date/time of first IMP administration.
Source: Table 6-7 of the KONFIDENT CSR report. (78)

Additional analyses of interest

Time to treatment correlation: earlier sebetralstat treatment associated with improved outcomes

Additional analysis of the KONFIDENT phase 3 trial includes a correlation of the time to treatment with attack duration. Analysis showed the probability for shorter attack duration was higher when attacks were treated earlier versus later in KONFIDENT (Figure 7).

Figure 7 Probability for Faster Complete Attack Resolution



H, hours; HR, Hazard ratio; IQR, interquartile range.
Source: Craig *et al.* 2024 (73)

When modelled as a continuous variable, the relationship between time to treatment and time to complete attack resolution was 0.88 (95% CI, 0.79-0.97).(73)

Table 12 Characteristics of sebetralstat-treated attacks

	"Earlier" n=45	"Later" n=44
Baseline PGI-S category, n (%)[a,b]		
Mild	28 (50.9)	11 (25.0)
Moderate	15 (27.3)	25 (56.8)
Severe/very severe	11 (20.0)	8 (18.2)
Baseline pooled attack location, n (%) [a,c,d]		
Mucosal	23 (41.8)	17 (38.6)
Larynx/throat	2 (3.6)	2 (4.5)

Subcutaneous	43 (78.2)	35 (79.5)

PGI-S, Patient Global Impression of Severity.
[a] Participants who had multiple attack locations were counted once in each reported location.
[b] None, n (%) = 0 earlier, 1 (1.3) later; Missing, n (%) = 1 (1.8) earlier, 0 later.
[c] All attack locations and severities were included in KONFIDENT except for laryngeal attacks that were considered severe at baseline.
[d] Missing, n (%) = 1 (1.8) earlier, 0 later.
Source: Craig *et al.* 2024 (73)

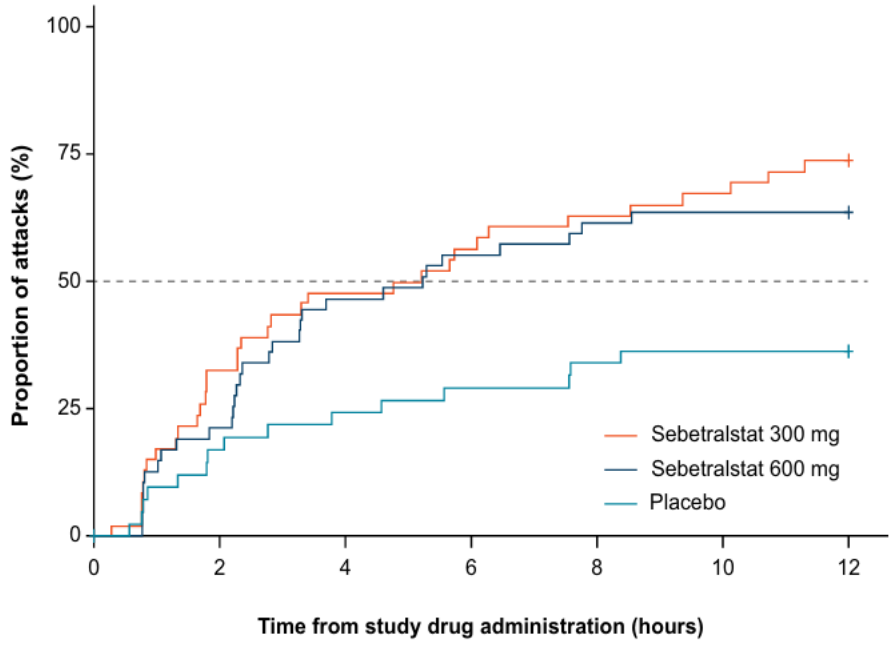
The largest proportion of sebetralstat-treated attacks treated “earlier” were mild at baseline, whereas the largest proportion of attacks treated “later” were moderate at baseline (Table 12).

Overall, this analysis showed that in KONFIDENT, attacks that were treated earlier were more likely to be mild than attacks treated later. Furthermore, complete attack resolution was reached faster (HR: 2.72 [1.33, 5.59]) in attacks that were treated "earlier" with sebetralstat compared with those that were treated "later" (at a time similar to parenteral on-demand treatments) (Figure 7).

Impact of sebetralstat on attacks that had progressed in severity prior to treatment

The benefit of treating HAE attacks early has already been demonstrated by icatibant (45) and the importance of treating HAE attacks early is advocated by WAO/EAACI clinical guidelines. Of interest, a post-hoc analysis with sebetralstat further validates the importance of treating early. In this post-hoc analysis, time to substantial reduction of symptom burden within 12 hours was defined as the duration until the PGI-S rating decreased to ‘mild’ for two consecutive assessments. The analysis shows that for attacks rated "Moderate" or worse at baseline, the median time to achieve this reduction was 5.0 hours for sebetralstat 300 mg (P=0.002) and 5.2 hours for sebetralstat 600 mg (P=0.034), compared to over 12 hours for placebo.(95)

Figure 8 Time to PGI-S Rating of "Mild" for Attacks Rated "Moderate" or Worse at Baseline



Abbreviations: PGI-S, Patient Global Impression of Severity.
Source: Lumry *et al.* (2024) (95)

Within 24 hours, 75.5% of participants receiving sebetralstat 300 mg and 67.3% receiving 600 mg experienced a substantial reduction in symptom burden, versus 54.3% with placebo. These findings suggest that sebetralstat provides a faster and more significant reduction in symptom burden for HAE attacks compared to placebo.(95) Thus, sebetralstat oral treatment offers a paradigm shift for early treatment in HAE with the potential for real clinical benefit.

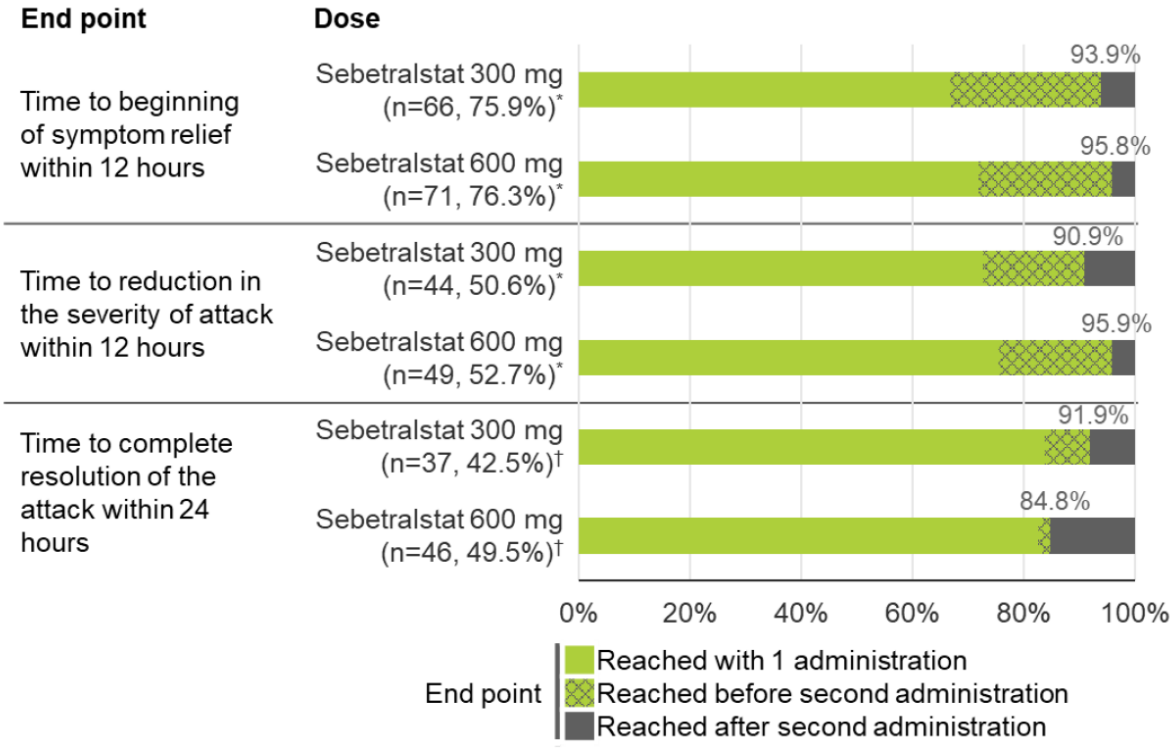
Achievement of endpoint before versus after second IMP dose in FAS

As mentioned previously, KONFIDENT trial subjects were asked to self-administer a single dose of 300 mg sebetralstat (1 × 300 mg sebetralstat tablet plus 1 placebo tablet), 600 mg sebetralstat (2 × 300 mg sebetralstat tablets), or 2 matching placebo tablets in response to each eligible attack of HAE. If needed (as determined by the subject), after at least 3 hours, a second dose of IMP may have been administered for each attack. The second dose of IMP matched the initial dose administered.

The option for subjects to take a second dose of IMP for an attack, as determined by themselves, may have an impact on the levels of sebetralstat additional dosing in the trials.

Of interest, ad-hoc efficacy analyses were performed to explore the achievement of endpoints before versus after a second IMP dose. The published KONFIDENT manuscript by Riedl *et al.* 2024, reports that in more than 90% of the attacks in which the beginning of symptom relief (primary endpoint) occurred with the 300 mg or 600 mg dose, relief occurred without a second administration or before a second administration (see Figure 4 for the proportion of attacks reaching primary or key secondary endpoints with 1 or 2 administrations of sebetralstat).(80)

Figure 9 Proportion of Attacks Reaching Primary or Key Secondary End Points with 1 or 2 Administrations of Sebetralstat



*Proportion of attacks reaching end point within 12 hours
†Proportion of attacks reaching end point within 24 hours
Source: Figure S4. Riedl 2024 supplementary appendix.(94)

Furthermore Table 13 below presents the summary of attacks achieving the key secondary endpoint 2 ["PGI-S: Time to HAE attack resolution defined as "none" within 24 hours of the first IMP administration" (i.e. time to reduction in severity)].

Table 13 Summary of attacks achieving key secondary endpoint 2 by treatment and dose (FAS)

	Sebetralstat 300 mg	Sebetralstat 600mg	Sebetralstat 300 mg + 600 mg	Placebo
Total number of attacks	[redacted]	[redacted]	[redacted]	[redacted]
Total achieving key secondary endpoint #2 (KSE2)	[redacted]	[redacted]	[redacted]	[redacted]
Achieve KSE2 with 1 dose or before 2nd IMP	[redacted]	[redacted]	[redacted]	[redacted]
1 dose	[redacted]	[redacted]	[redacted]	[redacted]
Before 2nd IMP	[redacted]	[redacted]	[redacted]	[redacted]
Achieve KSE2 on or after 2nd IMP	[redacted]	[redacted]	[redacted]	[redacted]

IMP: investigational medicinal product
KSE2: key secondary endpoint #2 [PGI-S: Time to HAE attack resolution defined as "none" within 24 hours of the first IMP administration]
Source: KONFIDENT CSR report 2024; Table A301-13.3. (78)

Table 13 shows that the majority of attacks reached the key secondary endpoint 2 following with 1 dose or before 2nd IMP ([redacted]%) with only a smaller proportion ([redacted]%) achieving the key secondary endpoint 2 on or after 2nd IMP. This demonstrates that the majority of subjects can achieve attack resolution without the need for a second dose of sebetralstat.

2.7 Subsequent treatments used in the relevant studies

Not applicable.

2.8 Subgroup analysis

KONFIDENT Phase 3 Subgroup analyses

Subgroup analyses of the primary and key secondary efficacy endpoints were performed by sex (if provided), race, age group, prophylactic treatment status, region,

type of HAE, baseline primary attack location, attack severity at baseline based on PGI-S, number of doses received, and time from onset of attack to the first IMP administration. Frequencies and survival estimates were presented for each subgroup. P-values were added for exploratory purposes.

The primary and key secondary results (by subgroup) according to attack characteristics (**Error! Reference source not found.**) and participant characteristics (**Error! Reference source not found.**) suggested that the treatment effects of sebetralstat at doses of 300 mg and 600 mg were consistent with the results in the overall trial population, across subgroups defined according to age, use of long-term prophylactic treatment, and geographic region. The consistency of the effect was also observed in attacks of varying severity and anatomic location (mucosal or subcutaneous). However, a subgroup analysis of laryngeal attacks at baseline was not feasible because only eight of these attacks occurred. Several laryngeal attacks were censored because of missing data, which further reduced the number available for analysis.(80)

Results of analyses of the intention-to-treat population (with the use of imputation) and analyses of attacks in which data were censored because the participant administered a second dose of the trial agent or conventional treatment suggested that the clinical benefits of sebetralstat were consistent with the results of the primary analysis. (see **Error! Reference source not found.** and **Error! Reference source not found.** in Appendix C).

As with the results for the overall population FAS, subgroup results for each sebetralstat dose level were similar and were consistent across all subgroups analysed. Please see Appendix C for subgroup analysis results.

2.9 Meta-analysis

Not applicable.

2.10 Indirect and mixed treatment comparisons

In Appendix B we have included a write up of the SLR to identify clinical studies relevant to this appraisal.

Summary of comparative effectiveness

Indirect comparisons of on-demand treatments have been challenging due to the heterogeneity in trial designs and outcomes. In Appendix L, we provide a summary overview of a recently published ITC with the objective of demonstrating the **method-of-administration** comparability between an **oral** on-demand treatment with an **intravenous** treatment.(96, 97)

- ITC was based on the primary endpoint ('time to beginning of symptom relief') and safety outcomes, between oral sebetralstat and intravenous rhC1-INH.
- ITC found no significant differences in time to beginning of symptom relief and overall treatment-related adverse events between sebetralstat and IV rhC1-INH. Although this ITC does **not** inform the economic analyses, it has been included in Appendix L for completeness.

In the absence of robust and feasible ITC to capture comparative effectiveness between sebetralstat and its comparators for utilisation in the cost-effectiveness model [developed for the purpose of this sebetralstat appraisal (see Section 3)]; the cost-effectiveness model considers that earlier on-demand treatment administration is associated with a shorter total attack duration.

- To alleviate the absence of direct or indirect evidence, the cohort State-Transition Model (cSTM) incorporates a statistical sub-model to estimate the effect moderation of TTA (time to treatment administration) on TTAR, to obtain an adjusted TTAR (time to attack resolution) for each treatment.

Background to the design of the KONFIDENT study and previous on-demand HAE studies

The design of the sebetralstat KONFIDENT phase 3 study had evolved to reflect the considerable recent changes in treatment guidelines and real-world clinical practice. This means that the KONFIDENT study design is current in terms of considering the HAE on-demand patient population examined, the timing of treatment administration, and efficacy endpoints. The phase 3 trials of previous on-demand treatments undertaken in the early 2000s were limited to individuals presenting with moderate to severe attacks.(77, 85, 90, 91, 98, 99) One exception to note was the FAST-3 trial of icatibant, which permitted enrollment of patients experiencing mild to moderate laryngeal attacks; attacks in other locations were required to be of moderate to severe intensity.(100) It was not until the KONFIDENT trial evaluating sebetralstat that patients with attacks of any severity in any location (except for severe laryngeal attacks) were eligible for participation.

As for the timing of treatment, all currently approved on-demand treatments were originally studied using HCP administration. This is reflected in the designs of their pivotal trials, which required patients to report to healthcare professionals within 4 to 12 hours of attack onset or of attacks becoming moderate to severe in intensity.

The only pivotal trial of a currently approved on-demand treatment to report on time to treatment was FAST-3 (median, 6.5 hours).(45) In contrast, the KONFIDENT study directed patients to self-administer oral treatment (sebetralstat) early after attack onset. The median time to treatment in KONFIDENT was 41 minutes.(80)

Evaluation of the clinical efficacy of on-demand treatments relies on patient-reported outcomes. However, there are no standard patient-reported outcome measures for HAE attacks. Consequently, several endpoints have been analysed. In the earliest phase 3 trials, patients were simply asked to inform investigators of when (or were asked at predefined intervals whether) their symptoms began to improve and/or had resolved completely. Such questions lacked granularity and prevented more nuanced assessments of treatment effect.(101) This began to change with the pivotal phase 3 trials of icatibant, which relied on VAS scores to evaluate treatment response (85, 100) and treatment effect questionnaire (TEQ) was used in a phase 3 trial of rhC1INH.(102)

Of note, sebetralstat's KONFIDENT trial and the ongoing RAPIDe-3 trial of investigational deucrictibant use the PGI-C and PGI-S to evaluate treatment

response.(80, 103) Unfortunately, because of differences in attack characteristics (e.g. location and severity), timing of treatment administration (early vs. within 4-12 hours of attack onset/moderate to severe intensity), and efficacy evaluations, cross-trial comparisons of the different approved/investigational on-demand treatments have not been feasible to date; however, contemporary trial designs may allow comparisons in the future.(101)

Other attempts at indirect comparison of on-demand treatments

Indirect comparisons of on-demand treatments have been challenging due to the heterogeneity in trial designs and outcomes. Indeed, results of a systematic review of 13 on-demand treatment trials revealed the use of 72 different standardised efficacy outcome terms, none of which was reported consistently across all trials.(104)

An attempt was made by Bork *et al.* (2016) to conduct an ITC of on-demand treatments for laryngeal attacks, however due to the heterogeneity in efficacy endpoints, the researchers were ultimately able to undertake only a descriptive comparison.(105) To the company's knowledge, a poster by Helbert *et al.* 2012 was the only publication that attempted to compare all on-demand treatments based on phase 3 trial data, which unfortunately contained limited information on study methodology and was not peer reviewed.(106) The included studies were not adequately discussed and appraised in terms of comparability of study designs, population and disease characteristics, endpoints, attack eligibility criteria and outcome measures used. Furthermore, using the median HR as a summary for all comparisons is misleading and difficult to interpret. Due to the potential for significant heterogeneity between the studies, therapeutic superiority or equivalence between Icatibant and other on-demand injectables, including Ruconest, cannot be confirmed, and a major advantage of sebetralstat cannot be conclusively established.

Despite the clear challenges with heterogeneity in trial designs and outcomes, the company conducted the ITC based on this single efficacy endpoint (time to beginning of symptom relief) for the primary purpose of assessing the method-of-administration comparability of an oral on-demand treatment with an intravenous treatment. This

study is yet to be published as a manuscript but summary findings have been presented at recent conferences.(96, 97) Despite matching for attack severity, the large difference in severity of the attacks remains a significant confounder of treatment efficacy and does not allow for a robust comparison of efficacy. That said, the ITC results suggest that there is no significant difference in time to beginning of symptom relief and overall treatment-related adverse events between sebetralstat and IV-rhC1-INH.

For the purposes of this sebetralstat HTA, the outcome of interest is time to attack resolution (TTAR). An ITC was unable to be conducted to address this outcome. Despite the limited comparative evidence for TTAR, there is, nevertheless, clear evidence that earlier OD treatment administration is associated with a shorter total attack duration. To alleviate the absence of direct or indirect evidence, the cohort State-Transition Model (cSTM) incorporates a statistical sub-model to estimate the effect moderation of TTA on TTAR, to obtain an adjusted TTAR for each treatment. Please see Section 3 for more details related to the cost-effectiveness methods and approach.

For completeness, we have provided a write up of the clinical SLR in Appendix B and also included a brief write up of the ITC (based on the 'time to beginning of symptom relief' and safety outcomes) in Appendix L.

Uncertainties in the indirect and mixed treatment comparisons

Not applicable. An ITC has not been able to capture comparative effectiveness between sebetralstat and its comparators for utilisation in the cost-effectiveness model.

2.11 Adverse reactions

KONFIDENT Phase 3 adverse reactions

The safety profile for sebetralstat was similar to placebo in the Phase 3 KONFIDENT study.

Adverse events (AEs) occurred in 17 of 86 participants (19.8%) who received 300 mg of sebetralstat, in 14 of 93 (15.1%) who received 600 mg, and in 17 of 83 (20.5%) who received placebo (Table 14 and Table 15). Three serious adverse events were reported (all led to hospitalisation); none were related to the trial agent or occurred within 3 days after sebetralstat or placebo was taken. In the 300 mg group, one case of herniated lumbar vertebrae was reported. In the 600 mg group, one case of anisocoria related to lisdexamfetamine use and one case of exacerbation of a hereditary angioedema attack, in which the patient did not take the trial agent, were reported. (See Table 17 for SAE summary table)

Table 14 KONFIDENT Phase 3 safety results

Event	Sebetralstat 300mg (N=86)		Sebetralstat 600mg (N=93)		Placebo (N=83)	
	no. (%)	*no. of events*	*no. (%)*	*no. of events*	*no. (%)*	*no. of events*
Any adverse event						
Overall	17 (19.8)	20	14 (15.1)	18	17 (20.5)	24
Related to trial agent	2 (2.3)	2	3 (3.2)	4	4 (4.8)	5
Any serious adverse event during treatment†						
Overall	1 (1.2)	1	2 (2.2)	2	0	0
Related to trial agent	0	0	0	0	0	0
Any severe adverse event during treatment‡						
Overall	1 (1.2)	1	0	0	0	0
Related to trial agent	0	0	0	0	0	0
Any adverse event within 3 days after an administration						
Overall	5 (5.8)	5	6 (6.5)	6	10 (12.0)	13
Related to trial agent	2 (2.3)	2	2 (2.2)	2	4 (4.8)	5
Any adverse event that led to hospitalisation (78)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event during treatment that led to trial discontinuation	0	0	0	0	0	0
Adverse event during treatment that led to death	0	0	0	0	0	0
Treatment-related adverse events within 3 days after an administration§						
Gastrointestinal disorders						
Dyspepsia	1 (1.2)	1	0	0	0	0
Nausea	0	0	1 (1.1)	1	1 (1.2)	1
General disorders and administration site conditions						
Fatigue	1 (1.2)	1	0	0	0	0
Nervous system disorders						
Headache	0	0	1 (1.1)	1	1 (1.2)	1
Dysgeusia	0	0	0	0	1 (1.2)	1
Reproductive system and breast disorders						
Menstruation irregular	0	0	0	0	1 (1.2)	1
Skin and subcutaneous tissue disorders						

Rash	0	0	0	0	1 (1.2)	1

* Shown are data for 110 participants who administered the indicated dose of sebetralstat or placebo to themselves for at least one angioedema attack.
† Serious adverse events during treatment were defined as any untoward medical occurrence that, at any dose, resulted in death, was life- threatening, resulted in inpatient hospitalization or prolongation of existing hospitalisation, resulted in persistent or substantial disability or incapacity, was a congenital anomaly or birth defect, or was considered to be an important medical event according to medical and scientific judgment. The three serious adverse events during treatment were the only adverse events that resulted in hospitalization.
‡ Severe adverse events during treatment were defined as adverse events of grade 3 in severity as assessed qualitatively by the investigator or as reported by the participant.
§ Treatment-related adverse events are categorized according to Medical Dictionary for Regulatory Activities, version 26.0, system organ class and preferred term.
Source: Riedl *et al.* (2024)(80) and (78)

Table 15 KONFIDENT study: Safety Summary by Number of Administrations

Event – no. (%)	**Sebetralstat**				**Placebo**	
	300 mg (N = 58)	**300 mg + 300 mg (N = 28)**	**600 mg (N = 60)**	**600 mg + 600 mg (N = 34)**	**1 administration (N = 44)**	**2 administrations (N = 39)**
Any adverse event	10 (17.2)	7 (25.0)	7 (11.7)	7 (20.6)	5 (11.4)	12 (30.8)
Treatment-related	2 (3.4)*	0	1 (1.7)*	2 (5.9)*	3 (6.8)*	1 (2.6)*
Serious adverse events during treatment†	1 (1.7)‡	0	2 (3.3)	0	0	0
Treatment-related	0	0	0	0	0	0
Severe adverse events during treatment§	1 (1.7)‡	0	0	0	0	0
Treatment-related	0	0	0	0	0	0
Adverse event during treatment that led to study discontinuation	0	0	0	0	0	0
Adverse event during treatment that led to death	0	0	0	0	0	0

*Treatment-related adverse events were fatigue and indigestion with sebetralstat 300 mg, nausea with sebetralstat 600 mg, dyspepsia and hot flash with sebetralstat 600 mg + 600 mg, headache and nausea (same patient), rash, and dysgeusia with 1 administration of placebo, and irregular menstruation with 2 administrations of placebo.
†Serious adverse event was defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or substantial disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event by medical and scientific judgement.
‡The severe adverse event and serious adverse event listed are the same event; lumbar disc herniation that required hospitalization and was deemed severe by the investigator.
§Severe adverse event was defined as a qualitative assessment of an AE of grade 3 severity by the investigator or as reported by the patient.
Source: Table S9 in Supplementary Appendix to Riedl *et al.* (2024)(94)

Details about adverse events that occurred within 3 days after an administration of sebetralstat or placebo for an attack and adverse events related to the trial agent are shown in Table 14 and Table 16. Physical examination, electrocardiograms, and laboratory assessments, including liver function tests, showed no safety signals.

Table 16 KONFIDENT Adverse Events Within 3 Days After an Administration

Event*	**Sebetralstat 300 mg (N = 86)**	**Sebetralstat 600 mg (N = 93)**	**Placebo (N = 83)**

	no. (%)	no. of events	no. (%)	no. of events	no. (%)	no. of events
Any adverse event within 3 days after an administration *,†						
Eye disorders	0	0	0	0	1 (1.2)	1
Eye hemorrhage	0	0	0	0	1 (1.2)	1
Gastrointestinal disorders	3 (3.5)	3	2 (2.2)	2	3 (3.6)	3
Vomiting	1 (1.2)	1	1 (1.1)	1	1 (1.2)	1
Nausea	0	0	1 (1.1)	1	1 (1.2)	1
Abdominal pain	0	0	0	0	1 (1.2)	1
Dyspepsia	1 (1.2)	1	0	0	0	0
Gingival bleeding	1 (1.2)	1	0	0	0	0
General disorders and administration site conditions	1 (1.2)	1	0	0	1 (1.2)	1
Fatigue	1 (1.2)	1	0	0	1 (1.2)	1
Infections and infestations	1 (1.2)	1	0	0	2 (2.4)	2
Influenza	0	0	0	0	1 (1.2)	1
Pharyngitis bacterial	0	0	0	0	1 (1.2)	1
Pharyngitis streptococcal	1 (1.2)	1	0	0	0	0
Musculoskeletal and connective tissue disorder	0	0	0	0	1 (1.2)	1
Neck pain	0	0	0	0	1 (1.2)	1
Nervous system disorders	0	0	4 (4.3)	4	2 (2.4)	2
Headache	0	0	3 (3.2)	3	1 (1.2)	1
Dizziness	0	0	1 (1.1)	1	0	0
Dysgeusia	0	0	0	0	1 (1.2)	1
Reproductive system and breast disorders	0	0	0	0	1 (1.2)	1
Menstruation irregular	0	0	0	0	1 (1.2)	1
Respiratory, thoracic, and mediastinal disorders	0	0	0	0	1 (1.2)	1
Epistaxis	0	0	0	0	1 (1.2)	1
Skin and subcutaneous tissue disorders	0	0	0	0	1 (1.2)	1
Rash	0	0	0	0	1 (1.2)	1

MedDRA denotes Medical Dictionary for Regulatory Activities.
*Shown are data for 110 participants who administered the indicated dose of sebetralstat or placebo to themselves for at least one angioedema attack.
†Categorised by system organ class and preferred term (coded using MedDRA, version 26.0)
Source: Table S10 in Supplementary Appendix to Riedl *et al.* (2024) (94)

Serious Adverse Events

No deaths were reported in this trial and, as mentioned above, there were no on-treatment serious adverse events (SAEs) reported. A summary of the SAEs is available in Table 17.

Table 17 Serious Adverse Events by system organ class and preferred term (Safety Set)

System Organ Class Preferred term	300 mg sebetralstat (N=86) n (%) E	600 mg sebetralstat (N=93) n (%) E	Placebo (N=83) n (%) E
Total number of SAEs	[redacted]	[redacted]	[redacted]
Congenital, familial, and genetic disorders	[redacted]	[redacted]	[redacted]
Hereditary angioedema	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]
Anisocoria	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Intervertebral disc protrusion	[redacted]	[redacted]	[redacted]

Notes: At each level of patient summarisation, a patient was counted once if the patient reported 1 or more events.
n represents the number of patients at each level of summarization. N is number of patients randomized using a permuted- block randomisation method to ensure a balanced assignment to each of the 6 treatment sequences, to receive that received 300 mg KVD900, 600 mg KVD900, or matching placebo for the analysed IMP-treated HAE attacks, according to the actual treatment received.
[E] represents the number of events at each level of summarisation.
Source: Table 7-5 of the KONFIDENT CSR report. (78)

2.12 Ongoing studies

KONFIDENT-S Open-label extension (OLE) study

- The open-label KONFIDENT-S (NCT05505916) trial is an ongoing, multicentre, open-label extension trial evaluating the long-term safety of sebetralstat in patients who are 12 years or older with HAE type 1 or 2. Compared to the KONFIDENT trial, the interim analysis data cut (14 September 2024) included a significantly larger number of sebetralstat-treated attacks ([redacted] versus 180 attacks), allowing for a more comprehensive assessment of effectiveness across diverse participant and attack subgroups.
- The effectiveness of sebetralstat in KONFIDENT-S was consistent with the results of the phase 2 and 3 KONFIDENT trials, with regard to times to beginning of symptom relief, reduction in attack severity, and complete attack resolution.
- A lower proportion of patients receiving 600 mg sebetralstat in KONFIDENT-S utilised conventional on-demand therapy within 12-hours of treatment compared to KONFIDENT ([redacted]% versus 8.6%, respectively).
- The observed safety profile to date in KONFIDENT-S aligns closely with findings from the phase 2 and phase 3 randomised, double-blind clinical trials. Across all three studies, gastrointestinal AEs were uncommon and were generally concurrent with abdominal attacks. In addition, no participants reported difficulty swallowing the film-coated tablets, including the attacks that involved the larynx.

KONFIDENT-S OLE trial design and methods

KONFIDENT-S is an ongoing multicenter open-label extension (OLE) trial (NCT05505916) to assess:

- [primary objective] the safety of long-term administration of sebetralstat in adolescent and adult patients with hereditary angioedema (HAE) Type I or II.

- [secondary objective] the long-term efficacy of sebetralstat in the treatment of attacks in adolescent and adult patients with HAE Type I or II.

- [secondary objective] the safety and efficacy of sebetralstat when used as short-term prophylaxis in adolescent and adult patients with HAE Type I or II prior to undergoing surgical, dental, or medical procedures. (Note: this study objective is not related to the decision problem of this appraisal).

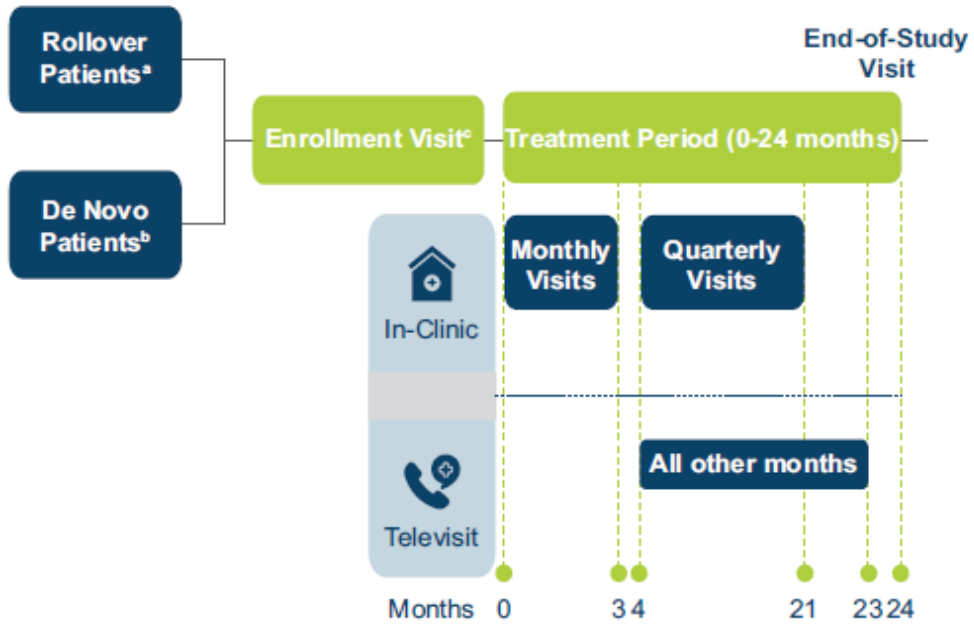
The patient recruitment stage of this study is now complete and participants are now actively participating in this trial (no further patients can enter the study).

Up to 150 adults and adolescents (≥12 years of age) with a confirmed diagnosis of HAE-C1INH (type 1 or 2) and at least two documented HAE-C1INH attacks within 3 months were enrolled either after completing the KONFIDENT trial (rollover) or *de novo* (see Figure 10). Patients receiving long-term prophylaxis (LTP) must be on a stable dose and regimen for ≥3 months immediately before and during the trial.

For up to 2 years, patients self-administer sebetralstat 600 mg (2 × 300 mg tablets) as early as possible after recognising the start of an attack. An optional second administration of sebetralstat is permitted ≥3 hours after the first administration (as determined by the participant).

Please note that from January 2025 the dose in KONFIDENT-S will change from 600 mg to 300 mg. The study was designed with the original 600 mg dose before results from the phase 3 KONFIDENT study were available. Since then, the 300 mg and 600 mg have been demonstrated to be dose equivalent so the open-label study will now change to 300 mg dosing from 2025.

Figure 10 KONFIDENT-S OLE Trial Design



a Completed the phase 3 KONFIDENT trial.
b All other participants, including those who participated in the phase 2 trial.
c For de novo participants, the enrolment visit is a screening visit.
Source: Farkas *et al. (*2024).(82)

The KONFIDENT-S trial design and methods is summarised in Table 18 below.

Table 18 KONFIDENT-S OLE Trial Design (ClinicalTrials.gov. 2024, Farkas, Riedl *et al.* 2024, KalVista 2024)

Trial number (acronym)	**NCT05505916 (KONFIDENT-S)**
Location	Total of 72 trial sites. Australia (1 site), Austria (1 site), Bulgaria (1 site), Canada (1 site), France (4 sites), Germany (4 sites), Greece (2 sites), Hungary (1 site), Israel (4 sites), Italy (4 sites), Japan (9 sites), Netherlands (1 site), New Zealand (1 site), North Macedonia (1 site), Poland (2 sites), Portugal (1 site), Romania (1 site), Saudi Arabia (1 site), Slovakia (1 site), South Africa (1 site), Spain (3 sites), United Kingdom*, United States (20 sites).(83)
Trial design	Open-label, multicentre extension trial to evaluate the long-term safety of sebetralstat in patients who are 12 years or older with HAE type I or II. Patients must have a confirmed diagnosis of HAE-C1INH (type 1 or 2) and at least two documented HAE-C1INH attacks within 3 months. Approximately 150 patients (including a minimum of 12 adolescents) in total are planned to be enrolled in HAE centres worldwide. These patients will include rollover patients (those randomised in the KONFIDENT phase 3 trial) and non-rollover patients (other patients including those randomised in the KVD900-201 Phase 2 trial or sebetralstat naïve).

Eligibility criteria for participants	Patients may roll over from Phase 3 KONFIDENT study (KVD900-301) as well as be recruited *de novo*. **Inclusion Criteria:** • Confirmed diagnosis of HAE type I or II at any time in the medical history • Patient has had at least 2 documented HAE attacks within 3 months prior to the Enrollment Visit. • If a patient is receiving long-term prophylactic treatment with one of the protocol-allowed therapies, they must have been on a stable dose and regimen for at least 3 months prior to the Enrollment Visit (except for danazol, which requires a stable dose and regimen for at least 6 months prior to the Enrollment Visit). • Male or female patients 12 years of age and older. • Patients must meet the contraception requirements. • Patients must be able to swallow trial tablets whole. • Patients, as assessed by the Investigator, must be able to appropriately receive and store IMP, and be able to read, understand, and complete the eDiary. • Investigator believes that the patient is willing and able to adhere to all protocol requirements. • Patient provides signed informed consent or assent (when applicable). A parent or legally authorized representative (LAR) must also provide signed informed consent when required. **Exclusion Criteria:** • Discontinued from the KONFIDENT phase 3 trial for reasons of noncompliance, withdrawal of consent, or safety. • Presence of any safety concerns that would preclude participation in the open-label trial as determined by the investigator. • Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1 inhibitor deficiency, HAE with normal C1-INH (previously known as HAE type III), idiopathic angioedema, or angioedema associated with urticaria. • A clinically significant history of poor response to bradykinin receptor 2 (BR2) blocker, C1-INH therapy, or plasma kallikrein inhibitor therapy for the management of HAE, in the opinion of the Investigator. • Use of attenuated androgens (e.g., stanozolol, oxandrolone, methyltestosterone, testosterone), or anti-fibrinolytics (e.g., tranexamic acid) within 28 days prior to the Enrollment Visit. • Use of Angiotensin-converting enzyme (ACE) inhibitors within 7 days prior to the Enrollment Visit. • Any oestrogen-containing medications with systemic absorption (such as oral contraceptives including ethinylestradiol or

	hormonal replacement therapy) within 7 days prior to the Enrollment Visit. • Inadequate organ function, including but not limited to: 1. Alanine aminotransferase (ALT) >2x Upper Limit Normal (ULN) 2. Aspartate aminotransferase (AST) >2x ULN 3. Bilirubin direct >1.25x ULN 4. International Normalized Ratio (INR) >1.2 5. Clinically significant hepatic impairment defined as a Child-Pugh B or C • Any clinically significant comorbidity or systemic dysfunction, which in the opinion of the Investigator, would jeopardize the safety of the patient by participating in the trial. • History of substance abuse or dependence that would interfere with the completion of the trial, as determined by the Investigator. • Known hypersensitivity to sebetralstat or to any of the excipients. • Participation in any gene therapy treatment or trial for HAE. • Participation in any interventional investigational clinical trial, including an investigational COVID-19 vaccine trial, within 4 weeks of the last dosing of investigational drug prior to the Enrollment Visit. • Any pregnant or breastfeeding patient.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	Oral sebetralstat 600 mg. Prior medications were defined as those medications taken within 4 weeks prior to the screening visit up to the first dose of IMP; concomitant medications were defined as those medications ongoing at or started after the first dose of IMP. Attacks that were not treated with IMP could be treated with conventional on-demand treatment per the patient's usual treatment regimen. Permitted therapies included conventional on-demand treatments, long- and short-term prophylactic treatment (berotralstat, lanadelumab, IV or SC plasma-derived C1-INH). Prohibited therapies during the trial included attenuated androgens, anti-fibrinolytics, investigational therapies for HAE, ACE inhibitors, oestrogen-containing medications with systemic absorption, sustained use of strong CYP3A4 inhibitors and inducers.(107)
Primary outcomes (including scoring methods and timings of assessments)	• Frequencies and percentages of patients with adverse events (AEs), AEs within 3 days of investigational medicinal product (IMP) administration, serious AEs, and AEs causing premature discontinuation. • Number and percentage of patients with normal or abnormal laboratory results at each scheduled visit. • Number and percentage of patients with normal or abnormal vital sign results at each scheduled visit. The primary estimand is the proportion of adolescents and adults with HAE Type I or II who take any sebetralstat dose, who experience any AEs (including fatal AEs) in the first 24 months, irrespective of uses of other medications and sebetralstat discontinuations for any reason.

Other outcomes used in the economic model/specified in the scope	Secondary efficacy outcomes in the KONFIDENT-S trial include: • PGI-C: time to beginning of symptom relief defined as at least "a little better" (2 time points in a row) within 12 hours of initial dose of IMP administration. • PGI-S: time to first incidence of 2 time points in a row decrease from baseline within 12 hours of initial dose of IMP administration. [Note: this reflects the time to reduction in severity] • PGI-S: time to HAE attack resolution defined as "none" within 24 hours of initial dose of IMP administration. • AE-QoL (exploratory): AE-QoL changes over time. • Time to first incidence of conventional on-demand attack treatment use within 12 hours and 24 hours.
Pre-planned subgroups	• Prespecified subgroup analyses of the primary and key secondary end points will be performed according to sex, race, age, prophylactic treatment status, region, HAE type, baseline primary attack location, attack severity at baseline based on PGI-S, number of doses received, time from onset of attack to the first IMP administration. • Note: Subgroup analyses will be conducted and presented as part of the final clinical study report.

* the UK now has 6 trial sites. Of these, 5 sites have patients enrolled. Total of 8 patients were enrolled in the UK. Of the 8 UK patients, 7 are still ongoing.

KONFIDENT-S OLE sample size

In KONFIDENT-S it is estimated that a sample size of 150 patients (including a minimum of 12 adolescents) will be reached. The sample size was considered appropriate to evaluate long-term safety and was based on clinical considerations since no inferential statistical analysis was planned.

KONFIDENT-S OLE population sets (84)

The population sets analysed for this trial will include:

- **Screened Set:** The screened set included all patients who signed the ICF.
- **Safety Set**: The safety set (SAF) included all patients who received at least 1 dose of IMP.
- **Short-Term Prophylactic Safety Set:** The short-term prophylactic safety set (STP-SAF) included all the patients who received at least 1 dose of IMP as short-term prophylactic therapy.

- **Full Analysis Set:** The full analysis set (FAS) included all enrolled patients who received at least 1 dose of IMP for a qualifying HAE attack. It is the population for efficacy analyses.

KONFIDENT-S OLE statistical analysis (84)

All statistical summaries were presented by rollover patients (rollover and non-rollover) and overall. Data were only summarised descriptively. No inferential statistical analysis was performed, and data were only summarised descriptively.

Continuous data were presented using descriptive statistics (i.e. N, mean, standard deviation [SD], median, first and third quartiles, minimum, and maximum). Categorical data were presented using the patient count and percentage in each category. The summary statistics of all numerical variables (unless otherwise specified), minimum and maximum were displayed to the same level of precision as the data collected.

Unless otherwise specified, baseline was defined as the last non-missing evaluation prior to or on the date that the first dose of treatment was taken. Trial day was defined in relation to the date of first IMP dose.

KONFIDENT-S OLE interim findings

Interim participant characteristics (based on an earlier 31 January 2024 cut-off date) were presented as a poster by Farkas *et al.* at the EAACI 2024 conference in Valencia in May 2024.(82) Since this poster, more recent interim data have become available based on a 14 September 2024 cut-off date and are available as an interim KONFIDENT-S CSR report (dated 19 November 2024).(84) The write up that follows in this section presents the latest available interim findings.

KONFIDENT-S OLE baseline characteristics

Overall, the mean (SD) age of patients was [redacted] years and ranged from [redacted] to [redacted] years. The majority ([redacted] [redacted%] patients) were ≥18 years of age. There were [redacted] ([redacted%]) female and [redacted] ([redacted%]) male patients. The majority of the patients were White by race ([redacted] [redacted%] patients) and not Hispanic or Latino ([redacted] [redacted%] patients) by ethnicity. The mean (SD) body mass index (BMI) was [redacted] kg/m^2. Demographic characteristics were well-balanced between rollover and nonrollover patients.

Regarding disease-specific history, the majority of patients presented with Type I HAE ([redacted] patients). More patients were receiving an on-demand only HAE treatment regimen ([redacted]%] patients) than were receiving a stable dose of prophylactic therapy ([redacted]%] patients). Of the prophylactic therapies, [redacted]%) patients used kallikrein-inhibiting treatments (including lanadelumab and berotralstat) and [redacted]%) patients used other prophylactic therapies.

Table 19 Demographics and Baseline Characteristics – Overall (Safety Set) KVD900-302 OLE (September 2024 Data Cut-off)

Characteristic	Rollover [redacted]	Non-rollover [redacted]	Total [redacted]
Age			
Years, Mean (SD)	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Female Male	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Geographic region, n (%)			
North America Europe Rest of world	[redacted]	[redacted]	[redacted]
HAE-C1INH type — no. (%)			
Type I	[redacted]	[redacted]	[redacted]

Type II	[redacted]	[redacted]	[redacted]
Body Mass Index (BMI) (kg/m^2)			
n Mean (SD)	[redacted]	[redacted]	[redacted]

[a] BMI was calculated as (body weight in kilograms)/(height in meters)^2
Source: KONFIDENT-S OLE CSR report Table 5-5 and Table 5-7 (84)

KONFIDENT-S OLE Primary endpoint results (Safety)

In the KONFIDENT-S open-label study, the primary estimand is the proportion of adolescents and adults with HAE Type I or II who take any sebetralstat dose, who experience any AEs (including fatal AEs) in the first 24 months, irrespective of uses of other medications and sebetralstat discontinuations for any reason.

Treatment-Emergent Adverse Events

Of the [redacted] patients in the SAF (safety set), [redacted] ([redacted]%) patients reported a total of [redacted] TEAEs. [redacted] ([redacted]%) patients reported [redacted] TEAEs considered related to the IMP. [redacted]%) patients reported a total of [redacted] TEAEs within 3 days of IMP administration (i.e. considered on-treatment). [redacted] ([redacted]%) patients reported [redacted] TEAEs leading to trial discontinuation. Twelve ([redacted]%) patients reported [redacted] TEAEs of Grade 3 severity. [redacted]%) patients reported [redacted] serious TEAEs, of which [redacted] patients reported [redacted] serious TEAEs leading to hospitalisation. None of the serious TEAEs were IMP-related. There were no TEAEs leading to death.

Table 20 Overview of Treatment-Emergent Adverse Events – Overall (Safety Set) KVD900-302 OLE (September 2024 Data Cut-off)

	Rollover	**Non-Rollover**	**Total**
	[redacted]	[redacted]	[redacted]
Number of Patients with	**n (%) E**	**n (%) E**	**n (%) E**
Any TEAE	[redacted]	[redacted]	[redacted]
Any related TEAE	[redacted]	[redacted]	[redacted]
Any TEAE within 3 days of IMP administration	[redacted]	[redacted]	[redacted]
Any Grade 3 or higher TEAE	[redacted]	[redacted]	[redacted]
Any related Grade 3 or higher TEAE	[redacted]	[redacted]	[redacted]
Any serious TEAE	[redacted]	[redacted]	[redacted]

Any related serious TEAE	[redacted]	[redacted]	[redacted]
Any TEAE leading to hospitalisation	[redacted]	[redacted]	[redacted]
Any TEAE leading to trial discontinuation	[redacted]	[redacted]	[redacted]
Any TEAE leading to death	[redacted]	[redacted]	[redacted]

Note: n represents the number of patients at each level of summarisation.
E represents the number of AEs at each level of summarisation.
A TEAE was defined as an AE that met any of the following conditions: (1) began on or after the first IMP dose date, (2) began before the first IMP dose date and increased in severity on or after the first IMP dose date, (3) was completely missing a start date and a stop date, (4) was completely missing a start date and the stop date was on or after the first IMP dose date.
AEs were coded using MedDRA, Version 26.0.
Source: KONFIDENT-S OLE CSR report Table 7-1 (84)

Frequency of TEAEs

Overall, the most frequently reported SOCs (≥5% of patients overall) were infections and infestations ([redacted] [redacted%] patients); gastrointestinal disorders ([redacted] [redacted%] patients); nervous system disorders ([redacted] [redacted%] patients); musculoskeletal and connective tissue disorders ([redacted] [redacted%] patients); respiratory, thoracic and mediastinal disorders ([redacted] [redacted%] patients); skin and subcutaneous tissue disorders ([redacted] [redacted%] patients); injury, poisoning and procedural complications ([redacted] [redacted%] patients); and investigations ([redacted] [redacted%] patients).

Most preferred terms (PT) were reported for [redacted] ([redacted%) patient each. The PTs reported for ≥5% of patients overall were headache ([redacted] [redacted%] patients), nasopharyngitis ([redacted] [redacted%] patients), COVID-19 ([redacted] [redacted%] patients), and upper respiratory tract infection ([redacted] [redacted%] patients).

Table 21 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Reported by ≥2% Patients Overall (Safety Set) KVD900-302 OLE (September 2024 Data Cut-off)

	Rollover	**Non-Rollover**	**Total**
SOC	[redacted]	[redacted]	[redacted]
PT	**n (%) E**	**n (%) E**	**n (%) E**
All TEAEs	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders			
Diarrhoea	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Gastrooesophageal reflux disease	[redacted]	[redacted]	[redacted]
Toothache	[redacted]	[redacted]	[redacted]
Immune system disorders			

Seasonal allergy	[redacted]	[redacted]	[redacted]
Infections and infestations			
Nasopharyngitis	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]
Pharyngitis streptococcal	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders			
Back pain	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]
Nervous system disorders			
Headache	[redacted]	[redacted]	[redacted]
Migraine	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders			
Urticaria	[redacted]	[redacted]	[redacted]

Note: At each level of patient summarization, a patient was counted once if the patient reported one or more events. N represents the number of patients at each level of summarization. E represents the number of AEs at each level of summarization.
AEs were coded using MedDRA, Version 26.0.
[a] Uncoded terms were due to the data included in this CSR up to 14 Sep 2024. Data for all patients were fully cleaned up to 16 Aug 2024, except for 6 patients for whom some electronic data capture data were not able to be source verified before the cutoff date. The only AE that was not fully cleaned was an AE of 'abdominal pain and cramping due to HAE attack' that was considered unrelated to the IMP at the time of data cut-off.
Source: KONFIDENT-S OLE CSR report Table 7-7 (84)

TEAEs by relationship to IMP

[redacted] ([redacted]%) patients reported [redacted] TEAEs considered related to the IMP. IMP-related TEAEs reported for ≥2 patients were headache ([redacted] [[redacted]%] patients), vomiting [redacted]%] patients), and nausea ([redacted]%] patients). All other PTs were reported for a single patient each.

On-treatment TEAEs

An on-treatment TEAE was defined as any TEAE occurring within 3 days after IMP administration. Overall, [redacted]%) patients reported [redacted] on-treatment TEAEs, of which [redacted] (in [redacted]%] patients) were considered related to the IMP.

On-treatment TEAEs were mostly Grade 1 ([redacted] TEAEs) or Grade 2 ([redacted] TEAEs) in severity; [redacted] Grade 3 on-treatment TEAEs were reported. The [redacted] on-treatment TEAEs considered related to the IMP were mostly mild ([redacted] TEAEs) or moderate ([redacted] TEAEs) in severity; a single Grade 3 IMP-related on-treatment TEAE was reported. Three patients ([redacted]%) reported [redacted] on-treatment serious TEAEs; none were considered related to the IMP. [redacted]%) patients reported [redacted] on-treatment TEAEs leading to trial discontinuation.

Table 22 Overview of On-Treatment Treatment-Emergent Adverse Events – Overall (Safety Set) KVD900-302 OLE (September 2024 Data Cut-off)

	Rollover	Non-Rollover	Total
	[redacted]	[redacted]	[redacted]
Number of Patients with	[redacted]	[redacted]	[redacted]
Any TEAE	[redacted]	[redacted]	[redacted]
Any related TEAE	[redacted]	[redacted]	[redacted]
Any Grade 3 or higher TEAE	[redacted]	[redacted]	[redacted]
Any related Grade 3 or higher TEAE	[redacted]	[redacted]	[redacted]
Any serious TEAE	[redacted]	[redacted]	[redacted]
Any related serious TEAE	[redacted]	[redacted]	[redacted]
Any TEAE leading to hospitalization	[redacted]	[redacted]	[redacted]
Any TEAE leading to trial discontinuation	[redacted]	[redacted]	[redacted]
Any TEAE leading to death	[redacted]	[redacted]	[redacted]

Notes: n represents the number of patients at each level of summarization. E represents the number of AEs at each level of summarization.
A TEAE was defined as an AE that met any of the following conditions: (1) began on or after the first IMP dose date, (2) began before the first IMP dose date and increased in severity on or after the first IMP dose date, (3) was completely missing a start date and a stop date, (4) was completely missing a start date and the stop date was on or after the first IMP dose date.
On-treatment TEAE was defined as any TEAE occurring within 3 days post-dose.
AEs were coded using MedDRA, Version 26.0.
Source: KONFIDENT-S OLE CSR report Table 7-3 (84)

Frequency of on-treatment AEs

On-treatment TEAEs were most commonly (≥5% of patients overall) reported in the SOCs of infections and infestations ([redacted]%] patients); nervous system disorders ([redacted]

[redacted]%] patients); and gastrointestinal disorders ([redacted]%] patients). The most frequently reported on-treatment PTs (≥5% of patients overall) were headache ([redacted]%] patients) and nasopharyngitis ([redacted]%] patients).

On-Treatment TEAEs by Relationship to IMP

Of the [redacted] TEAEs in [redacted] patients considered related to the IMP, the majority ([redacted] TEAEs in [redacted] patients) occurred within 3 days post-IMP administration (i.e. were considered on-treatment). The only IMP-related TEAEs that did not occur on-treatment were [redacted].

Deaths

No deaths were reported in the trial.

Serious adverse events

Overall, [redacted]%) patients reported [redacted] serious TEAEs:

- Meningitis viral (Grade 3) in [redacted]
- Hypotension (Grade 3) in [redacted]
- Hiatus hernia (Grade 2) and dehydration (Grade 3) in [redacted]
- Bronchitis (Grade 3) in [redacted]
- Hyperthermia (Grade 1), headache (Grade 1), and intracranial mass (Grade 3) in [redacted]
- Erysipelas (Grade 3) in [redacted]
- Inguinal hernia (Grade 3) in [redacted]
- Waldenstrom's macroglobulinemia (Grade 2) in [redacted]
- HAE ([redacted] Grade 3 events) ([redacted] events of laryngeal HAE attack and [redacted] event of abdominal HAE attack) in [redacted]

None of the serious TEAEs were considered by the investigator to be related to the IMP.

There were no on-treatment serious TEAEs.

Discontinuations due to AEs

[redacted]%) patients reported a total of [redacted] TEAEs leading to trial discontinuation:

- ALT increased (Grade 2) in [redacted]
- Intracranial mass (Grade 3) in [redacted] (also an SAE)
- Skin burning sensation (Grade 2) in [redacted]
- Nausea (Grade 2) in [redacted]
- Nausea (Grade 2) and vomiting (Grade 2) in [redacted]

The events of [redacted] were considered by the investigator to be related to the IMP.

Clinical laboratory values over time

Both overall and in Japanese patients, no clinically significant mean changes were observed in haematology, clinical chemistry, urinalysis, liver enzymes, electrolytes, coagulation, or other laboratory parameters from baseline to any post-baseline timepoints.

KONFIDENT-S OLE secondary endpoint results (Efficacy)

Please note that all efficacy endpoints were analysed by rollover and non-rollover subgroups and pooled by attack number (e.g. first attack, second attack). Due to patient numbers, efficacy endpoints were not powered for statistical comparisons and are presented descriptively.

PGI-C: time to beginning of symptom relief defined as at least "a little better" (2 time points in a row) within 12 hours of initial dose of IMP administration

A total of [redacted] HAE attacks were analysed, with [redacted] attacks ([redacted]%; range [redacted]% to [redacted]% for attacks [redacted]) achieving the beginning of symptom relief within 12 hours. This indicates that time to beginning of symptom relief within 12 hours was achieved for the [redacted] Overall, the median time to beginning of symptom relief was [redacted] hours (95% CI: [redacted]). There was no discernible trend with repeated treatment in time to beginning of symptom

relief. The 95% CIs for median time to symptom relief overlapped between rollover and non-rollover patients, and there were no clinically meaningful differences between rollover and non-rollover groups.

Sensitivity Analysis of the Primary Endpoint

A sensitivity analysis was conducted on the primary endpoint to determine the impact of missing data. When missing data were allowed, the time to beginning of symptom relief was consistent with the main analysis. When attacks lacking post-baseline assessments were excluded from the analyses, the proportion of attacks achieving the beginning of symptom relief within 12 hours was [redacted]%.

PGI-S: time to first incidence of 2 time points in a row decrease from baseline within 12 hours of initial dose of IMP administration

A total of [redacted] HAE attacks were analysed, with [redacted] attacks ([redacted]%; range [redacted]% for attacks [redacted]) achieving a reduction in severity within 12 hours. The median time to reduction in severity was [redacted] hours (95% CI: [redacted], NE [i.e. [redacted]]). There was no discernible trend with repeated treatment in time to reduction in severity. The 95% CIs for median time to reduction in severity overlapped between rollover and non-rollover patients, and there were no clinically meaningful differences between rollover and non-rollover groups.

PGI-S: time to HAE attack resolution defined as "none" within 24 hours of initial dose of IMP administration

Overall, a total of [redacted] HAE attacks were analysed, with [redacted] attacks ([redacted]%; range [redacted]% for attacks [redacted]) achieving complete HAE attack resolution within 24 hours. The median time to achieve complete HAE attack resolution was [redacted] hours (95% CI: [redacted]). There was no discernible trend with repeated treatment in time to complete HAE attack resolution. The 95% CIs for median time to complete HAE attack resolution overlapped between rollover and nonrollover patients, and there were no clinically meaningful differences between rollover and non-rollover groups.

AE-QoL (exploratory): AE-QoL changes over time

Total and domain scores varied from month to month but were generally comparable to baseline. The results will be addressed in the final CSR when more patients are observed for longer time periods.

Time to first incidence of conventional on-demand attack treatment use within 12 hours and 24 hours

A total of [redacted] HAE attacks were analysed. Conventional on-demand treatment was used within 12 hours in [redacted]%) attacks and within 24 hours in [redacted]%) attacks. The use of conventional on-demand treatment within 12 or 24 hours was consistent with repeated treatment. There were no clinically meaningful differences between rollover and non-rollover patients.

KONFIDENT-S OLE additional data

Data from KONFIDENT-S was reviewed to assess the time from onset of attack to first dose (see Table 23).

Table 23 KONFIDENT-S OLE: Summary of Time to First Dose by Rollover Status (Full Analysis Set)

Parameters	Rollover Attack=[redacted]	Non rollover Attack=[redacted]	Overall Attack=[redacted]
Time (minutes) from onset of attack to the first IMP administration Number of IMP records Mean (SD) Median Q1, Q3 Min, Max	[redacted]	[redacted]	[redacted]
Time from onset of attack to the first IMP administration category 1 n(%) < 30 minutes >= 30 - < 60 minutes >= 60 minutes Missing	[redacted]	[redacted]	[redacted]
Time from onset of attack to the first IMP administration category 2 n(%) <= median (10) > median (10) Missing	[redacted]	[redacted]	[redacted]

IMP: investigational medicinal product; SD: standard deviation; Q1: first quartile; Q3: third quartile
Data cut-off: 14 September 2024
Source: Table A302-4 KONFIDENT-S (Data on file) (108)

2.13 Interpretation of clinical effectiveness and safety evidence

The efficacy and safety of sebetralstat vs. placebo has been demonstrated in the Phase 2 KVD900-201 and the Phase 3 KONFIDENT studies. An ongoing, long-term open-label extension study (KONFIDENT-S) is underway to further assess safety and efficacy (see Section 2.12 Ongoing studies for interim findings from the open-label study). Please note that KVD900-201 phase 2 study is not used in the model but an overview of this study is available in Appendix J for completeness.

Findings from the Phase 2 study show that sebetralstat is statistically significant versus placebo in halting the progression of and symptomatically improving HAE attacks. The primary endpoint, all secondary endpoints and the key exploratory endpoints were all met (i.e. with a p value <0.05). Overall, this study demonstrated that oral administration of sebetralstat was well tolerated and led to rapid suppression of plasma kallikrein activity, resulting in increased time to use of conventional attack treatment and faster symptom relief versus placebo.

The pivotal Phase 3 KONFIDENT study provided added confirmation with sebetralstat demonstrating faster times to the beginning of symptom relief, reduction in attack severity, and complete attack resolution than placebo with a similar safety profile to placebo, and no serious adverse events related to trial agents reported. Regarding subgroups, results with each sebetralstat dose level were similar and were consistent across clinically relevant subgroups defined according to age, treatment approach (with or without long-term prophylaxis), and geographic region. The consistency of the effect was also observed in attacks of varying severity and anatomic location (mucosal or subcutaneous). A treatment effect in the laryngeal subset of mucosal attacks could not be adequately assessed owing to the small number of events, which was further compounded by missing data.

Potential limitations of the KONFIDENT trial include the potential effect of increasingly extended intervals between assessments after the first 4 hours of data collection for each attack, which may have led to the delayed capture of data on participant-reported outcomes. Investigational agents that have shown efficacy as long-term prophylaxis in patients with hereditary angioedema were excluded. Approximately 19% of the participants who underwent randomisation were not included in the safety or efficacy

analyses because they did not have an eligible attack during the trial. However, an intention-to-treat analysis that used imputed data for these excluded participants showed results similar to those for the full analysis population.

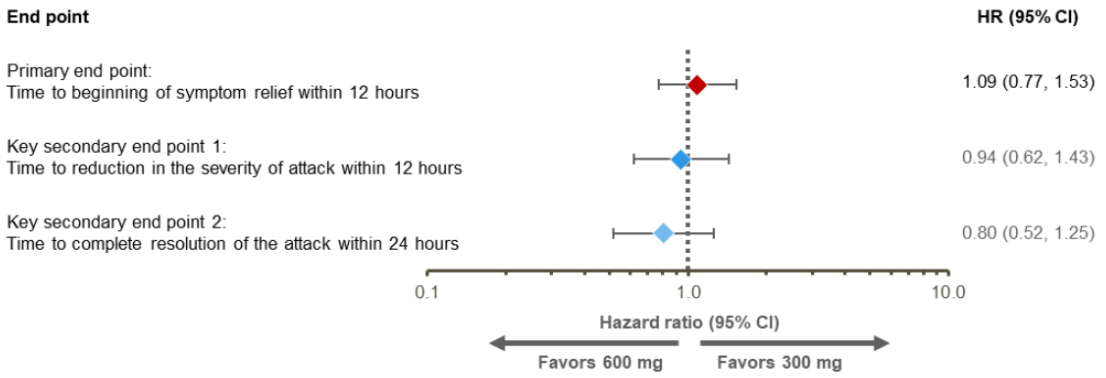
Equivalence between 300 mg and 600 mg dosing

Importantly, the pharmacokinetic evidence from the sebetralstat evidence base demonstrate the two doses to be equivalent. The totality of sebetralstat clinical data supports the recommended dosage of sebetralstat 300 mg (1 x 300 mg film-coated tablet) taken orally at the earliest recognition of an HAE attack in adults and paediatrics aged 12 years and older. An additional dose may be taken if needed. Sebetralstat can be taken with or without food. The proposed dosing regimen is supported by clinical efficacy, safety and tolerability, and PK of sebetralstat from the clinical trials.(109)

The double-blind Phase 2-3 trials demonstrated statistically significant and clinically meaningful improvements in time to beginning of symptom relief, time to reduction in severity, and time to complete attack resolution following administration of sebetralstat 300 mg or 600 mg compared with placebo.(109)

In the phase 3 KONFIDENT study, there was no statistical difference demonstrated between the 300mg and 600mg dose as shown by hazard ratios for the primary and key secondary endpoints. (Figure 11) Ad hoc proportional hazard regression analysis was conducted for the KONFIDENT study to compare the treatment effect on the primary and key secondary endpoints between 300 mg and 600 mg dose levels; this showed that no differences in efficacy outcomes were observed between 300mg and 600 mg sebetralstat. Therefore, data from both 300 mg and 600 mg are considered supportive of the proposed 300 mg dose.(94, 109)

Figure 11 KONFIDENT study: Hazard ratios of sebetralstat 300mg and 600mg doses for primary or key secondary endpoints



HR: hazard ratio
Source: Figure S5 from Riedl *et al.* 2024 supplementary appendix(94)

Based on pooled analyses of the double-blind trials and based on the pivotal KONFIDENT trial individually, all subgroups examined based on intrinsic and extrinsic factors were consistent with the overall results of the primary and key secondary efficacy endpoints, favouring the efficacy of both dose levels of sebetralstat over placebo. The data indicate that adjustment of the recommended dose regimen is not necessary for any subgroup examined based on age, sex, race, geographic region, type of HAE, or prophylactic treatment status. In addition to the subgroup analysis of efficacy, population PK analyses also support the recommendation that no differences in dosing are required based on age group.(109)

Clinical safety of sebetralstat has been evaluated at [redacted] in Phase 1 trials; single administrations of 600 mg in the Phase 2 trial; up to 2 administrations of 300 mg and 600 mg per attack in the pivotal Phase 3 trial; and up to 2 administrations of 600 mg per 24 hours in the ongoing open-label Phase 3 trial.(109)

Overall, across the clinical development program, sebetralstat has been safe and well tolerated. with an acceptable, consistent, and well characterised safety profile. The safety profile in HAE patients in the Phase 2 and 3 trials was consistent with that observed in healthy volunteers in the Phase 1 trials. The safety profile in paediatric patients (12 years and over) was consistent with that observed in adult patients. In the phase 3 KONFIDENT study, safety profiles of sebetralstat (300 mg or 600 mg) were comparable to placebo.(109)

In summary, the pharmacokinetic evidence from the sebetralstat evidence base demonstrate the two doses to be equivalent in terms of both efficacy and safety. Furthermore, the demonstration of dose equivalence has led to the KONFIDENT-S open-label extension study implementing a dose change from the original 600 mg dose to the 300 mg dose from January 2025.

Generalisability to the UK population

In the KONFIDENT study, of the 110 participants who received at least one dose of double-blind treatment, 66 were female (60.0%), and 101 (91.8%) had hereditary angioedema type 1. The median age was 39.5 years, and 30 participants (27.3%) were adolescents between 12 and 17 years of age. Only on-demand therapy at enrollment was received by 86 participants (78.2%), and 24 participants (21.8%) were receiving a stable regiment of long-term prophylaxis with berotralstat, lanadelumab, or C1 inhibitor replacement. Race was self-reported as White in the majority of participants (83.6%), followed by Asian (9.1%), Black/African American (0.9%), and other (0.9%). Other than the higher prevalence in White participants, the participants included in the trial were generally representative of the overall population with HAE. Other than the higher prevalence in White participants, the participants included in the trial were generally representative of the overall worldwide population with hereditary angioedema.(80) Additionally, UK clinical experts engaged during the development of this submission informed us that the proportion of patients receiving long-term prophylaxis in addition to on-demand treatment in clinical practice would likely be higher than the 21.8% in the KONFIDENT trial, however, they added that this would not affect the sebetralstat clinical findings. (31)

Of note, the KONFIDENT study included 5 UK trial sites with the following number of subjects enrolled:

- Royal London Hospital, London (1 subject)
- Frimley Park Hospital, Surrey (2 subjects)
- St James University Hospital, Leeds (4 subjects)
- University Hospital Birmingham (1 subject)

- Immunodeficiency Centre for Wales, Cardiff (0 subjects).

Final interpretation

In summary, the efficacy of sebetralstat versus placebo is well demonstrated to enable early treatment of attacks, providing faster time to symptom relief, reducing attack severity and complete resolution of attacks versus placebo, at a similar safety profile.

Whilst patients in the KONFIDENT study were permitted to take a further dose of sebetralstat dose, as determined by the patient themselves, ad hoc efficacy analyses show that the majority of patients go onto achieve HAE attack resolution without the need of a second dose of sebetralstat. Furthermore, in KONFIDENT, attacks that were treated earlier were more likely to be mild than attacks treated later. Complete attack resolution was reached faster (HR: 2.72 [1.33, 5.59]) in attacks that were treated "earlier" with sebetralstat compared with those that were treated "later" (at a time similar to parenteral on-demand treatments).(73). Additionally, regarding symptom burden, Lumry *et al.* reported that HAE attacks that had progressed in severity were associated with faster and more significant reduction in symptom burden compared to placebo.(95)

As discussed in Section 2.10, an ITC comparing sebetralstat with comparators was not feasible for the outcomes of interest due to the vast challenges posed by the heterogeneity in trial designs and outcomes. In the absence of robust and feasible ITC to capture comparative effectiveness between sebetralstat and its comparators for utilisation in the cost-effectiveness model [developed for the purpose of sebetralstat health technology assessment (see GVD Section 10)]; the cost-effectiveness model considers that earlier on-demand treatment administration is associated with a shorter total attack duration. To alleviate the absence of direct or indirect evidence, the cohort State-Transition Model (cSTM) incorporates a statistical sub-model to estimate the effect moderation of TTA on TTAR, to obtain an adjusted TTAR for each treatment.

An oral treatment option for the on-demand treatment of hereditary angioedema attacks is desired by the clinical and patient community to improve compliance with treatment guidelines, avoid adverse drug reactions related to current treatment options

that are injectables or infusions, and thereby improve patient HRQoL. International treatment guidelines recommend that all people living with hereditary angioedema, including those who receive long-term prophylaxis, should 1) consider the treatment of all attacks, irrespective of location or severity; 2) have ready access to and carry an effective on-demand medication for the treatment of at least 2 attacks, and 3) treat attacks as early as possible to arrest progression.(94) Sebetralstat will provide a much anticipated solution to this area of unmet need.

3 Cost effectiveness

3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted to identify published studies reporting cost-effectiveness, cost-utility analysis, and costs of healthcare resource utilization (HCRU) of all relevant and available interventions to any comparators of interest for the on-demand (OD) treatment of hereditary angioedema. Modelling structures and assumptions employed in identified studies were examined to determine any important differences in approaches and areas of remaining uncertainty.

Of the 99 included studies in the final economic SLR results, 19 were cost-effectiveness analysis (CEA) studies and six were cost-utility analyses (CUA) studies. However, only three of these published CUA studies assessed OD treatment. Of these three published studies assessing OD treatment, two used a decision-tree model and one used a Discrete-Event Simulation (DES). See **Error! Reference source not found.**for more details.

Grey literature searches returned an additional 18 studies. Of these 18 studies, only two were considered relevant to the CUA decision problem. Additional ad-hoc searches returned one further study (110).

Please see Table 24 for a summary of the six CUA studies considered relevant to the decision problem. Please see **Error! Reference source not found.** for details on the SLR methods identifying published cost-effectiveness studies.

Table 24: Summary of published cost-effectiveness studies

Study	Year	Description of model	Population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost per QALY)
Bernstein *et al.*(111)	2020	Decision-tree model (time horizon not reported) and 15% annual discounting. Assumed that an HAE attack refers to a 72-hour period in which the primary attack initially occurs and during which follow-up attacks can occur because of ineffective treatment. Thus, the calculation of cost per QALY from per attack cost effectiveness requires subtracting the number of annual hours during which the patient is experiencing attack symptoms (attack hours) from annual non attack hours. Assumed a United States commercial payer perspective; 2019 US Dollars.	NR	Total QALYs: rhC1-INH: 0.825 Icatibant: 0.816 Ecallantide: 0.822 pdC1-INH: 0.817	Costs per year (mean): rhC1-INH: $347,145 Icatibant: $398,281 Ecallantide: $566,729 pdC1-INH: $395,107	NR

Tyson *et al.* (112)	2019	Decision-tree model developed using TreeAgePro software. US Dollars (cost year not reported).	NR	<u>Total QALYs:</u> rhC1-INH: 0.804 Icatibant: 0.762 Ecallantide: 0.786 pdC1-INH: 0.759	<u>Total costs:</u> rhC1-INH: $12,342 Icatibant: $13,611 Ecallantide: $20,315 pdC1-INH: $13,993	<u>ICER:</u> rhC1-INH: $403,000 Icatibant: $449,000 Ecallantide: $666,000 pdC1-INH: $462,000
Kawalec *et al.*(113)	2013	Discrete event simulation (DES), 1-year time horizon. Reported from a Polish National Health Fund and patient perspective; 2011: € (EUR); zł (PLN).	NR	<u>Total QALYs:</u> rhC1INH: 0.0261 Berinert: 0.0262	<u>Total costs:</u> rhC1INH: €419.27, zł1,719 Berinert: €754.63, zł3,094	<u>ICER:</u> rhC1INH: €15225.61; zł62,425 Berinert: €27,786; zł113,924

AWMSG (114)	2012	Model structure not reported but described as a simple decision analytic model intended to represent the mean average costs and outcomes associated with a single moderate to severe HAE attack over a period of 96 hours.	Paediatric	NR	<u>Total costs:</u> Icatibant (expert opinion): £1,577.38 Berinert (expert opinion): £1,754.44 Berinert (Welsh audit data): £1,378.39	NR
SMC(115)	2012	A cost-utility analysis comparing icatibant with Berinert. The time horizon of the model was the duration of one attack of HAE (assumed to be 96 hours). In the model patients experience a moderate to severe attack which is either (i) laryngeal or (ii) non-laryngeal (cutaneous, peripheral, or abdominal). Patients either have therapy administered in A&E, following which the patient is either discharged or admitted, or self-administer, and either require no further care or attend A&E with the possibility of admission.	Adult patients with C1-esterase inhibitor deficiency treated for moderate to severe attacks of type I and II HAE.	Incremental QALYs (icatibant vs Berinert): 0.0000852	NR	NR

PBAC (110)	2016	A Markov model comprising 9 health states to describe attack-free, within attack, and post attack (recovery period) states by severity levels (mild, moderate, and severe). Assumed 5.49 treated attacks per patient per year.	NR	NR	NR	ICER: Ranged from less than $15,000 per QALY gained with one treated attack per year to $105,000 - $200,000 per QALY gained among patients with 19-24 attacks treated per year

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; NR, Not Reported; US, United States; AWTTC, All Wales Therapeutics and Toxicology Centre; SMC, Scottish Medicines Consortium; PBAC, Pharmaceutical Benefits Advisory Committee

3.2 Economic analysis

The SLR of cost-effectiveness studies identified no studies comparing sebetralstat, for the OD treatment of acute HAE attacks, to icatibant, or a C1-esterase inhibitor (C1-INH) like Ruconest, Berinert, and Cinryze. Therefore, a *de novo* economic model was developed to appraise the cost-effectiveness of sebetralstat versus icatibant, recombinant C1-INH (Ruconest), pC1-INH (Berinert), and C1-INH-nf (Cinryze), for treating acute attacks of hereditary angioedema (HAE) in patients aged 12 years and over.

Patient population

The patient population included in the economic evaluation is defined as patients 12 years and over with type I and type II HAE. Since there are no differences in the clinical and economic outcomes between type I and type II HAE patients (24, 78), these sub-types are assumed homogenous and are not separately modelled. Baseline patient characteristics are derived from KONFIDENT Phase III Randomized Control Trial (RCT) (78), KONFIDENT Open-Label Extension (OLE) data (84), and, if applicable, literature.

Mean age at baseline is 37.7 years and 60% of the patient cohort are assumed to be female (78). Patient weight is required in the model for estimating the costs of treatments requiring weight-based dosing. However, weight is assumed to be age-and gender-dependent. Therefore, all patients follow the weight distribution of the general population (116), accounting for modelled patients' baseline age and gender. All patients are alive at model entry.

Of the modelled cohort, 45% of patients are on a combination of long-term prophylaxis and on-demand (LTP + OD) treatment; 55% are on on-demand only (OD only) treatment (4). The distribution of different treatment strategies is specified in the model to calculate an average cohort attack rate. LTP + OD and OD only patients differ in their expected annual attack rate, since LTP treatment reduces attack frequency (24). The calculated cohort average attack rate per year is 14.7. As mentioned, LTP + OD and OD only patients experience the same clinical and economic outcomes. Patient baseline characteristics are summarised in Table 25.

Table 25: Baseline characteristics

Variable	Value	Reference
Patient Demographics		
Age (years)	37.7	KONFIDENT (78)
Female (%)	60	
Baseline Health State Distribution (%)		
Alive	100	Assumption
Dead (Natural Mortality)	0	
Dead (HAE Mortality)	0	
Treatment Strategy Distribution (%)		
LTP + OD	45	Yong *et al.* (2023) (4)
OD Only	55	

Abbreviations: LTP, Long-Term Prophylaxis; OD, On-Demand

Model structure

Of the six cost-effectiveness studies considered relevant to the decision problem, four studies reported sufficient information on the modelling approach. Of these four studies, two studies applied a decision-tree model structure (111, 112), one applied a Discrete Event Simulation (DES) approach (113) and one study used a cohort State-Transition Model (cSTM) approach (110).

Whilst recurrent angioedema attacks are the primary feature of HAE, patients experience significant disruption to their daily lives because of the unpredictability of the disease, compounded by treatment side-effects and barriers to administration, leading to a continuous burden on HRQoL (12, 24, 27, 36-38, 46, 48, 65-67, 69, 117, 118). HAE thus has further long-term impacts on patients' lives even when they are not having an attack (12, 24, 27, 36-38, 46, 48, 65-67, 69, 117, 118). Please see section 1.3 for further discussion on the burden of HAE and current barriers to

treatment administration. To provide a comprehensive evaluation of the comparative value of OD treatments, both direct costs and outcomes associated with acute attacks as well as the ongoing burden of HAE on patients' day-to-day HRQoL ought to be counted.

While a decision-tree framework is simple, it cannot capture the day-to-day HRQoL burden of HAE, which includes aspects such as anticipating the next attack, the treatment route of administration, and treatment associated side effects (119). An alternative approach that can incorporate such domains of health status and utility is DES – a patient-level simulation approach.

The DES framework can provide several advantages. For example, it can improve model accuracy if baseline characteristics are not jointly, normally distributed and not linear in effect (120). DES is also especially suited to modelling continuous events (120). This is valuable when extrapolating disease outcomes over long-periods of time, which is especially advantageous – compared to discrete frameworks – when modelling competing risks within non-absorbing health states (120). OD treatment for HAE, however, is primarily targeted at reducing symptoms and resolving acute attacks, and so assessing the long-term efficacy of OD treatments does not require extrapolation over an extended period. Additionally, there is limited data indicating known competing comorbidities. Other than anxiety and depression, excess of comorbidities within HAE patients relative to general population rates is highly uncertain (24, 121). This was affirmed by expert clinical opinion. Regardless, current OD treatments do not modify the presentation of comorbidities in HAE patients.

From a technical perspective, the predicted outcomes of DES and cSTM models converge as the cycle lengths of these models are reduced (120). If a short cycle length is applicable, e.g., one month or less, such as in HAE, the predictive advantages of DES become negligible (120). DES thus provides no clear advantages within the context of HAE, but significantly increases model complexity.

From grey literature, a single HTA economic model applied a cSTM framework to assess the cost-effectiveness of OD treatment for acute HAE attacks. This model was used in the PBAC appraisal of icatibant (110). The model applied a Markov structure, comprising 9 health states. The rationale for using a Markov structure was that it

allowed additional benefits of OD treatment, outside of the attack period, to be estimated over a longer period presenting multiple attacks (110).

A cSTM framework thus provides the necessary flexibility to assess the of full impact of HAE on patient HRQoL, between and during attacks. Furthermore, a cSTM is far more flexible compared to a decision-tree approach. An cSTM can be collapsed into a decision-tree framework if the cycle length and the time horizon are assumed to be a single discrete period. An cSTM framework is also much easier to interpret and communicate to decision makers compared to a DES approach. Overall, therefore, a cSTM framework offers the most appropriate balance between model simplicity and comprehensibility, while effectively capturing the complex burden of HAE.

Given these considerations, an cSTM was considered the most suitable modelling framework for this decision problem. The model was developed in Microsoft Excel® 365. A summary of features of the *de novo* economic model are provided in Table 26. The core model structure is presented in Figure 12.

Table 26: Features of the base case economic analysis

Factor	Current evaluation, value	Current evaluation justification
Time horizon	Lifetime	As per NICE reference case (122). Although there is limited evidence indicating HAE progresses in severity or causes excess comorbidities over a patient's lifetime, HAE patients experience meaningful impacts on their day-to-day HRQoL due to disease-related anxiety, ongoing and unpredictable treatment administration, and treatment side effects. To appropriately capture the burden of HAE, and these impacts of different treatment administration routes and side effects, a lifetime time horizon is applied.
Cycle length	21 days	Sufficient to capture meaningful changes in treatment effects for on-demand treatments while reducing the probability of an attack event occurring more than once per cycle.

Discount rate	3.5%	As per NICE reference case (122)
Source of utilities	Vignettes	Suitable EQ-5D data are not available from the pivotal trial (78). Health state utility values (HSUVs) are derived from a Discrete Choice Experiment (DCE) vignette study (123). The vignette study informs HSUVs for each treatment, estimated using the DCE elicitation method (123). The model applies utilities from the literature as a scenario. For acute attack disutilities, values are derived from a vignette study sourced from literature (50).
Source of costs	NHS and PSS	Costs are sourced as per the NICE reference case (122).

Abbreviations: NICE, National Institute for Health and Care Excellence; HAE, hereditary angioedema; NHS, National Health Service; PSS, Personal Social Services; EQ-5D, EuroQoL 5-Dimensions; HSUV, health state utility value; DCE, discrete choice experiment

Figure 12: Core model health states

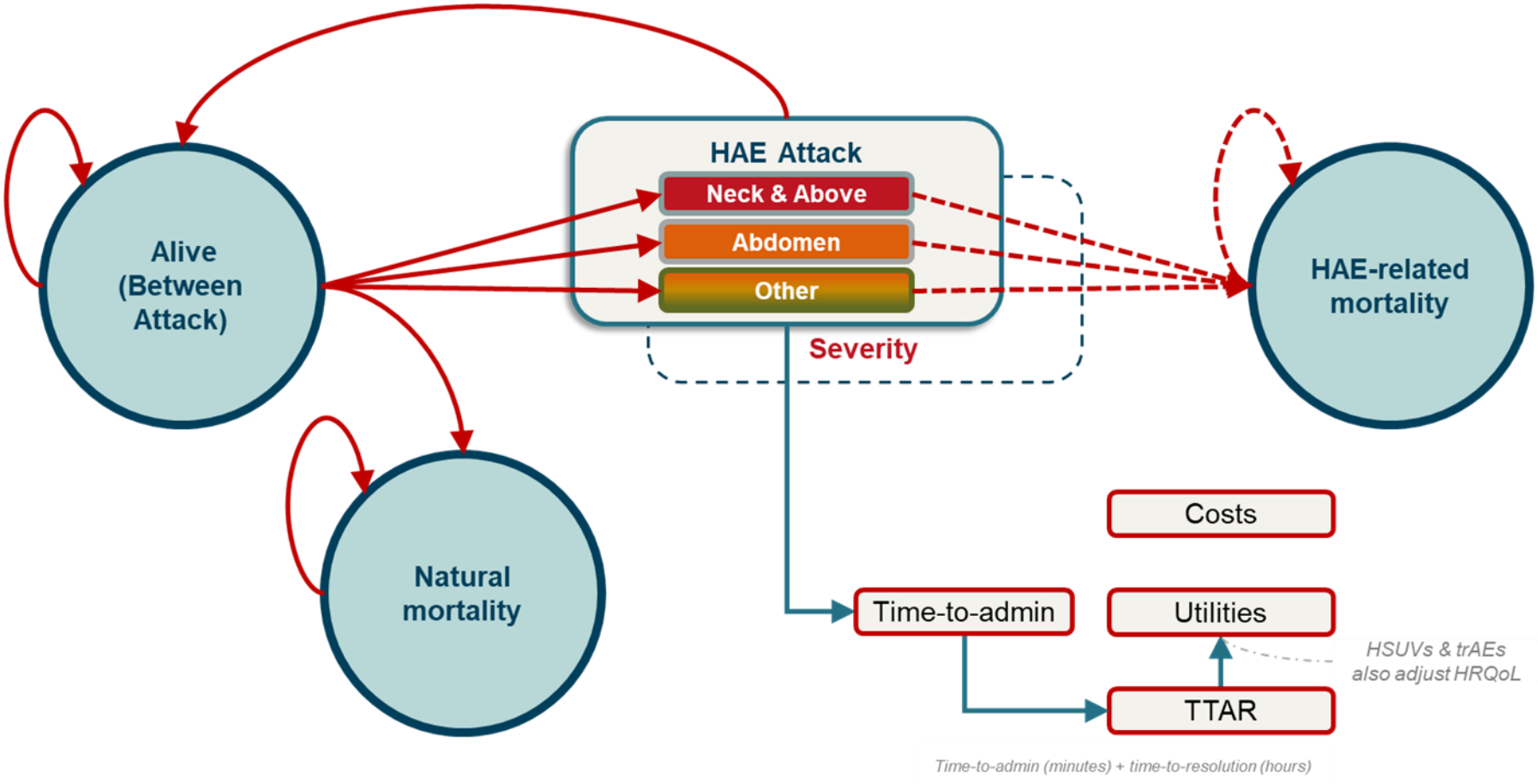
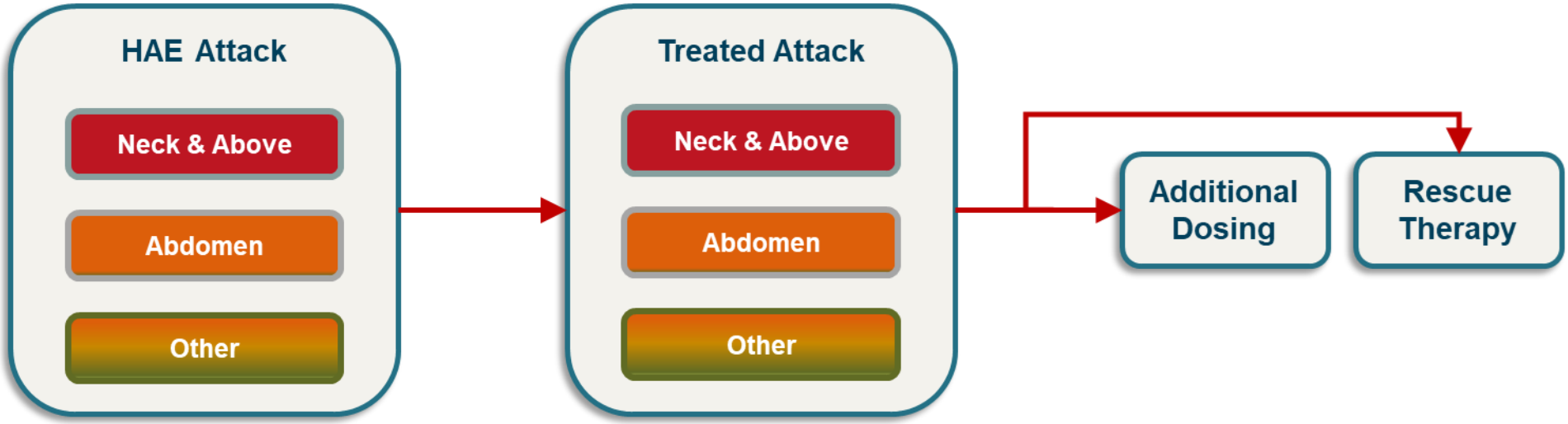


Figure 13: Modelled HAE attack pathways



For each treatment arm, the base case cSTM model comprises two core health states: Alive and Dead (Natural Mortality). See Figure 12 for a visualisation of the model. The Alive health state is used to track the key clinical and economic outcomes associated with HAE attacks. A half-cycle correction is applied to all health states to reduce time bias (122). Where applicable, utilities and costs are adjusted to the cycle and appropriate event period. Patients within the Alive health state are at risk of experiencing an HAE attack in every model cycle. HAE attacks are modelled as acute, transient events (and are not explicit health states). The risk of experiencing an HAE attack is time homogenous and does not change over the modelled time horizon. The model also assumes that all attacks are treated, thus adhering to WAO treatment guidelines as well as precedence in models evaluating the cost-effectiveness of OD treatments for HAE (24, 110).

To appropriately count attack-related costs and utilities, the proportion of patients experiencing an attack, within each cycle, is converted to an attack rate within the model trace before being counted as a utility or cost event. Utilities comprise attack disutilities, side effects, and health state disutilities. Costs related to HAE attacks comprise treatment acquisition, administration and healthcare resource utilisation (HRU), and adverse events. For side effects, these events are assumed to resolve without additional costs to the NHS.

The impact of an attack on a patient's HRQoL is highly variable and dependent upon severity and attack location (23, 27, 50, 69). All patients experience a wide range of attack severities and locations throughout their lifetime. In the base case model, attack location categories are preferred to severity categories. This is because the severity of an attack is highly uncertain: it is strongly influenced by subjective responses to the circumstance of the attack, duration of attack, previous experiences of attacks, anxiety, and the experienced functional deficit (36, 40). (124) This psychological aspect of attack severity is extremely difficult to statistically control. Attack location is therefore a more reliable and consistent indicator for the impact of an attack on patient HRQoL. This assumption was supported by expert clinical opinion.

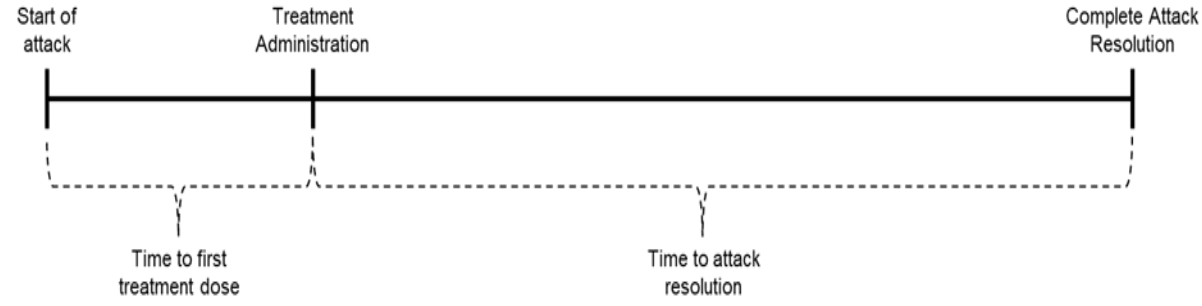
In the base case model, attacks can thus occur in either the 'Neck and Above', 'Abdominal', or 'Other' areas of the body. The attack location 'Other' comprises any

location other than 'Neck and Above' and 'Abdominal' areas. Attacks occurring at the 'Neck and Above' have the largest impact on patient HRQoL, followed by 'Abdominal' attacks, and then 'Other' attacks. Please see Table 25 for a summary of the base case distribution of attack locations.

Using attack severity as the indicator for the magnitude of an attack's impact on patient HRQoL can be applied as a scenario. However, since no HAE HRQoL studies provide the marginal disutilities of an attack by location and severity, choosing attack location or severity is mutually exclusive to avoid double counting.

Once an attack occurs at a specific body location, the disutility is then adjusted by the expected TTAR. See Figure 14 for a visualisation of the modelled attack pathway. We highlight that TTAR is the preferred efficacy outcome for this economic analysis. This is because it is a harder clinical endpoint which captures the entire range of HRQoL impacts of an attack and any treatment effects experienced throughout an attack period. Other endpoints, such as time to minimal symptoms or time to the onset of symptom relief, are more susceptible to patient perception and variability in baseline attack severity.

Figure 14: Attack treatment pathway



While TTAR is the preferred clinical outcome for determining the impact of an acute attack, there is no direct evidence available to compare sebetralstat to comparators between TTAR or any other trial endpoints. Using an indirect treatment comparison (ITC) for decision making is also highly tentative. This is due to significant heterogeneity in trial criteria and endpoint definitions across all OD treatment trials. For instance, significant and statistically unvalidated assumptions on the equivalence of disparate clinical scoring systems are required to perform an ITC. This is compounded by differences in treatment eligibility criteria across trials. As mentioned

in Section 1.3, an attempt was made by Bork *et al.* (2016) to conduct an ITC of on-demand treatments for laryngeal attacks, however due to the heterogeneity in efficacy endpoints, the authors were only able to undertake a descriptive comparison (105).

While a comparison of sebetralstat with rhC1INH was deemed feasible, this ITC was only able to compare the relative time to beginning of symptom relief. Moreover, to perform the analysis, an assumption of equivalence between disparate clinical scoring systems was required. This is because the KONFIDENT trial protocol reflected changes in treatment guidelines, which now advocate for the early treatment of all attacks (24, 125, 126). Its design was distinct from the pivotal phase 3 trials of currently approved on-demand treatments (127). Specifically, for the data used in the ITC by Wang *et al. (*2024), the KONFIDENT used the PGI-C scale to measure time to beginning of symptom relief; the trial of rhC1INH used TEQ (97). Performing an ITC thus requires considerable assumptions that greatly hinder precision and reliability of the indirect evidence for decision making (128, 129). Other clinical outcomes, such as TRAEs, were also highly uncertain, indicated by extremely wide confidence intervals which included a null difference (97). See **Error! Reference source not found.** for further details.

Despite the limited comparative evidence for relative differences in TTAR, there is, nevertheless, clear evidence that earlier OD treatment administration is associated with a shorter total attack duration (24, 127). To alleviate the absence of direct or indirect evidence, the cSTM incorporates a statistical sub-model to estimate the association between TTA and TTAR (130), to obtain an adjusted TTAR for each treatment. Please see section 3.3 for a more detailed discussion on the differences in TTA between treatments and the statistical sub-model.

Once patients have administered their initial dose of OD treatment, patients can also administer additional treatment doses (using the same OD treatment) and use rescue therapy (administer alternative OD treatment). Inputs for additional dosing and rescue therapy do not adjust TTAR. The adjusted TTAR of each treatment is assumed to include adjustment for the TTA of the first dose, any additional doses, and rescue therapy use. Additional doses and rescue therapy are, however, associated with added direct costs. See the section 3.5 for more details. It is important to acknowledge

that, in the absence of appropriate data on the conditional use of rescue therapy, i.e., differentiating between patients not taking additional doses or taking additional doses prior to use of rescue therapy, the proportions of patients requiring additional doses and using rescue therapy are modelled independently.

Patients are also at risk of hospitalization whenever an attack occurs. The risk is conditional on whether treatment is self-administered or administered by an HCP. This implicitly assumes that HCP-assisted administration has a greater delay in treatment administration and thus carries a higher risk of hospitalization due to delayed treatment. This assumption is uncertain given the limited evidence of hospitalization rates between treatments, but it was applied in NICE TA606 (57). Hospitalization is also associated with a cost per event, based on NICE TA606 committee's preferred cost input for hospitalization due to an acute HAE attack (57).

While patients are advised to immediately seek A&E care for any attack in the Neck and Above area, this cost was not included in the model. This is because all treatment cohorts experience the same distribution of attack locations and so this cost would not alter the incremental costs between treatments.

Lastly, patients are at risk of dying in every model cycle. The base case model applies mortality rates from UK general population life tables (131). Within contemporary HAE populations, mortality due to HAE is extremely rare and almost exclusively occurs in undiagnosed HAE patients (24). Since the cSTM assumes all patients are diagnosed at model entry, mortality due to HAE is omitted from the model base case. This assumption was recommended by clinical experts. Nevertheless, mortality due to HAE can be applied in the model as a scenario, which extends the cSTM to three core health states: Alive, Dead (Natural Mortality), and Dead (HAE-related Mortality). The risk of mortality due to HAE is conditional on attack location or attack severity, depending on whether attack location or severity is selected as the indicator for an attack's impact on patient HRQoL.

Intervention technology and comparators

The intervention considered in the cost-effectiveness model is sebetralstat. The comparator is SoC, a basket comparator comprising a share of current OD treatments.

This basket comparator approach is preferred as treatment is typically individualised to each patient and follows current WAO treatment guidelines (24). The base case comparator treatments included in the basket of SoC are icatibant, Ruconest, Berinert. The base case thus compares the incremental outcomes of sebetralstat to a weighted average of the incremental outcomes of these comparators. The weighted incremental outcomes of SoC are calculated based on each comparator's baseline market share. Please see section 3.5 for more information on the share of basket treatments.

The model can also compare sebetralstat to Cinryze. Pairwise cost-effectiveness comparisons of sebetralstat versus each individual comparator are provided as scenario analyses.

3.3 Clinical parameters and variables

As evidenced in the SLR and ITC feasibility assessment, there is no direct or indirect evidence available comparing the TTAR of sebetralstat to comparators. Clinical inputs thus primarily comprise attack related and treatment TTA inputs, derived from KONFIDENT data (78, 84) and literature. TTAR related inputs are also derived from KONFIDENT data (78, 84), where applicable, as well as a post-hoc statistical model (130), which is used to estimate the association between TTA and TTAR.

Attack-related inputs

Attack inputs comprise TTA for each treatment and the distribution of attack locations. The cohort attack rate is time homogenous and does not change from the baseline attack rate, shown in Table 25. There is limited evidence demonstrating predictable changes in HAE attack rates over time, based on, for example, a patient's age or other characteristics. Since OD treatments do not impact long-term attack rates, this assumption is reasonable. However, key aspects of value of an OD treatment are the ability of a patient to treat an attack as early as possible and its ease of administration (24).

Data indicate significant differences in the average TTA of OD treatments, driven largely by route of administration (69, 70). Likewise, there is a significant body of evidence demonstrating that delayed TTA results in poorer response to OD treatments - regardless of administration route – which leads to longer attack duration (24).

Generally, OD treatments are most effective when administered during the start of an attack before swelling has peaked. OD treatments can only halt the attack and prevent additional swelling and do not directly reverse or eliminate swelling that has already occurred. The relationship between TTA and TTAR is thus a direct result of the pathophysiology of HAE and treatment pharmacodynamics, demonstrated across contemporary OD treatments (45, 69, 132, 133).

Delayed TTA is especially prominent in intravenous OD treatments. Consistent delay in the TTA of subcutaneous OD treatment has also been observed albeit less. The mean TTA for sebetralstat is ~[redacted] hours, sourced from KONFIDENT OLE (84). For icatibant, the average TTA is reported to be ~2.9 hours within the UK (86). For IV treatments, several studies report an average TTA of between 6-7 hours (88, 90). However, the identified studies reporting TTA for IV treatment comprised large proportions of patients being administered treatment at secondary healthcare facilities (88, 90). Therefore, data from Christian *et al. (*2024) (69) are used to inform the TTA inputs for all intravenous OD treatments. Christian *et al. (*2024) report an average TTA of ~3.8 hours for OD treatments, regardless of administration route (69). This is a conservative assumption; data from Christian *et al. (*2024) do not differentiate between SC and IV treatment. For a summary of the TTA for each treatment, please see Table 27.

As noted in the model structure section, to distinguish the varying impact of an attack on patient HRQoL and physical functioning, the base case model assumes that an acute attack occurs at a specific body location. The proportions of attacks occurring at specific areas of the body, within each model cycle, are defined by the baseline distribution of attack locations shown in Table 27.

Table 27: Attack related model inputs

Variable	Value	Reference
Duration of HAE Attack (hours)	96	SMC No. (476/08)(115)
Time to Administration (minutes)		

Sebetralstat	[redacted]	Post-hoc analysis. Data on file (130)
Icatibant	174	Longhurst *et al. (*2018) (86)
Ruconest	228	Christian *et al. (*2024) (69)
Berinert	228	
Cinryze	228	
Attack Location (%)		
Neck and Above	13.74	KONFIDENT (78)
Abdominal	40.08	
Other	46.18	
Attack Severity (%) – scenario		
Severe	16.47	KONFIDENT (78)
Moderate	41.18	
Mild	42.35	

Abbreviations: HAE, hereditary angioedema

Attack-resolution

As shown in Figure 12, once an attack occurs and is subsequently treated, the model adjusts the disutility of an attack by the expected TTAR of each treatment. To incorporate the association effect of TTA on TTAR, the economic model applies a hazard ratio to adjust each treatment's TTAR conditional on TTA. The hazard ratio has been estimated using a Cox proportional hazards model (130).

The Cox model uses data from KONFIDENT and controls for treatment sequence, attack number, baseline attack severity, baseline attack location, and TTA. The Cox model adjusts for within subject correlation (i.e., clustered observations). We have applied a fixed effects clustered model (i.e., robust standard errors) rather than a random effects model for two key reasons. Firstly, we are primarily interested in the

coefficient hazards of the model. Secondly, differences between the random effects model and fixed effects clustered model are negligible (130) (134). Therefore, the fixed effects clustered model is easier to interpret and reduces model complexity without comprising validity.

The Cox model used to estimate the hazard ratio can be expressed as

$$h(t \mid X) = h_0(t) \exp\left(\beta_1 X_{i,1} + \beta_2 X_{i,2} + \cdots + \beta_{12} X_{i,12}\right)$$

where $h(t \mid X)$ is the hazard at time t conditional on variates X, $h_0(t)$ is the baseline hazard, and $\beta_1, \ldots, \beta_{12}$ are the coefficients, for the $X_{i,1}, \ldots, X_{i,12}$ covariates, of the categorical variables treatment sequence, attack number, baseline attack severity, baseline attack location and, lastly, a continuous variable, TTA, for individual i (130). Please see Table 28 for a summary of the Cox model results.

Table 28: Cox model results

Explanatory Variable	ln(HR)	95% CI	Robust SE	p-value
Treatment Sequence (ref. group 6)				
6	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
HAE Attack Number (ref. group 3)				
3	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]

1	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Attack Severity (ref. group None or Mild)				
None or Mild	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe or Very Severe	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Attack Location (ref. group Other)				
Other	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal	[redacted]	[redacted]	[redacted]	[redacted]
Neck and Above	[redacted]	[redacted]	[redacted]	[redacted]
Time to Administration (TTA)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HR, hazard ratio; CI, confidence interval; SE, Standard Error; NE, not estimated

After adjusting for treatment sequence, attack number, baseline attack severity, and baseline attack location, the coefficient value estimated by the Cox model for the relationship between TTA and TTAR is $\beta_{10} \approx$ [redacted]. This indicates a negative relationship between TTA and TTAR, which aligns with literature and clinical expert opinion (24) (69) (45, 70, 87, 132, 135). From the Cox model, we can estimate the average association between TTA and TTAR, for each treatment, using a function which accounts for the expected TTA of treatment as follows:

$$TTAR_{adjusted} = \phi + \exp(-\beta_{12}) \cdot (t_j - \bar{t}\,) + \exp(-\beta_k) \cdot X_k$$

where ϕ is the baseline TTAR, i.e., the average TTAR, $exp(-\beta_{10})$ is the hazard ratio estimating the relationship between TTA and TTAR, t_j is the average TTA for treatment j (in hours), $\bar{t}$ is the mean cohort TTA (obtained from the KONFIDENT data which are used to inform the statistical model), $exp(-\beta_k)$ is the hazard ratio for attack location k, and X_k is the attack location covariate.

In the economic model, the hazard ratio is intended to indicate how increases in TTA reduce the hazard of reaching the TTAR endpoint (i.e., attack resolution). Therefore, to obtain the appropriate model input, the inverse hazard ratio from the Cox model is taken, [redacted]. An inverse hazard ratio of [redacted] indicates that for each unit increase in TTA, the hazard of not reaching the TTAR endpoint increases by a factor of roughly [redacted], i.e., the hazard of an attack not resolving within the period increases. The same logic applies to the attack location (or severity) hazard ratios. Additionally, we apply a means difference to TTA, i.e., $(t_j - \bar{t})$, to centre the expected TTA of each treatment. This allows for a relative comparison for the TTA of each treatment. In the economic model, the predictive function is thus defined as:

$$\mathrm{TTA}R_{adjusted} = \phi + \mathrm{HR}_{\mathrm{TTA}}{}^{-1} \cdot \left(\frac{t_j}{60} - \bar{t}\right) + HR_{Location}^{-1} \cdot X_k$$

where $HR_{TTA}{}^{-1}$ is the inverse hazard ratio for TTA (i.e., [redacted]), $HR_{Location}^{-1}$ is the inverse hazard ratio for the specific attack location, and X_k is the proportion of patients experiencing an attack at location k. We provide the following example to illustrate how the function calculates an adjusted TTAR within the economic model. Assuming an average baseline TTAR of [redacted] hours, a TTA hazard ratio of [redacted], a TTA of [redacted], a hazard ratio of [redacted] for Neck and Above attacks, and that [redacted]% of attacks occur in this area, we calculate an adjusted TTAR as follows:

[redacted]

For a summary of the adjusted TTAR calculated for each treatment, as well as other TTAR related inputs, please see Table 29.

Table 29: Time to attack resolution inputs

Variable	Value	Reference

Baseline TTAR (hours)	[redacted]	Post-hoc analysis. Data on file (130)
TTA ~ TTAR Hazard Ratio	[redacted]	
Attack Location Hazard (base case)		
Neck and Above	[redacted]	Post-hoc analysis. Data on file (130)
Abdominal	[redacted]	
Other	[redacted]	
Attack Severity Hazard (scenario)		
Severe	[redacted]	Post-hoc analysis. Data on file (130)
Moderate	[redacted]	
Mild	[redacted]	
Adjusted TTAR (hours) by Treatment and Attack Location		
Sebetralstat		Calculation
Neck and Above	[redacted]	
Abdominal	[redacted]	
Other	[redacted]	
Icatibant		
Neck and Above	[redacted]	
Abdominal	[redacted]	
Other	[redacted]	
Ruconest		

Neck and Above	[redacted]	
Abdominal	[redacted]	
Other	[redacted]	
Berinert		
Neck and Above	[redacted]	
Abdominal	[redacted]	
Other	[redacted]	
Cinryze		
Neck and Above	[redacted]	
Abdominal	[redacted]	
Other	[redacted]	

Abbreviations: TTAR, time to attack resolution; TTA, time to administration

Other clinical inputs

During an HAE attack, and once a patient has administered OD treatment, patients can then take an additional dose of the same treatment and use rescue therapy (24, 78).

The proportion of attacks requiring additional dosing per cycle is fixed and does not change over time, but it is specific to each treatment. The number of additional doses per cycle is calculated as the product between the number of acute attacks and the proportion of attacks requiring additional treatment doses, per cycle.

The same logic is applied to the proportion of attacks that require rescue therapy: calculated as the product between the number of attacks and the proportion of attacks requiring rescue therapy, per cycle. For details on the costs and HRU of additional dosing and rescue therapy, see the section 3.5. For a summary of clinical inputs associated with additional dosing and rescue therapy use, please see Table 30.

The only AE included in the model is risk of hospitalisation. The risk of hospitalisation is an annualised probability and dependent on whether treatment is self-administered or administered by a healthcare professional (57).

Several side effects for each treatment are included. Treatment side effects include injection site reactions, painful burning or stinging during injection, and headaches, nausea, or indigestion (69). The risk of each side effects is specified as a risk per treatment administration and specific to each treatment, based on data derived from literature (69, 85, 87).

Table 30: Other clinical inputs

Variable	Value	Reference
Additional Dosing (% per attack)		
Sebetralstat	24.10	KONFIDENT (84)
Icatibant	12.70	Longhurst *et al. (*2018) (86)
Ruconest	18.18	Riedl *et al. (*2017) (91)
Berinert	1.11	Craig *et al. (*2011) (88)
Cinryze	18.18	Assumption [equivalent to Ruconest]
Rescue Therapy (% per attack)		
Sebetralstat	8.10	KONFIDENT (84)
Icatibant	16.67	Circadi *et al. (*2010) (85)
Ruconest	7.32	Zuraw *et al. (*2010) (90)
Berinert	7.32	Assumption [equivalent to Ruconest]
Cinryze	7.32	
Adverse Events (annual %)		
Risk of Hospitalization		

Self-Administration	5.80	NICE [TA606] (57)
HCP Administration	12.50	
Treatment Side Effects (% per admin)		
Icatibant		
Injection skin reaction	97.22	Cicardi *et al. (*2010) (85)
Injection painful burning, stinging	50.90	Christian *et al. (*2024) (69)
Ruconest		
Injection skin reaction	10.00	Christian *et al. (*2024) (69)
Injection painful burning, stinging	20.00	
Berinert		
Injection skin reaction	24.78	Zanichelli *et al. (*2018) (87)
Injection painful burning, stinging	12.50	Christian *et al. (*2024) (69)
Cinryze		
Injection skin reaction	24.78	Assumption [equivalent to Berinert]
Injection painful burning, stinging	12.50	

Abbreviations: HCP, health care professional

Lastly, patients are at risk of mortality throughout the modelled time horizon. The base case assumes that the HAE patients experience the same risk of mortality as the general population. Risk of mortality is derived from UK general population lifetables (131), adjusted to a per cycle risk and conditional on simulated patient age and baseline gender distribution.

3.4 Measurement and valuation of health effects

In line with the NICE reference case (122), health effects in the model are measured in quality-adjusted life years (QALYs). QALYs are calculated based on life years and various utility and disutility inputs. These utilities and disutilities include age- and gender-related utility adjustments and decrements in utility for acute HAE attacks and between-attack health states.

Health-related quality-of-life data from clinical trials

HRQoL data was not collected in the KONFIDENT trial (78). HRQoL data are therefore sourced from literature and a single commissioned study. Please see Appendix F for detailed discussion on the SLR methods used to identify utility data from the literature.

Mapping

Not applicable.

Health-related quality-of-life studies

The SLR identified a single study, Aygoren-Pursun *et al. (*2016), using the EuroQoL 5-Dimensions (EQ-5D) to estimate the burden of acute attacks using UK population-based EQ-5D utility weights (136). Aygoren-Pursun *et al. (*2016) used data from the cross-sectional HAE-BOIS-Europe survey. However, the study used an indirect non-validated approach for obtaining EQ-5D-based utilities. Moreover, the study did not evaluate the impact on HRQoL by attack location (136).

One other study evaluated the HRQoL of HAE patients within the UK (50). However, the study applied a Time Trade-Off method using vignette descriptions of health states (50). The EQ-5D tool is typically preferred as a tool to measure disease burden and utility weights for health technology assessment (HTA) in England (50). Nevertheless, when appropriate, a vignette study can be used to generate utility weights, using the time trade-off (TTO) method for example, with public or patient participants valuating vignette descriptions of health states (137). As noted by Lo *et al. (*2022) (50), a key issue with the EQ-5D is that it is less sensitive to short-term fluctuations in health status (50). This is relevant for acute HAE attacks, as it is challenging to assess HAE patients during an attack given the variable and unpredictable nature of these events.

Given to the limitations of the EQ-5D tool for assessing acute HAE attacks, the objective of the study by Lo *et al. (*2022) was to capture the relative burden of HAE health and caregiver states, including different attack locations, through a TTO analysis involving participants from the general population. For the development of the health state vignettes, qualitative interviews with 15 patients, 5 caregivers and 1 clinical expert were performed. TTO analysis was based on vignette valuation completed by 100 members of the general population (50).

In addition to acute attacks, patients experience a burden and impact on their daily lives from the disease and treatment (123). Injectable treatments are considered burdensome, hard to prepare and administer, especially when in public, and are associated with consistent side effects. Issues with portability also mean people with HAE do not always carry OD treatments, leading to an extended delay in treatment when attacks occur (123). However, utility values of relevant treatment process attributes are challenging to capture.

Capturing utilities in a clinical trial would require randomizing participants to an injectable on-demand and oral on-demand treatment arm with large sample sizes and is not feasible in a double-blind trial design. Observational utility data collection is also not possible due to no prior oral on-demand treatments currently being on the market. Moreover, direct valuation of HRQL using a generic instrument designed to assess overall health status - such as the EQ-5D - is unlikely to be sensitive enough to isolate differences in utility associated with treatment administration. Stated preference methods, specifically discrete choice experiment (DCE) methods, provide an appropriate alternative (123).

For the disutility associated with the day-to-day burden of disease and treatment administration, a vignette Discrete Choice Elicitation (DCE) study was therefore commissioned to estimate these disutilities for OD treatments, including oral versus injectable administration and treatment-related side effects. Health states were valued by HAE patients and the general population in DCE preference tasks. Responses collected from the DCE were then analyzed using logit models to understand how the changes in treatment attributes influence preferences (123).

The DCE approach was chosen based on two key considerations. First, the DCE method can be adapted more easily for eliciting preferences from multiple stakeholder groups, i.e. patient and general population. Second, the DCE method has an experimental design at its core which allows for independent, precise utility estimates to be obtained for treatment administration and treatment side effects, while considering other treatment-related attributes and their impact on HRQL (123). Please see Appendix M for further discussion.

Adverse reactions

No consistent Grade 3+ trAEs occur for any OD treatment, and so utilities associated with adverse reactions are not applied in the economic model.

Health-related quality-of-life data used in the cost-effectiveness analysis

Given the above, the base case economic model applies data from Lo *et al. (*2022) to inform the disutility of acute HAE attacks by location (50). From Table 3 in Lo *et al. (*2022), the attack-free health state utility value is 0.783. The utility value within the abdominal attack health state is 0.345. Therefore, in the model, the annual disutility of an attack within the abdominal area is calculated as 0.345 - 0.783 = -0.438. The baseline annual disutility of an attack occurring in the Neck and Above area is -0.478. For Abdominal attacks, it is -0.438. For Other attacks, the baseline annual disutility is -0.201 (50). To obtain a disutility appropriate to the acute attack period, the disutility of each attack location is adjusted by the duration of the event and annualised cycle length. The baseline disutility of an attack by location is further adjusted by each treatment's expected TTAR.

As Lo *et al. (*2022) elicited HSUVs for both facial and laryngeal attacks, the model applies the average decrement between these two HSUVs to obtain an acute disutility for the Neck and Above location. The disutility values for acute attacks by location are summarised in Table 31.

For health states utilities, UK general population health state utilities are applied to all patients, regardless of treatment. To reflect decreases in HRQoL seen in the UK general population, an age- and gender-related utility adjustment based on Ara and Brazier (2010) (138) is also applied to health state utilities over the model time

horizon. The utility adjustment is estimated by a regression model with age and gender as variables. The regression model is defined as:

$$y_i = \beta_0 + \beta_1 Male_i - \beta_2 Age_i - \beta_3 Age_i^2$$

$$y_i = 0.95086 + 0.02121 \times \%Male - 0.00026 \times Age - 0.00003 \times Age^2$$

In addition to general population utility norms, HSUV decrements are applied to each treatment cohort. These values are sourced from the commissioned DCE study (123). These utility decrements value patient preferences between treatment types and the impact of treatment side effects on patient day-to-day HRQoL. The DCE values used in the base case model are sampled from the patient population (n = 285) and are duration-rescaled (123). Please see the Appendix M for further technical details on the study methodology. We highlight that the preference utility between subcutaneous and oral treatment is not applied in the model base case. This is because the result was not statistically significant, and the 95% confidence interval included a null difference (123). This decision was based on expert recommendation.

Table 31: Summary of utility values for cost-effectiveness analysis

State/Event	**Utility value: mean (SE)**	**95% CI**	**Reference in submission (section and page number)**	**Justification**
HSUVs				
Type of Treatment (Duration-rescaled)				
Oral tablet	0.000	N/A	Section 3.4	See section 3.2, section 3.3, and section 3.4
Self-administered injection under skin	0.000	N/A		
Self-administered infusion into the vein	[redacted]	[redacted]		

HCP-administered infusion into the vein	[redacted]	[redacted]		
Side Effects (Duration-rescaled)				
None	0.0	N/A	Section 3.4	See section 3.2, section 3.3, and section 3.4
Skin reaction to the injection	[redacted]	[redacted]		
Painful burning or stinging sensation when medication is administered	[redacted]	[redacted]		
Headaches, diarrhoea, nausea and/or indigestion	[redacted]	[redacted]		
Attack Disutility (prior to duration adjustment in model)				
Neck and Above	-0.478 (0.049)	N/A	Section 3.4	See section 3.2, section 3.3, and section 3.4
Abdominal	-0.438 (0.046)	N/A		
Other	-0.201 (0.038)	N/A		

Abbreviations: HSUV, health state utility value; SE, standard error; CI, confidence interval

3.5 Cost and healthcare resource use identification, measurement and valuation

The cost-effectiveness analysis is conducted from the UK NHS and Personal Social Services (PSS) perspective. Therefore, only direct costs are considered in the base-case analysis (122). Where applicable, costs are inflated to 2024 UK pound sterling using the UK Health Consumer Price Index (139).

Intervention and comparators' costs and resource use

Drug acquisition costs of each OD treatment are calculated as a cost per attack. These costs comprise the initial OD drug administration cost (which is the first dose of OD treatment administered at the start of an attack), additional dosing costs, and rescue therapy costs.

The cost of OD treatment per attack is dependent upon the dose required per attack, for each OD treatment. For all treatments, the cost per administration is estimated by first calculating the quotient between the treatment pack size and treatment dose. This gives the proportion of the treatment pack used per dose. Then, to calculate the overall cost per dose, the proportion of the treatment pack used for a single dose of OD treatment is multiplied by the drug acquisition cost per pack. This provides the expected drug cost per dose.

For treatments that require weight-based dosing, dosage is calculated as the treatment's dose strength multiplied by the cohort weight - which is age-and gender-dependent derived from the UK general population weight distribution (116) - and then divided by the treatment's pack size. To illustrate, Ruconest requires a dosage of 50 IU/kg, up to a maximum dosage of 4200 IU. The standard pack size of Ruconest is 2100 IU. Assuming a patient weight of 77.86 kg, the expected dose is calculated as $(77.86 \times 50)/2100 \approx 1390$ units.

In addition, the base case model assumes reasonable drug wastage for weight-based dosing. To account for drug wastage, the model applies a ceiling function to the weight-based dose, which rounds the dose to the nearest multiple of 0.2. Using the same Ruconest example, the expected dose for Ruconest is hence rounded to 1500 IU. Assuming no drug wastage in the model can be applied as a scenario.

Since patients use the same OD treatment for any additional doses during an attack, OD drug costs are applied in the same way as the initial administration cost. However, the per cycle cost of additional dosing is conditional on the number of attacks requiring an additional dose per cycle.

The cost of rescue therapy is a weighted average cost, calculated using the costs of each treatment used for rescue therapy multiplied by the expected HRU frequency of rescue therapy treatments. Over the modelled time horizon, the average cost of rescue therapy is £1,403. It is important to highlight that the cost of rescue therapy, when weight-based treatments are included, can vary over the modelled time horizon because the average cohort weight is age-dependent.

Administration costs are also counted per attack. These costs are applied to the proportion of patients who require healthcare professional (HCP) assisted administration. A full hour cost of HCP time is applied for both subcutaneous and intravenous treatments. It is assumed that oral treatments do not incur HCP assisted administration costs. In the base case, the cost per working hour of an HCP is assumed equivalent to a band-6 nurse, sourced from Personal Social Services Research Unit (PSSRU) (140).

The cost of assisted administration is also added to the total costs of rescue therapy. The calculated cost of assisted administration associated with rescue therapy use is £11.76. For a summary of intervention and comparator costs and HRU, see Table 32. When appropriate, costs and HRU are per-cycle adjusted.

Table 32: Base case acquisition, administration, and monitoring costs

Variable	Value	Reference
Market Share of Comparators comprising SoC (%)		
Icatibant	[redacted]	Hospital Pharmacy Audit for OD HAE treatments (141)
Ruconest	[redacted]	
Berinert	[redacted]	

Cinryze	[redacted]	
Treatments Used as Rescue Therapy (%)		
Sebetralstat	0.00	Assumption
Icatibant	[redacted]	Assumption [equivalent to baseline market share]
Ruconest	[redacted]	
Berinert	[redacted]	
Cinryze	[redacted]	
Treatment Acquisition Cost (per pack)		
Sebetralstat	£[redacted]	Assumption
Icatibant	£837	BNF (142)
Ruconest	£750	BNF (143)
Berinert	£670	BNF (144)
Cinryze	£668	BNF (145)
Treatment Pack Size		
Sebetralstat	1800 mg	Assumption
Icatibant	30 mg	BNF (142)
Ruconest	2100 IU	BNF (143)
Berinert	500 IU	BNF (144)
Cinryze	500 IU	BNF (145)
Treatment Dosing Assumptions		
Sebetralstat	300 mg	Assumption

Icatibant	30 mg	BNF (142)
Ruconest	50 IU/kg	BNF (143)
Berinert	20 IU/kg	BNF (144)
Cinryze	1000 IU	BNF (145)
Rescue Therapy Costs		
Drug Costs	£1,403	Assumption [average of lifetime distribution]
HCP Administration Costs	£11.76	Assumption [weighted average of assisted administration costs]
Total Rescue Therapy Costs	£1,414.76	Calculation [time horizon average]
Treatment Self-Administration (%)		
Sebetralstat	100	Assumption
Icatibant	95.80	Longhurst *et al. (*2018) (86)
Ruconest	61.00	Yong *et al. (*2023) (4)
Berinert	61.00	Yong *et al. (*2023) (4)
Cinryze	61.00	Yong *et al. (*2023) (4)
Assisted Administration Costs		
Oral	£0.0	Assumption
Subcutaneous	£57.0	PSSRU Unit Costs Table 9.2.1 (140)
Intravenous	£57.0	PSSRU Unit Costs Table 9.2.1 (140)

Adverse Event Costs		
Hospitalisation	£582.0	NICE TA606 (57)

Abbreviations: BNF, British National Formulary; PSSRU, Personal Social Services Research Unit; SoC, standard of care; HCP, health care professional

Health-state unit costs and resource use

There are no known differences in routine costs between OD HAE treatments and so no direct costs are associated with sojourning in any model health states. This is because OD treatments do not affect the frequency of routine costs or reduce health state costs associated with HAE.

Adverse reaction unit costs and resource use

No consistent Grade 3+ trAEs occur for any OD treatment, and so these costs are not applied in the economic model. Any treatment side effects are assumed to spontaneously resolve within a defined period without additional costs to the NHS.

3.6 Uncertainty

Current on-demand treatments for HAE attacks are delivered either intravenously or subcutaneously. This poses challenges for the ability to generate high-quality blinded trial evidence comparing sebetralstat with currently-available on-demand treatments.

A randomised double-blind placebo controlled head-to-head trial between sebetralstat and the current on-demand treatments was not possible for the following reasons:

- Time to treatment for SC or IV treatments vs oral sebetralstat would impact the comparability of outcomes. For icatibant, after training in a prospective multi-centre study, mean time to treatment was significantly shorter with self-administration (143 ± 226 minutes) than with HCP-administration (361 ± 503 minutes; P <.0001).(146) For IV C1INH, after training in a prospective single-centre study, median time to treatment was 2 h (IQR: 1–4) (87).

- Only a minority of adult and adolescent patients are comfortable (even after training) self-administering intravenous on-demand treatments in an acute setting. Given these challenges, all pivotal trials (double-blind RCTs) for

intravenous C1-inhibitor preparations required injection by health care professionals in an outpatient setting. Studies assessing self-administration with C1 inhibitor preparations were conducted with open-label designs.

- An additional challenge for C1INH is that multiple approved proprietary intravenous preparations of plasma-derived C1-inhibitor or recombinant human C1-inhibitor from different companies using different manufacturing methods are available across various countries which each represent a minority of on-demand treatments used in those countries. Different purity profiles have been demonstrated (147) and comparability of clinical outcomes has not been published.

- Even if it were possible to treat simultaneously, for the most commonly used on-demand treatment, icatibant, nearly all patients experience an active substance driven injection site reaction driven by binding to the skin mast cell receptor MRGPRX2 as noted previously, making blinding challenging. Indeed, in the clinical review by the FDA [NDA 22150], Dr. Brian Porter highlighted that "blinding of the randomized treatment phase in all three trials may have been compromised due to the emergence of local injection site reactions almost exclusively in the active treatment arms versus placebo groups."

- Icatibant is not approved in the US for adolescents, which would also limit the opportunity to do a global trial with one comparator.

- Lastly, HAE is a rare disease with great intra-patient and intra-attack variability, and to find sufficient patients with sufficient numbers of attacks to conduct a trial with meaningful statistical power to detect differences (or similarities) between sebetralstat and another approved on-demand treatment would be challenging. The pivotal phase 3 trial, KONFIDENT (KVD900-301) is already the largest pivotal controlled HAE trial conducted to date, and it had a total of 136 patients.

For these reasons, the company has sought alternative methods to explore comparative effectiveness in the form of an indirect treatment comparison (ITC). Please see Section 2.10 for details of the ITC.

3.7 Managed access proposal

Not applicable.

3.8 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

Please see Table 33 for a summary of the base case analysis inputs.

Table 33: Summary of variables applied in the economic model

Variable	Value (reference in submission)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Discount costs (%)	3.5	Fixed	Section 3.2
Discount QALYs (%)	3.5	Fixed	
Time horizon (years)	62.30	Fixed	
Cycle length (days)	21	Fixed	
Baseline Patient Characteristics			
Mean number of attacks per year	14.71	[10.71; 19.34] (Gamma)	Section 3.2
Female (%)	60	[41.8; 76.8] (Beta)	

Age at baseline	37.7	[34.96; 40.55] (Gamma)	
Clinical Inputs			
Untreated attack duration (hours)	72	[52.41; 94.66] (Gamma)	Section 3.3
Time to administration (minutes)			
Sebetralstat	[redacted]	[redacted] (Gamma)	Section 3.3
Icatibant	174	[114.32; 246.02] (Gamma)	
Ruconest	228	[158.08; 310.52] (Gamma)	
Berinert	228	[158.08; 310.52] (Gamma)	
Cinryze	228	[158.08; 310.52] (Gamma)	
Unadjusted Time to attack resolution (hours)	[redacted]	Fixed	
TTA ~ TTAR Hazard Ratio	[redacted]	[redacted] (Log-Normal)	
% patients additional doses (per attack)			
Sebetralstat	24.1	[17.4; 31.5] (Beta)	Section 3.3

Icatibant	12.7	[9.2; 16.7] (Beta)	
Ruconest	18.2	[13.2; 23.8] (Beta)	
Berinert	1.11	[0.8; 1.5] (Beta)	
Cinryze	18.2	[13.2; 23.8] (Beta)	
% patients using rescue therapy (per attack)			
Sebetralstat	8.1	[5.9; 10.6] (Beta)	Section 3.3
Icatibant	16.7	[12.1; 21.8] (Beta)	
Ruconest	7.3	[5.3; 9.6] (Beta)	
Berinert	7.3	[5.3; 9.6] (Beta)	
Cinryze	7.3	[5.3; 9.6] (Beta)	
Distribution of attack locations (% per attack)			
Neck and Above	13.7	[0.0; 20.6] (Multivariate)	Section 3.3
Abdominal	40.1	[22.2; 38.1] (Multivariate)	

Other	46.2	[77.8; 41.2] (Multivariate)	
Distribution of attack severity (% per attack - scenario)			
Severe	16.5	[0.0; 22.8] (Multivariate)	Section 3.3
Moderate	41.2	[43.6; 38.3] (Multivariate)	
Mild	42.4	[56.4; 38.9] (Multivariate)	
Risk of hospitalization (% per year)			
Self-Administration	5.8	[4.2; 7.6] (Beta)	Section 3.3
HCP Administration	12.5	[9.1; 16.4] (Beta)	
Side effects (% per administration)			
Icatibant			
Injection skin reaction	97.2	[43.1; 100] (Beta)	Section 3.3
Injection painful burning, stinging	50.9	[36.0; 65.7] (Beta)	
Ruconest			

Injection skin reaction	10.0	[7.3; 13.1] (Beta)	Section 3.3
Injection painful burning, stinging	20.0	[14.5; 26.2] (Beta)	
Berinert			
Injection skin reaction	24.8	[17.9; 32.4] (Beta)	Section 3.3
Injection painful burning, stinging	12.5	[9.1; 16.4] (Beta)	
Cinryze			
Injection skin reaction	24.8	[17.9; 32.4] (Beta)	Section 3.3
Injection painful burning, stinging	12.5	[9.1; 16.4] (Beta)	
HRQoL Inputs			
Acute attack disutility by location			
Neck and Above	-0.48	[-0.38; -0.57] (Beta)	Section 3.4
Abdominal	-0.44	[-0.35; -0.53] (Beta)	
Other	-0.20	[-0.13; -0.28] (Beta)	

Health state utility values (by treatment type)			
Oral	0.00	Fixed	Section 3.4
Subcutaneous	0.00	Fixed	
Intravenous (self-administered)	[redacted]	[redacted] (Beta)	
Intravenous (HCP administered)	[redacted]	[redacted] (Beta)	
Side effects (unadjusted disutilities)			
Injection site reaction	[redacted]	[redacted] (Beta)	Section 3.4
Injection painful burning, stinging	[redacted]	[redacted] (Beta)	
Headaches, diarrhea, nausea	[redacted]	[redacted] (Beta)	
Costs and HRU Inputs			
% market share of comparator treatment (%)t			
Icatibant	[redacted]	Fixed	Section 3.2 and 3.5
Ruconest	[redacted]	Fixed	

Berinert	[redacted]	Fixed	
Cinryze	[redacted]	Fixed	
Mean number of additional doses required			
Sebetralstat	1.00	Fixed	Section 3.5
Icatibant	1.00	[0.73.; 1.32] (Gamma)	
Ruconest	1.00	Fixed	
Berinert	1.00	Fixed	
Cinryze	1.00	Fixed	
% treatment used for rescue therapy (fixed %)			
Sebetralstat	0.00	Fixed	Section 3.5
Icatibant	[redacted]	Fixed	
Ruconest	[redacted]	Fixed	
Berinert	[redacted]	Fixed	

Cinryze	[redacted]	Fixed	
Treatment cost per pack			
Sebetralstat	£[redacted]	Fixed	Section 3.5
Icatibant	£837	Fixed	
Ruconest	£750	Fixed	
Berinert	£670	Fixed	
Cinryze	£668	Fixed	
Treatment pack size			
Sebetralstat	1800mg	Fixed	Section 3.5
Icatibant	30mg	Fixed	
Ruconest	2100 IU	Fixed	
Berinert	500 IU	Fixed	
Cinryze	500 IU	Fixed	

Treatment dose per administration			
Sebetralstat	300mg	Fixed	Section 3.5
Icatibant	30mg	Fixed	
Ruconest	50 IU/kg	Fixed	
Berinert	20 IU/kg	Fixed	
Cinryze	1000 IU	Fixed	
% patients self-administering treatment (%)			
Sebetralstat	100	Fixed	Section 3.3
Icatibant	95.8	[41.8.; 100] (Beta)	
Ruconest	61.0	[42.5.; 78.0] (Beta)	
Berinert	61.0	[42.5.; 78.0] (Beta)	
Cinryze	61.0	[42.5.; 78.0] (Beta)	
Cost of administration by admin route			

Oral	0.0	Fixed	Section 3.5
Subcutaneous	57.0	[41.5.; 75.9] (Gamma)	
Intravenous	57.0	[41.5.; 75.9] (Gamma)	
Cost of hospitalisation	582.3	[423.8; 765.5] (Gamma)	

Abbreviations: CI, confidence interval; TTA, time to administration; TTAR, time to attack resolution; HCP, health care professional

Assumptions

Table 34: Key model assumptions

Model Parameters	Assumptions
Type I and Type II HAE	Type I and Type II patients experience the same clinical and economic outcomes
Treatment Strategy	Patients experience the same clinical and economic outcomes, regardless of if they are on LTP + OD or OD only treatment.
Acute HAE Attacks	HAE attacks are modelled as acute, transient events associated with per event costs and health effects.
Time to Administration	Time to treatment administration moderates the expected time to attack resolution of each treatment.
Time to Attack Resolution	All treatments have an equal baseline efficacy. However, time to attack resolution is conditional on a treatment's time to administration. The estimated time to attack resolution adjusts the disutility of an acute attack event.
Route of Administration	Route of administration impacts the day-to-day HRQoL of patients.
Treatment Side Effects	Health state disutilities are applied to each treatment arm, based on the impact of the treatment's side effects.
Comparator	The base case comparator is a basket of current treatment options, reflecting the individualised approach to treatment in HAE and current WAOO treatment guidelines.
Mortality	Mortality from HAE is assumed to be extremely rare and only relevant to undiagnosed patients. All patients in the model are assumed diagnosed and,

	therefore, only natural mortality is applied in the model base case.

Abbreviations: HAE, hereditary angioedema; LTP, long-term prophylaxis; OD, on-demand; HRQoL, health-related quality-of-life

3.9 Base-case results

Base-case incremental cost-effectiveness analysis results

The base case cost-effectiveness results are presented in Table 35 and Table 36. NHB is negative at the £20,000 and £30,000 willingness to pay thresholds (Table 36).

Table 35: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Sebetralstat	£[redacted]	22.01	18.35	-	-	-	-
Standard of care	£556,122	22.01	18.24	£[redacted]	0.00	0.11	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 36: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Sebetralstat	[redacted]	18.35	-	-	-	-
Standard of care	£556,122	18.24	[redacted]	0.11	[redacted]	[redacted]

Abbreviations: LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years

3.10 Exploring uncertainty

Extensive sensitivity analyses were carried out including Probabilistic sensitivity analyses (PSA), one-way deterministic sensitivity analysis (OWSA), and scenario analyses.

Probabilistic sensitivity analysis

3000 iterations of the model were simulated for PSA. The running ICER stabilizes after approximately 1750-2250 iterations. Please see Figure 15 for a visualization of the cost-effectiveness plane. See

Figure 16 for the cost-effectiveness acceptability curve (CEAC). The ICER from the PSA at a 3.5% discount rate was £[redacted], compared with £[redacted] in the deterministic base case. This illustrates minor decision uncertainty, driven primarily by the proportion of patients within each of the sebetralstat, icatibant, and Berinert treatment cohorts taking additional doses or rescue therapy per attack. At a £30,000 willingness-to-pay (WTP) threshold, sebetralstat has a [redacted]% probability of being cost-effective. At a £20,000 WTP, sebetralstat has a [redacted]% probability of being cost-effective.

Figure 15: Base case probabilistic cost-effectiveness plane (CEP)

Figure 16: Base case cost-effective acceptability curve (CEAC)

Deterministic sensitivity analysis

At a 3.5% discount rate, the most sensitive parameters in the OWSA were the proportion of patients using additional doses per attack, the proportion of patients requiring rescue therapy, the number of icatibant doses required when taking an additional dose, the mean cohort attack rate, and changes to the proportion of attacks occurring at 'Other' attack locations. Please refer to Figure 17 for the OWSA tornado diagram.

Figure 17: Base case one-way sensitivity analysis (OWSA)

Scenario analysis

The most sensitive parameters in the scenario analysis were the pairwise cost-effectiveness comparisons versus icatibant and Berinert, the proportion of sebetralstat patients taking an additional dose, and setting the baseline age to 12 years.

Please see Table 37 for a summary of the scenario analysis results.

Table 37: Scenario analysis results

Base case	Scenario	Incremental costs	Incremental QALYs	ICER
Base case	-	[redacted]	[redacted]	[redacted]
Sebetralstat vs SoC	Sebetralstat vs Icatibant	[redacted]	[redacted]	[redacted]
Sebetralstat vs SoC	Sebetralstat vs Ruconest	[redacted]	[redacted]	[redacted]
Sebetralstat vs SoC	Sebetralstat vs Berinert	[redacted]	[redacted]	[redacted]
Sebetralstat vs SoC	Sebetralstat vs Cinryze	[redacted]	[redacted]	[redacted]
Sebetralstat TTA: 56 minutes	Sebetralstat TTA: 9 minutes	[redacted]	[redacted]	[redacted]
% sebetralstat patients requiring additional dosing: 24.1%	% sebetralstat patients requiring additional dosing: 12.7%	[redacted]	[redacted]	[redacted]
% Female: 60%	% Female: 33.3%	[redacted]	[redacted]	[redacted]
Age at baseline: 37.7 years and carer disutility excluded	Age at baseline: 12 years and carer disutility included (cared up to max age = 18 years)	[redacted]	[redacted]	[redacted]
Attack Location as indicator for HRQoL impact of acute attack	Attack Severity as indicator for HRQoL impact of acute attack	[redacted]	[redacted]	[redacted]

Abbreviations: QALYs, quality-adjusted life years

3.11 Subgroup analysis

No subgroups have been identified in the clinical evidence which would benefit more or less from treatment with sebetralstat. Please see section 2.8**Error! Reference source not found.** for more details.

3.12 Benefits not captured in the QALY calculation

Not applicable.

3.13 Validation

Validation of cost-effectiveness analysis

A comprehensive model validation was performed in which the internal validity, face validity, and external validity of the model was assessed.

Several internal quality control procedures were undertaken to verify the results of the *de novo* cost-effectiveness model. All source inputs and calculations in the Excel model were generated by one researcher and verified by another independent researcher to ensure accuracy. Quality control also included a line-by-line audit of the Visual Basic for Applications (VBA) code used in the model. In addition, the model structure, assumptions, and data were reviewed by health economists who have extensive experience in model construction.

The conceptual structure of the model was validated by four clinicians, to ensure that they model captures the core clinical features and pathways of HAE patients using OD treatment (148). Nevertheless, assessing the external validity of the model in HAE is difficult due to the variable and unpredictable nature of the disease. Moreover, comparing the key clinical outcome (TTAR) in the model, to comparator values reported in the literature is tentative. This is primarily because most comparator treatments report data on TTAR, for example, with less stringent definitions than the KONFIDENT trial or only provide the median value of TTAR. However, the SMC appraisal of icatibant (115) provides a single source to test the external validity of the sebetralstat model.

The icatibant model submitted to the SMC estimated an incremental QALY gain of 0.0000852 for icatibant versus Berinert. (115) Incremental costs were not reported. The model applied a 96-hour time horizon with 1 cycle of 96 hours, representing a single acute HAE attack.(115). When setting the sebetralstat model to the same analysis assumptions, i.e., the same time horizon and cycle length, with 1 attack occurring over the modelled horizon, and the same comparators, the estimated incremental QALY gain between icatibant versus Berinert is 0.0000476.

Based on this comparison, the sebetralstat model potentially underestimates the value gained from an oral treatment and is possibly conservative compared to the icatibant SMC model. Nonetheless, it is important to interpret this comparison with caution due to differences in the modelled clinical outcomes and unknown discrepancies between model structures.

3.14 Interpretation and conclusions of economic evidence

Data for sebetralstat was informed by the KONFIDENT RCT and OLE data (78, 84). The RCT and OLE population is considered representative of the population expected to be treated for acute HAE attacks in the UK. Sebetralstat provides an unmet need for the OD treatment of acute HAE attacks, providing patients with an easier route of administration, enabling them to treat attacks rapidly, and thus more effectively, and improves patients' day-to-day HRQoL due to reduced barriers to treatment administration and treatment side effects.

This *de novo* health economic evaluation examined the cost-effectiveness of sebetralstat for the on-demand treatment of acute HAE attacks. On average, the estimated TTAR for sebetralstat was [redacted] hours for 'Neck and Above' attacks, [redacted] hours for 'Abdominal' attacks, and [redacted] hours for other attacks. This is lower than the predicted TTAR of all comparator treatments which, on average, were estimated to resolve attacks within [redacted] hours for 'Neck and Above' attacks, [redacted] for 'Abdominal' attacks, and [redacted] for 'Other' attacks.

The model predicted that, over a lifetime horizon, patients experienced meaningful gains in HRQoL due to reduced burden of treatment and side effects. Patients who were prescribed sebetralstat for the OD treatment of acute HAE attacks experienced approximately 1081 fewer side effects related to injection site reactions and pain, over the lifetime horizon, compared to patients treated with icatibant. Compared to IV treatments, such as Berinert, Ruconest, and Cinryze, patients prescribed sebetralstat experienced approximately 200-300 fewer side effects associated with injection. For patients taking an additional dose, sebetralstat patients used 156 additional doses compared to 82 for icatibant. When compared to IV treatments, sebetralstat patients used an average of 75 more additional doses over their lifetime.

At a £30,000 WTP threshold, sebetralstat has a [redacted]% probability of being cost-effective. At a £20,000 WTP, sebetralstat has a [redacted]% probability of being cost-effective.

Over a lifetime horizon, the incremental costs associated with treating with sebetralstat compared to SoC are £[redacted]. The model estimated an incremental QALY gain of 0.11. These results yielded an ICER of £[redacted] per discounted QALY gained.

4 References

1. KalVista. [Data on file] Draft Summary of Product Characteristics (SmPc). 2025.
2. Ghazi A, Grant JA. Hereditary angioedema: epidemiology, management, and role of icatibant. Biologics: Targets and Therapy. 2013.
3. Farkas H, Martinez-Saguer I, Bork K, Bowen T, Craig T, Frank M, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. Allergy. 2017;72(2):300-13.
4. Yong PFK, Coulter T, El-Shanawany T, Garcez T, Hackett S, Jain R, et al. A National Survey of Hereditary Angioedema and Acquired C1 Inhibitor Deficiency in the United Kingdom. The Journal of Allergy and Clinical Immunology: In Practice. 2023;11(8):2476-83.
5. Bork K, Barnstedt S-E, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. The Lancet. 2000;356(9225):213-7.
6. Bafunno V, Firinu D, D'Apolito M, Cordisco G, Loffredo S, Leccese A, et al. Mutation of the angiopoietin-1 gene (ANGPT1) associates with a new type of hereditary angioedema. Journal of Allergy and Clinical Immunology. 2017;141(3):1009-17.
7. Bork K, Wulff K, Steinmüller-Magin L, Brænne I, Staubach-Renz P, Witzke G, et al. Hereditary angioedema with a mutation in the plasminogen gene. Allergy. 2017;73(2):442-50.
8. Bork K, Wulff K, Rossmann H, Steinmuller-Magin L, Braenne I, Witzke G, et al. Hereditary angioedema cosegregating with a novel kininogen 1 gene mutation changing the N-terminal cleavage site of bradykinin. Allergy. 2019;74(12):2479-81.
9. Bork K, Staubach P, Eckardt AJ, Hardt J. Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. Am J Gastroenterol. 2006;101(3):619-27.
10. Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression. Allergy Asthma Proc. 2010;31(5):407-14.
11. Chong-Neto HJ. A narrative review of recent literature of the quality of life in hereditary angioedema patients. World Allergy Organ J. 2023;16(3):100758.
12. Granero-Molina J, Sanchez-Hernandez F, Fernandez-Sola C, Jimenez-Lasserrotte MDM, Antequera-Raynal LH, Hernandez-Padilla JM. The Diagnosis of Hereditary Angioedema: Family Caregivers' Experiences. Clinical Nursing Research. 2020;29(2):117-26.
13. Busse PJ, Christiansen SC. Hereditary Angioedema. New England Journal of Medicine. 2020;382(12):1136-48.
14. Nordenfelt P, Dawson S, Wahlgren C-F, Lindfors A, Mallbris L, Björkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. Allergy and Asthma Proceedings. 2014;35(2):185-90.
15. NHS. NHS Commissioning Board Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angiodema (Adult). 2013.
16. Staller K, Lembo A, Banerji A, Bernstein JA, Shah ED, Riedl MA. Consider Hereditary Angioedema in the Differential Diagnosis for Unexplained Recurring Abdominal Pain. J Clin Gastroenterol. 2022;56(9):740-7.

17. Li H. Self-administered C1 esterase inhibitor concentrates for the management of hereditary angioedema: usability and patient acceptance. Patient Preference and Adherence. 2016;Volume 10:1727-37.
18. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol. 2012;130(3):692-7.
19. Perego F, Gidaro A, Zanichelli A, Duca P, Cicardi M. Life expectancy in Italian patients with hereditary angioedema due to C1-inhibitor deficiency. The Journal of Allergy and Clinical Immunology: In Practice. 2020;8(5):1772-4.
20. Yong PFK, Annals R, Diwakar L, Elkhalifa S, Gompels M. Prophylaxis in hereditary angioedema: a United Kingdom
Delphi consensus. Clinical and Experimental Immunology. 2024;217.
21. Prematta MJ, Laudadio C, Craig T. Frequency and Types of Hereditary Angioedema Prodromes as Reported by Patients. Journal of Allergy and Clinical Immunology. 2010;125(2).
22. Craig T, Aygoeren-Puersuen E, Bernstein J, Busse P, Caballero T, Cohn D, et al. [DRAFT manuscript] Impact of Oral Sebetralstat on Anxiety Associated with Hereditary Angioedema Attacks. 2025.
23. Bygum A, Busse P, Caballero T, Maurer M. Disease Severity, Activity, Impact, and Control and How to Assess Them in Patients with Hereditary Angioedema. Front Med (Lausanne). 2017;4:212.
24. Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygoren-Pursun E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. Allergy. 2022;77(7):1961-90.
25. El-Shanawany T. Hereditary angioedema British Society for Immuology British Society for Immunology; [Available from: https://www.immunology.org/public-information/bitesized-immunology/immune-dysfunction/hereditary-angioedema.
26. Banerji A, Riedl M. Managing the female patient with hereditary angioedema. Womens Health (Lond). 2016;12(3):351-61.
27. Guan X, Sheng Y, Liu S, He M, Chen T, Zhi Y. Epidemiology, economic, and humanistic burden of hereditary angioedema: a systematic review. Orphanet J Rare Dis. 2024;19(1):256.
28. Zotter Z, Csuka D, Szabo E, Czaller I, Nebenfuhrer Z, Temesszentandrasi G, et al. The influence of trigger factors on hereditary angioedema due to C1-inhibitor deficiency. Orphanet J Rare Dis. 2014;9:44.
29. Katelaris CH, Boicos K, Button PH, McCloud PI, Burton PK, Perram FA, et al. Living With Hereditary Angioedema in Australia: Findings From a National Observational Study Using Short Message Service to Monitor the Burden of Disease. J Allergy Clin Immunol Pract. 2023;11(8):2457-67.e1.
30. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. Am J Med. 2006;119(3):267-74.
31. KalVista. [Data on File] HCP validation and Clinician survey. [Summary report]. In press 2024.
32. Yong PFK, El-Shanawany T, Gurugama P, Jain G, Danese S, Ulloa J, et al. [EAACI 2024 Burden of Treatment poster] Anxiety Associated with On-Demand Treatment for Hereditary Angioedema (HAE) Attacks. EAACI (European Academy of Allergy and Clinical Immunology) 2024; June 2024; Valencia, Spain. 2024.

33. Kuman Tunçel Ö, Gökmen NM, Demir E, Gülbahar O, Pırıldar Ş. The impact of hereditary angioedema on quality of life and family planning decisions. Int J Psychiatry Med. 2019;54(6):377-94.
34. Caballero T, Sala-Cunill A, Cancian M, Craig TJ, Neri S, Keith PK, et al. Current status of implementation of self-administration training in various regions of Europe, Canada and the USA in the management of hereditary angioedema. Int Arch Allergy Immunol. 2013;161 Suppl 1:10-6.
35. Christiansen SC, Davis DK, Castaldo AJ, Zuraw BL. Pediatric Hereditary Angioedema: Onset, Diagnostic Delay, and Disease Severity. Clin Pediatr (Phila). 2016;55(10):935-42.
36. Savarese L, Mormile I, Bova M, Petraroli A, Maiello A, Spadaro G, et al. Psychology and hereditary angioedema: A systematic review. Allergy Asthma Proc. 2021;42(1):e1-e7.
37. Banerji A, Davis KH, Brown TM, Hollis K, Hunter SM, Long J, et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States. Ann Allergy Asthma Immunol. 2020;124(6):600-7.
38. Banerji A. The burden of illness in patients with hereditary angioedema. Ann Allergy Asthma Immunol. 2013;111(5):329-36.
39. Cicardi M, Agostoni A. Hereditary Angioedema. The New England Journal of Medicine. 1996;334 NO.25.
40. National Institute for Health and Care Excellence. [Public observer slides-redacted.] Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]. . https://www.nice.org.uk/guidance/ta738/documents/1: National Institute for Health and Care Excellence; 2021 2021.
41. Longhurst H, Bygum A. The Humanistic, Societal, and Pharmaco-economic Burden of Angioedema. Clin Rev Allergy Immunol. 2016;51(2):230-9.
42. Bork K, Hardt J, Schicketanze K, Ressel N. Clinical Studies of Sudden Upper Airway Obstruction in Patients With Hereditary Angioedema Due to C1 Esterase Inhibitor Deficiency. Arch Intern Med. 2003;163 (10).
43. Geba D, Mohd Sani J, Gascon M, Hahn R, Aggarwal K, Rosselli J. Hereditary angioedema patients would prefer newer-generation oral prophylaxis. J Drug Assess. 2021;10(1):51-6.
44. KalVista. [Data on File] Patient qualitative interviews interim deck. 2024 4 November 2024.
45. Maurer M, Aberer W, Bouillet L, Caballero T, Fabien V, Kanny G, et al. Hereditary angioedema attacks resolve faster and are shorter after early icatibant treatment. PLoS One. 2013;8(2):e53773.
46. Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, Wait S, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. Journal of Rare Diseases. 2014;9(99):1-9.
47. Castaldo AJ, Jervelund C, Corcoran D, Boysen HB, Christiansen SC, Zuraw BL. Assessing the cost and quality-of-life impact of on-demand-only medications for adults with hereditary angioedema. Allergy Asthma Proc. 2021;42(2):108-17.
48. Helbert M, Drogon E, Mannan A, Holbrook T, Murray H, Piercy J. Exploring the Burden of Illness of Hereditary Angioedema in the United Kingdom. Value in Health. 2013;16(7).

49. Bygum A, Aygoren-Pursun E, Beusterien K, Hautamaki E, Sisic Z, Wait S, et al. Burden of Illness in Hereditary Angioedema: A Conceptual Model. Acta Derm Venereol. 2015;95(6):706-10.
50. Lo SH, Lloyd A, Elkhalifa S, Sisic Z, van Nooten FE. Time Trade-Off Utilities for Hereditary Angioedema Health and Caregiver States. Pharmacoecon Open. 2022;6(2):231-9.
51. Kiani-Alikhan S, Banerji A, Busse P, Craig T, Yong PFK, Hall R, et al. [Data on file] Psychological Burden Associated with Injectable HAE On-Demand Treatments: A Patient and Caregiver Interview Study [Unpublished, accepted EAACI abstract]. EAACI2025.
52. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst H, Zuraw B. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. ALLERGY, ASTHMA & CLINICAL IMMUNOLOGY. 2010;Jul 28;6(1):24.
53. Sinnathamby ES, Issa PP, Roberts L, Norwood H, Malone K, Vemulapalli H, et al. Hereditary Angioedema: Diagnosis, Clinical Implications, and Pathophysiology. Adv Ther. 2023;40(3):814-27.
54. Longhurst HJ, Tarzi MD, Ashworth F, Bethune C, Cale C, Dempster J, et al. C1 inhibitor deficiency: 2014 United Kingdom consensus document. Clin Exp Immunol. 2015;180(3):475-83.
55. Yong P, Banerji A, Busse P, Craig T, Kiani-Alikhan S, Hall R, et al. [Data on file] Impact of injectable HAE on-demand treatments on health-related quality of life: a patient and caregiver interview study. [Unpublished until conference date 29 May - 1 June 2025]. 14th C1-Inhibitor Deficiency and Angioedema Workshop2025.
56. Cancian M, Bocquet A, Busse P, Craig T, El-Shanawany T, Garcez T, et al., editors. [Data on file] Survey results from Italy, the US, UK, and France: Anxiety in patients using injectable on-demand treatments for hereditary angioedema attacks. To be presented at the 2025 C1-INH workshop]. 14th C1-Inhibitor Deficiency and Angioedema Workshop; 2025 Conference date: 29 May - 1 June 2025; Budapest.
57. National Institute for Health and Care Excellence. Lanadelumab for preventing recurrent attacks of hereditary angioedema Technology Appraisal Guidance. 2019 16 October 2019.
58. National Institute for Health and Care Excellence. Final appraisal document. Berotralstat for preventing recurrent attacks of hereditary angioedema. 2021 September 2021.
59. Lumry WR, Grumach AS, Betschel SD, Radojicic C, van Kooten S, Heckmann M, et al. Management of hereditary angioedema attacks by patients on long-term prophylaxis versus on-demand therapy only. Allergy Asthma Proc. 2025;46(1):32-7.
60. Maurer M, Magerl M, Aygoren-Pursun E, Bork K, Farkas H, Longhurst H, et al. Attenuated androgen discontinuation in patients with hereditary angioedema: a commented case series. Allergy Asthma Clin Immunol. 2022;18(1):4.
61. Bork K, Bygum A, Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. Annals of Allergy, Asthma & Immunology. 2008;100(2).
62. Zuraw BL, Davis DK, Castaldo AJ, Christiansen SC. Tolerability and Effectiveness of 17-alpha-Alkylated Androgen Therapy for Hereditary Angioedema: A Re-examination. J Allergy Clin Immunol Pract. 2016;4(5):948-55 e15.
63. Riedl MA. Critical appraisal of androgen use in hereditary angioedema: a systematic review. Ann Allergy Asthma Immunol. 2015;114(4):281-8 e7.

64. NHSE. Clinical Commissioning Policy: Plasma derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema (HAE) types I and II. 2016.
65. Betschel S, Kooten S, Heckmann M, Danese S, Goga L, Caballero T. Remaining Burden of Hereditary Angioedema (HAE) Attacks Despite Modern Long-term Prophylaxis. EEACI; 2023.
66. Soteres D, Grumach AS, Kooten S, Malloy N, Heckmann M. Anxiety Associated with Refilling On-demand Therapy for HAE Attacks
Contributes to Treatment Delay and Non-Treatment. 2024.
67. Betschel S, Kooten S, Heckmann M, Danese S, Goga L, Guilarte M. HAE Patients' Decision to Carry On-Demand Treatment When Away from Home. 2023 2023.
68. Grumach AS, Kooten S, Heckmann M, Danese S, Goga L. Understanding the complex decision-making associated with on-demand treatment of hereditary angioedema (HAE) attacks. Abstract presented at: EAACI. EAACI 2023 Hybrid Congress, June 9-11, 2023; Hamburg, Germany. Allergy. 2023;78(suppl 1): 504. ; 2023.
69. Christiansen S, O'Connor M, Craig T, Radojicic C, Wedner HJ, Danese S, et al. On-demand treatment of hereditary angioedema attacks: Patient-reported utilization, barriers, and outcomes. Ann Allergy Asthma Immunol. 2024.
70. Christiansen SC, O'Connor M, Ulloa J, Danese S. Delayed On-demand Treatment of Hereditary Angioedema Attacks: Patient Perceptions and Associated Barriers. AAAAI Annual Meeting 2024 poster. Allergy Asthma Clin Immunol. 2024;153(2) Suppl 1 A-4A: AB1-AB386. ; 2024.
71. Betschel S, Rodojicic C, Kooten S, Heckmann M, Ulloa J, Lumry WR. Characterizing the Perspective of Patients With HAE on Prophylactic Treatment. 2024.
72. Valerieva A, Jones D, Kooten S, Malloy N, Heckmann M. Treatment of HAE Attacks with Anticipated Future Oral On-Demand Therapies as Reported by Patients. 2024.
73. Craig T, Bernstein JA, Longhurst H, Hao J, Smith MD, Audhya PK, et al. [ACAAI 2024 Time to Treatment Phase 3 poster] Correlation of Time to Treatment with Attack Duration in the Sebetralstat KONFIDENT Phase 3 Trial. ACAAI (American College of Allergy, Asthma & Immunology) 2024; October 2024; Boston, USA2024.
74. Gov.uk website. Decision: Sebetralstat in the treatment of hereditary angioedema (HAE) attacks Gov.uk: Gov.uk; 2025 [Available from: https://www.gov.uk/government/publications/sebetralstat-in-the-treatment-of-hereditary-angioedema-hae-attacks.
75. Aygören-Pürsün E, Zanichelli A, Cohn DM, Cancian M, Hakl R, Kinaciyan T, et al. An investigational oral plasma kallikrein inhibitor for on-demand treatment of hereditary angioedema: a two-part, randomised, double-blind, placebo-controlled, crossover phase 2 trial. Lancet. 2023;401(10375):458-69.
76. ClinicalTrials.gov. [Phase 2] A Phase II, Cross-over Clinical Trial Evaluating the Efficacy and Safety of KVD900 in the On-demand Treatment of Angioedema Attacks in Adult Subjects With Hereditary Angioedema Type I or II ClinicalTrials.gov website: National Library of Medicine; 2024 [Available from: https://www.clinicaltrials.gov/study/NCT04208412?intr=kvd900&rank=3.
77. Cohn DM. [Phase 3 EAACI 2024 oral presentation] Oral sebetralstat for on-demand treatment of hereditary angioedema: phase 3 KONFIDENT trial results. EAACI (European Academy of Allergy & Clinical Immunology) 2024; 31 May 2024; Valencia, Spain2024.

78. KalVista. [KONFIDENT CSR report] A Randomized, Double-Blind, Placebo-Controlled, Phase 3, Three-way Crossover Trial to Evaluate the Efficacy and Safety of Two Dose Levels of KVD900, an Oral Plasma Kallikrein Inhibitor, for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients with Hereditary Angioedema Type I or II (KONFIDENT). 2024 03 May 2024.
79. Riedl MA, Aygören-Pürsün E, Lumry WR, Farkas H, Zanichelli A, Hao J, et al. [AAAAI 2024 Phase 3 poster] Sebetralstat for On-demand Treatment of Hereditary Angioedema Attacks: Results of the Double-blind, Placebo-controlled, Phase 3 KONFIDENT Trial. AAAAI (American Academy of Allergy, Asthma & Immunology) 2024; 23 February 2024; Washington, USA2024.
80. Riedl MA, Farkas H, Aygören-Pürsün E, Psarros F, Soteres DF, Staevska M, et al. [NEJM manuscript] Oral Sebetralstat for On-Demand Treatment of Hereditary Angioedema Attacks. N Engl J Med. 2024;391(1):32-43.
81. ClinicalTrials.gov. A Phase III, Crossover Trial Evaluating the Efficacy and Safety of KVD900 for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients With Hereditary Angioedema (HAE) ClinicalTrials.gov website: National Library of Medicine; 2024 [Available from: https://www.clinicaltrials.gov/study/NCT05259917?term=NCT05259917&rank=1.
82. Farkas H, Riedl MA, Aygören-Pürsün E, Lumry WR, Zanichelli A, Hao J, et al. [OLE EAACI 2024] Sebetralstat as Oral On-demand Treatment for Hereditary Angioedema: Interim Analysis of the Open-label KONFIDENT-S Trial. EAACI (European Academy of Allergy & Clinical Immunology) 2024; May 2024; Valencia, Spain2024.
83. ClinicalTrials.gov. An Open-label Extension Trial to Evaluate the Long-term Safety of KVD900 for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients With Hereditary Angioedema (HAE) ClinicalTrials.gov website: National Library of Medicine; 2024 [Available from: https://www.clinicaltrials.gov/study/NCT05505916?term=NCT05505916&rank=1.
84. KalVista. [KONFIDENT-S OLE interim CSR report - 14 Sept 2024 data cut off date] Interim Clinical Trial Report: An Open-Label Extension Trial to Evaluate the Long-term Safety of KVD900, an Oral Plasma Kallikrein Inhibitor, for On-demand Treatment of Angioedema Attacks in Adolescent and Adult Patients with Hereditary Angioedema Type I or II (KONFIDENT-S). 2024 19 November 2024.
85. Cicardi M, Banerji A, Bracho F, Malbrán A, Rosenkranz B, Riedl M, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med. 2010;363(6):532-41.
86. Longhurst HJ, Dempster J, Lorenzo L, Buckland M, Grigoriadou S, Symons C, et al. Real-world outcomes in hereditary angioedema: first experience from the Icatibant Outcome Survey in the United Kingdom. Allergy Asthma Clin Immunol. 2018;14:28.
87. Zanichelli A, Azin GM, Cristina F, Vacchini R, Caballero T. Safety, effectiveness, and impact on quality of life of self-administration with plasma-derived nanofiltered C1 inhibitor (Berinert) in patients with hereditary angioedema: the SABHA study. Orphanet J Rare Dis. 2018;13(1):51.
88. Craig TJ, Bewtra AK, Bahna SL, Hurewitz D, Schneider LC, Levy RJ, et al. C1 esterase inhibitor concentrate in 1085 Hereditary Angioedema attacks--final results of the I.M.P.A.C.T.2 study. Allergy. 2011;66(12):1604-11.

89. Zanichelli A, Mansi M, Azin GM, Wu MA, Periti G, Casazza G, et al. Efficacy of on-demand treatment in reducing morbidity in patients with hereditary angioedema due to C1 inhibitor deficiency. Allergy. 2015;70(12):1553-8.
90. Zuraw B, Cicardi M, Levy RJ, Nuijens JH, Relan A, Visscher S, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. J Allergy Clin Immunol. 2010;126(4):821-7.e14.
91. Riedl MA, Li HH, Cicardi M, Harper JR, Relan A. Recombinant human C1 esterase inhibitor for acute hereditary angioedema attacks with upper airway involvement. Allergy Asthma Proc. 2017;38(6):462-6.
92. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med. 2010;363(6):513-22.
93. Lumry WR, Aygören-Pürsün E, Zanichelli A, Cohn DM, Farkas H, Bernstein JA, et al. [EAC 2022 poster] KONFIDENT Phase 3 Trial Design for Sebetralstat (KVD900), a Novel Investigational Oral Plasma Kallikrein Inhibitor for the On-Demand Treatment of Hereditary Angioedema Attacks. Eastern Allergy Conference 2022; June 2022; Palm Beach, USA2022.
94. Riedl MA, Farkas H, Aygören-Pürsün E, Psarros F, Soteres DF, Staevska M, et al. [NEJM Supplementary Appendix] Oral Sebetralstat for On-Demand Treatment of Hereditary Angioedema Attacks. N Engl J Med. 2024;391(1):32-43.
95. Lumry WR, Cohn DM, Bernstein JA, Audhya PK, Hao J, Smith MD, et al. [ACAAI 2024 poster] Substantial Reduction of Hereditary Angioedema Attack Symptom Burden in the Sebetralstat Phase 3 KONFIDENT Trial. ACAAI (American College of Allergy, Asthma & Immunology) 2024; October 2022; Boston, USA2024.
96. Li HH, Magerl M, Craig T, Manning ME, Hummel N, Wang A, et al. [AAAAI 2024 ITC poster] Indirect Treatment Comparison of Oral Sebetralstat and Intravenous rhC1-INH as On-demand Treatments for Hereditary Angioedema. R083. . AAAAI (American Academy of Allergy, Asthma & Immunology) 2024; October 2024; Boston, USA2024.
97. Wang A, Li H, Magerl M, Craig T, Manning M, Hummel N, et al. Indirect Treatment Comparison of Oral Sebetralstat and Intravenous RHC1-INH as On-demand Treatments for Hereditary Angioedema. AAAI 2024: Annals of Allergy, Asthma & Immunology; 2024. p. Supplement S28-S9.
98. Craig TJ, Levy RJ, Wasserman RL, Bewtra AK, Hurewitz D, Obtułowicz K, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. J Allergy Clin Immunol. 2009;124(4):801-8.
99. Levy RJ, Lumry WR, McNeil DL, Li HH, Campion M, Horn PT, et al. EDEMA4: a phase 3, double-blind study of subcutaneous ecallantide treatment for acute attacks of hereditary angioedema. Ann Allergy Asthma Immunol. 2010;104(6):523-9.
100. Lumry WR, Li HH, Levy RJ, Potter PC, Farkas H, Moldovan D, et al. Randomized placebo-controlled trial of the bradykinin B_2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. Ann Allergy Asthma Immunol. 2011;107(6):529-37.
101. Cohn DM, Soteres DF, Craig TJ, Lumry WR, Magerl M, Riedl MA, et al. Interplay between on-demand treatment trials for hereditary angioedema and treatment guidelines. J Allergy Clin Immunol. 2024.

102. Riedl MA, Bernstein JA, Li H, Reshef A, Lumry W, Moldovan D, et al. Recombinant human C1-esterase inhibitor relieves symptoms of hereditary angioedema attacks: phase 3, randomized, placebo-controlled trial. Ann Allergy Asthma Immunol. 2014;112(2):163-9.e1.
103. ClinicalTrials.gov. Study of Oral Deucrictibant Soft Capsule for On-Demand Treatment of Angioedema Attacks in Adolescents and Adults With Hereditary Angioedema (RAPIDe-3) ClinicalTrials.gov website: National Library of Medicine; 2025 [Available from: https://clinicaltrials.gov/study/NCT06343779.
104. Fijen LM, Petersen RS, Cohn DM. Outcome measures in randomized controlled studies of acute therapy for hereditary angioedema: A systematic review. Allergy. 2022;77(7):2222-4.
105. Bork K, Bernstein JA, Machnig T, Craig TJ. Efficacy of Different Medical Therapies for the Treatment of Acute Laryngeal Attacks of Hereditary Angioedema due to C1-esterase Inhibitor Deficiency. J Emerg Med. 2016;50(4):567-80.e1.
106. Helbert M, Pang F, Alvarez-Reyes M, Roskell NS, Diwakar L. (PSY10) An Indirect Comparison of Icatibant and Four Other Therapies for the Symptomatic Treatment of Acute Attacks of Hereditary Angioedema Types I and II. Value in Health. 2012;15(7):PA509-A10.
107. KalVista. [Protocol for KONFIDENT] A Randomized, Double-Blind, Placebo-Controlled, Phase 3, Three-way Crossover Trial to Evaluate the Efficacy and Safety of Two Dose Levels of KVD900, an Oral Plasma Kallikrein Inhibitor, for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients with Hereditary Angioedema Type I or II. 2023 26 April 2023.
108. KalVista. [KONFIDENT-S OLE Table A302-4; 14 Sept 2024 data cut off date] KONFIDENT- S Table A302-4 Summary of Time to First Dose by Rollover Status - Full Analysis Set. 2024 19 November 2024.
109. KalVista. [Data on File] 2.5.4.8 Dose selection of the Clinical Overview (submitted to MHRA). 2024.
110. PBAC. Icatibant Public Summary Document November 2016 PBAC meeting. PBAC; 2016.
111. Bernstein J, Tyson C, Relan A, Adams P, Magar R. Modeling Cost-Effectiveness of On-Demand Treatment for Hereditary Angioedema Attacks. Managed Care & Specialty Pharmacy. 2020;26(2):203-11.
112. Tyson C, Magar R, Adams P, A R. Cost-effectiveness model for on-demand treatment of HAE attacks. Managed Care & Specialty Pharmacy. 2019;25(3):37-8.
113. Kawalec P, Holko P, Paszulewicz A. Cost-utility analysis of Ruconest (conestat alfa) compared to Berinert P (human C1 esterase inhibitor) in the treatment of acute, life-threatening angioedema attacks in patients with hereditary angioedema. Postepy Dermatol Alergol. 2013;30(3):152-8.
114. All Wales Therapeutics and Toxicology Centre (AWTTC). AWMSG SECRETARIAT ASSESSMENT REPORT C1-esterase inhibitor (Berinert®) 500 units powder and solvent for solution for injection/infusion. 2013.
115. Scottish Medicines Consortium. icatibant acetate, 30mg, solution for injection in pre-filled syringe (Firazyr®) SMC No. (476/08). 2012.

116. Health Survey for England 2022 [Internet]. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2022-part-2/health-survey-for-england-hse-2022-part-2-data-tables.
117. Bork K, Anderson J, Caballero Molina M, Johnson DT, Henry H, Henry Li H, et al. Assessment and management of disease burden and quality of life in patients with hereditary angioedema: a consensus report. Allergy, Asthma & Clinical Immunology. 2021;17(1).
118. Bygum A. Hereditary angioedema - consequences of a new treatment paradigm in Denmark. Acta Derm Venereol. 2014;94(4):436-41.
119. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation: Oxford University Press; 2006.
120. Karnon J, Afzali HHA. When to Use Discrete Event Simulation (DES) for the Economic Evaluation of Health Technologies? A Review and Critique of the Costs and Benefits of DES. PharmacoEconomics. 2014;32:547–58.
121. Bjorkman LS, Persson B, Aronsson D, Skattum L, Nordenfelt P, Egesten A. Comorbidities in hereditary angioedema - A population-based cohort study. Clinical and translational allergy. 2022;12(3).
122. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2013.
123. KalVista. [Data on file]. Hereditary Angioedema (HAE) Utilities. 2025.
124. National Institute for Health and Care Excellence. Single Technology Appraisal. Berotralstat for preventing acute attacks of hereditary angioedema [ID1624] Draft guidance Committee papers. 2021 2021.
125. Betschel S, Badiou J, Binkley K, Borici-Mazi R, Hébert J, Kanani A, et al. The International/Canadian Hereditary Angioedema Guideline. Allergy Asthma Clin Immunol. 2019;15:72.
126. Busse PJ, Christiansen SC, Riedl MA, Banerji A, Bernstein JA, Castaldo AJ, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. J Allergy Clin Immunol Pract. 2021;9(1):132-50.e3.
127. Cohn DM, Aygören-Pürsün E, Bernstein JA, Farkas H, Lumry WR, Maurer M, et al. Evaluation of patient-reported outcome measures for on-demand treatment of hereditary angioedema attacks and design of KONFIDENT, a phase 3 trial of sebetralstat. Clin Transl Allergy. 2023;13(9):e12288.
128. Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. Network Meta-Analysis for Decision-Making: Wiley; 2018.
129. Decision Support Unit. NICE DSU Technical Support Document 18: Methods for Population-Adjusted Indirect Comparisons in Submissions to NICE. University of Sheffield; 2016.
130. KalVista. [Data on file]. Post-hoc statistical analysis: Association between Time to Administration and Time to Attack Resolution. 2025.
131. National life tables – life expectancy in the UK: 2021 to 2023 [Internet]. Office for National Statistics. 2025. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2021to2023additionaldata.

132. Craig TJ, Rojavin MA, Machnig T, Keinecke HO, Bernstein JA. Effect of time to treatment on response to C1 esterase inhibitor concentrate for hereditary angioedema attacks. Ann Allergy Asthma Immunol. 2013;111(3):211-5.
133. Andrasi N, Veszeli N, Holdonner A, Temesszentandrási G, Kohalmi KV, Varga L, et al. Evaluation of the efficacy and safety of home treatment with the recombinant human C1-inhibitor in hereditary angioedema resulting from C1-inhibitor deficiency. International Immunopharmacology. 2020;80.
134. Collett D. Modelling Survival Data in Medical Research. Fourth ed: CRC Press; 2023.
135. Riedl MA, Hurewitz DS, Levy R, Busse PJ, Fitts D, Kalfus I. Nanofiltered C1 esterase inhibitor (human) for the treatment of acute attacks of hereditary angioedema: an open-label trial. Ann Allergy Asthma Immunol. 2012;108(1):49-53.
136. Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, Boysen HB, et al. Estimation of EuroQol 5-Dimensions health status utility values in hereditary angioedema. Patient Prefer Adherence. 2016;10:1699-707.
137. Matza LS, Stweart KD, Lloyd AJ, Rowen D, Brazier J. Vignette-based utilities: usefulness, limitations, and methodological recommendations. Value Health. 2021;24:812-21.
138. Ara R, Brazier J. Populating an Economic Model with Health State Utility Values: Moving toward Better Practice. Value in Health. 2010;24:812-21.
139. ONS. Consumer price inflation, UK: March 2025. ONS website; 2025.
140. Unit Costs of Health and Social Care. Table 9.2.1 Nurse, Band 6, Cost per working hour [Internet]. 2022/2023. Available from: https://kar.kent.ac.uk/109563/1/The%20unit%20costs%20of%20health%20and%20social%20care%202024%20%28for%20publication%29_Final.pdf.
141. IQVIA. [Data on file] HAE UK monthly IQVIA; 2025.
142. BNF. Icatibant 30mg/3ml solution for injection pre-filled syringes [Internet]. 2024 [cited 5 November 2024]. Available from: https://bnf.nice.org.uk/drugs/icatibant/medicinal-forms/.
143. BNF. Ruconest 2,100unit powder and solvent for solution for injection vials [Internet]. 2024 [cited 5 November 2024]. Available from: https://bnf.nice.org.uk/drugs/conestat-alfa/medicinal-forms/#powder-and-solvent-for-solution-for-injection.
144. BNF. Berinert 500unit powder and solvent for solution for injection vials [Internet]. 2024 [cited 5 November 2024]. Available from: https://bnf.nice.org.uk/drugs/c1-esterase-inhibitor/medicinal-forms/.
145. BNF. Cinryze 500unit powder and solvent for solution for injection vials [Internet]. 2024 [cited 5 November 2024]. Available from: https://bnf.nice.org.uk/drugs/c1-esterase-inhibitor/medicinal-forms/#powder-and-solvent-for-solution-for-injection.
146. Otani IM, Lumry WR, Hurwitz S, Li HH, Craig TJ, Holtzman NS, et al. Subcutaneous Icatibant for the Treatment of Hereditary Angioedema Attacks: Comparison of Home Self-Administration with Administration at a Medical Facility. J Allergy Clin Immunol Pract. 2017;5(2):442-7.e1.
147. Feussner A, Kalina U, Hofmann P, Machnig T, Henkel G. Biochemical comparison of four commercially available C1 esterase inhibitor concentrates for treatment of hereditary angioedema. Transfusion. 2014;54(10):2566-73.

148. KalVista. [Data on file]. Sebetralstat Conceptual Model KoL Validation. 2024.
149. Centre for Reviews and Dissemination. Sytematic Reviews, CRDs guidance for undertaking reviews in health care: University of York 2009.
150. Higgins JPT, J, Chandler , J, Cumpston, M, Li, T, Page, M.J, Welch, V.A.,. Cochrane Handbook for Systematic Reviews of Interventions.2022.
151. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-12.
152. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. Int J Surg. 2021;88:105906.
153. Toubi E BJ, Moldovan D, Levy R, Relan A,. Safety and efficacy evaluation of rhC1INH for the treatment of hereditary angioedema attacks in adolescent patients. Allergy. 2012;67(10):199.
154. Li H MD, Bernstein J, Reshef A, Porebski G, Stobiecki M, Baker J, Levy R, Hardiman Y, Relan A, Cicardi M, Riedl M,. Efficacy and safety of recombinant human C1 esterase inhibitor for acute attacks of hereditary angioedema: an open-label study. Annals of allergy, asthma and immunology. 2013(5):A92-A3.
155. Li H RA, Farkas H, Baker J, Porebski G, McNeil D, Relan A, Zanichelli A,. Efficacy of recombinant human C1 inhibitor for the treatment of hereditary angioedema patients with severe attacks. Annals of allergy, asthma and immunology. 2014;113(5):A5.
156. Riedl M CM. Efficacy of recombinant C1 inhibitor for laryngeal attacks of hereditary angioedema. Allergy. 2015;70:470.
157. Baker J.W, Bernstein J.A, Harper J.R, Relan A, Riedl M.A, editors. 736- Efficacy of recombinant human C1 esterase inhibitor (rhC1INH) across anatomical locations in acute hereditary angioedema (HAE) Attacks. Journal of allergy and clinical immunology; 2017.
158. Smith MD DE, Hampton SL, Yea CM, Audhya P, Feener EP,. Oral KVD900 provides rapid inhibition of plasma kallikrein and fast improvement in attack symptoms in patients with hereditary angioedema. Allergy and asthma proceedings. 2022;43(6):563.
159. Audhya PK SM, Williams P, Yea CM, Cohn DM,. Agreement between improvements in patient global impression of change and other measures of improvement and attack resolution observed in a phase 2 trial with KVD900 in patients with hereditary angioedema. Allergy and asthma proceedings. 2022;43(6):563.
160. Longhurst HJ SM, Yea C, Audhya P,. SEBETRALSTAT EFFECTIVENESS IN THE TREATMENT OF HEREDITARY ANGIOEDEMA ATTACKS RATED MILD OR MODERATE AT BASELINE IN THE PHASE 2 TRIAL. Internal medicine journal. 2022;52(11):29.
161. Bernstein J RM, Lumry W, Audhya P, Smith M, Yea C,. Treatment with Sebetralstat Reduces the Cumulative Symptom Severity of Hereditary Angioedema Attacks in a Phase 2 Trial. Journal of allergy and clinical immunology. 2023;151(2):AB130.
162. Hofstra JJ, Kleine Budde I, van Twuyver E, Choi G, Levi M, Leebeek FW, et al. Treatment of hereditary angioedema with nanofiltered C1-esterase inhibitor concentrate (Cetor®): multi-center phase II and III studies to assess pharmacokinetics, clinical efficacy and safety. Clin Immunol. 2012;142(3):280-90.
163. Lumry W, Manning ME, Hurewitz DS, Davis-Lorton M, Fitts D, Kalfus IN, et al. Nanofiltered C1-esterase inhibitor for the acute management and prevention of hereditary

angioedema attacks due to C1-inhibitor deficiency in children. J Pediatr. 2013;162(5):1017-22.e1-2.
164. Riedl MA, Lumry WR, Li HH, Craig TJ, Fitts D, Kalfus I, et al. Nanofiltered C1 esterase inhibitor for treatment of laryngeal attacks in patients with hereditary angioedema. Am J Rhinol Allergy. 2013;27(6):517-21.
165. Kalfus I TG, Zuraw B,. C1 inhibitor in the treatment of laryngeal attacks of hereditary angioedema (hae). Chest. 2009;136(4):44S-a.
166. Malbrán A, Riedl M, Ritchie B, Smith WB, Yang W, Banerji A, et al. Repeat treatment of acute hereditary angioedema attacks with open-label icatibant in the FAST-1 trial. Clin Exp Immunol. 2014;177(2):544-53.
167. Baş M, Greve J, Hoffmann TK, Reshef A, Aberer W, Maurer M, et al. Repeat treatment with icatibant for multiple hereditary angioedema attacks: FAST-2 open-label study. Allergy. 2013;68(11):1452-9.
168. Lumry WR, Farkas H, Moldovan D, Toubi E, Baptista J, Craig T, et al. Icatibant for Multiple Hereditary Angioedema Attacks across the Controlled and Open-Label Extension Phases of FAST-3. Int Arch Allergy Immunol. 2015;168(1):44-55.
169. Farkas H KC, Riedl M, Kivity S,. Integrated results from three phase III trials to explore the efficacy of icatibant in non-laryngeal attacks of type I and II hereditary angioedema. Allergy. 2012;67:195.
170. Farkas H RM. Efficacy of icatibant in non-laryngeal attacks of type I and II hereditary angioedema: integrated results from three phase III trials. Journal of allergy and clinical immunology. 2012;129(2):AB218
171. Maurer M RA, Craig T, Cicardi M,. Icatibant effectively alleviates non-laryngeal attacks of hereditary angioedema type I and II irrespective of attack severity or historical attack frequency. ALLERGY. 2012;67:199-200.
172. Reshef A LR, Craig T,. Efficacy of icatibant is consistent by attack frequency and baseline severity in the treatment of type I and II hereditary angioedema (HAE) attacks. Journal of allergy and clinical immunology. 2012;129(2):AB218
173. Riedl M. Icatibant a selective Bradykinin B2 receptor antagonist proves effective and safe in treating the symptoms of hereditary angioedema (HAE) attacks. Journal of allergy and clinical immunology. 2008;21:S103 [398].
174. Yang W HJ, Ritchie B, Baptista J, Riedl M, Lumry WR,. Analysis of icatibant for the treatment of laryngeal hereditary angioedema attacks in the FAST-3 study. Allergy, Asthma and Clinical Immunology. 2014;10(2):A51.
175. Li HH CT. Efficacy of icatibant persists over 8 h in patients with hereditaryangioedema: results froma phase III study. Annals of allergy, asthma and immunology. 2011;107:A113
176. Moldovan D BJ, Bernstein JA, Grivcheva-Panovska V, Reshef A, Relan A, Riedl M,. Efficacy of RHC1INH for the treatment of peripheral angioedema in patients with HAE. Annals of allergy, asthma and immunology. 2015;115(5):A33.
177. Bernstein JA, Relan A, Harper JR, Riedl M. Sustained response of recombinant human C1 esterase inhibitor for acute treatment of hereditary angioedema attacks. Ann Allergy Asthma Immunol. 2017;118(4):452-5.
178. Baker JW, Bernstein JA, Harper JR, Relan A, Riedl MA. Efficacy of recombinant human C1 esterase inhibitor across anatomic locations in acute hereditary angioedema attacks. Allergy Asthma Proc. 2018;39(5):359-64.

179. Schneider L, Hurewitz D, Wasserman R, Obtulowicz K, Machnig T, Moldovan D, et al. C1-INH concentrate for treatment of acute hereditary angioedema: a pediatric cohort from the I.M.P.A.C.T. studies. Pediatr Allergy Immunol. 2013;24(1):54-60.
180. Bernstein JA, Machnig T, Keinecke HO, Whelan GJ, Craig TJ. The effect of weight on the efficacy and safety of C1 esterase inhibitor concentrate for the treatment of acute hereditary angioedema. Clin Ther. 2014;36(4):518-25.
181. Craig TJ, Bewtra AK, Hurewitz D, Levy R, Janss G, Jacobson KW, et al. Treatment response after repeated administration of C1 esterase inhibitor for successive acute hereditary angioedema attacks. Allergy Asthma Proc. 2012;33(4):354-61.
182. Aygören- Pürsün E AJ, Baeza M L., Bouillet H, Chapdelaine; D. Cohn D, Du-Thanh A, Fain O, Farkas H, Greve J, Guilarte-Clavero M, Hagin D, Hakl R, Jacobs JS, Kessel A, Kiani-Alikhan S, Králíčková P, Li HH Lleonart bellfill R, Magerl M, Manning ME, Reshef A, Riedl MA, Ritchie B, Spadaro G, Staevska M Staubach P, Stobiecki M, Sussman GL, Tarzi MD, Valerieva A, Yang W, Jouvin MH, Crabbé R, Van Leeuwen S, Chen H, Zhi L, Knolle J, Lesage A, Lu P,. Maurer M, . Treatment with oral administered bradykinin B2 receptor inhibitor PHVS416 improves hereditary angioedema attack symptoms. Allergy. 2023;78(S112).
183. Farkas H AJ, Aygören-Pürsün W, Baeza ML, Bouillet L, Chapdelaine H, Cohn DM, Du-Thanh A, Fain O, Greve J, Guilarte M, Hagin D, Hakl R, Jacobs JS, Kessel A, Kiani-Alikhan S, Králíčková P, Henry H, Lleonart R, Magerl M, Manning ME, Reshef A, Riedl MA, Ritchie B, Spadaro G, Staevska M, Staubach P, Stobiecki M, Sussman GL, Tarzi MD, Valerieva A, Yang WH, Jouvin M-H, Crabbé R, van Leeuwen S, Chen H, Zhu L, Knolle J, Lesage A, Lu P, Maure M,. Efficacy and safety of the oral bradykinin B2 receptor antagonist PHVS416 in treatment of Hereditary Angioedema attacks: topline results of RAPIDe-1 phase 2 trial. Allergy, Asthma & Clinical Immunology 2023;19(1):O-19.
184. Riedl MA AJ, Aygören-Pürsün E, Baeza M-L, Bouillet L, Chapdelaine H, Cohn DM, Du-Thanh A, Fain O, Farkas H, Greve J, Guilarte M, Hagin D, Hakl R, Jacobs JS, Kessel A, Kiani-Alikhan S, Králícková P, Li H Lleonart R, Magerl M, Manning ME, Reshef A, Ritchie B, Spadaro G, Staevska M, Staubach P , Stobiecki M, Sussman GL, Tarzi MD, Valerieva A,, Yang WH JM-H, Crabbé R, van Leeuwen S, Chen H, Zhu L, Knolle J, Lesage A, Lu P, Maurer M,. Early symptom relief following treatment with the oral bradykinin 2 receptor antagonist PHVS416 in patients with hereditary angioedema attacks. Allergy, Asthma & Clinical Immunology 2023;19(1):P-25.
185. Longhurst HJ SM, Zanichelli A, Huissoon A, Moldovan D, Maurer M, Magerl M, Cancian M, Senter R, Manson A, Aygoren-Pursun E, Grivcheva-Panovska V, Hagin D, Steiner U, Kiani-Alikhan S, Agmon-Levin N, Bygum A, Aberer W, Faust SN, Launay D, Gompels M, Triggiani M, Bethune C, Reshef A, Cornpropst M, Dobo S, Van Dyke S, Murray S, Collis P, Sheridan WP, Farkas H, Cicardi M,. Final results from the ZENITH-1 study: oral administration of plasma kallikrein inhibitor BCX7353 for the treatment of attacks in patients with hereditary angioedema. Allergy. 2019;74:10-1.
186. Stobiecki M APE, Andarawewa S, Zanichelli A, Cicardi M, Huissoon A, Moldovan D, Bara N, Mihaly E, Magerl M, Cancian M, Senter R, Manson A, Grivcheva-Panovska V, Hagin D, Steiner U, Kiani-Alikhan S, Agmon-Levin N, Bygum A, Aberer W, Faust SN, Launay D, Gompels M, Triggiani M, Bethune C, Reshef A, Kohalmi KV, Farkas H, Mathis A, Cornpropst M, Dobo S, Van Dyke S, Murray S, Collis P, Sheridan WP, Maurer M,

Longhurst H,. Clinical evaluation of pharmacokinetics, pharmacodynamics, safety, and efcacy dose-response of BCX7353 as an acute treatment for angioedema in patients with hereditary angioedema (HAE). Allergy, asthma and clinical immunology. 2019;15.
187. Kunschak M, Engl W, Maritsch F, Rosen FS, Eder G, Zerlauth G, et al. A randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. Transfusion. 1998;38(6):540-9.
188. Riedl MA, Levy RJ, Suez D, Lockey RF, Baker JW, Relan A, et al. Efficacy and safety of recombinant C1 inhibitor for the treatment of hereditary angioedema attacks: a North American open-label study. Ann Allergy Asthma Immunol. 2013;110(4):295-9.
189. Baker JW, Reshef A, Moldovan D, Harper JR, Relan A, Riedl MA. Recombinant Human C1-Esterase Inhibitor to Treat Acute Hereditary Angioedema Attacks in Adolescents. J Allergy Clin Immunol Pract. 2017;5(4):1091-7.
190. Moldovan D, Reshef A, Fabiani J, Kivity S, Toubi E, Shlesinger M, et al. Efficacy and safety of recombinant human C1-inhibitor for the treatment of attacks of hereditary angioedema: European open-label extension study. Clin Exp Allergy. 2012;42(6):929-35.
191. Li HH, Moldovan D, Bernstein JA, Reshef A, Porebski G, Stobiecki M, et al. Recombinant human-C1 inhibitor is effective and safe for repeat hereditary angioedema attacks. J Allergy Clin Immunol Pract. 2015;3(3):417-23.
192. Li HH, Reshef A, Baker JW, Harper JR, Relan A. Efficacy of recombinant human C1 esterase inhibitor for the treatment of severe hereditary angioedema attacks. Allergy Asthma Proc. 2017;38(6):456-61.
193. BioCryst Pharmaceuticals. Study of BCX7353 as a Treatment for Attacks of Hereditary Angioedema [Available from: https://clinicaltrials.gov/study/NCT03240133/.
194. Aygören-Pürsün E, Zanichelli A, Cohn D, Audhya P, Williams P, Yea CM, et al. [Phase 2 poster] Efficacy of the Oral Plasma Kallikrein Inhibitor Sebetralstat (KVD900) by Attack Location in a Phase 2 Clinical Trial in Patients With Hereditary Angioedema EAACI (European Academy of Allergy & Clinical Immunology) Hybrid Congress July 2022; Prague, Czech Republic2022.
195. Sultanov M, Almadiyeva A, K A. C1-Esterase Inhibitor for LONG-TERM Prophylaxis inPatients with Hereditary Angioedema in Kazakhstan: AnEconomic Evaluation. Value in Health. 2020;23(2):1-2.
196. Arjunji R, Venkitaramani D, Wiesner T, Maru B, Dabbous O. Assessment of Cost-Effectiveness Results from Icer Ultra-Rare Disorder Reviews. Value in Health. 2019;22.
197. Lubinga SJ, Agboola FO, Lin G, Seidner M, Rind D, Carlson J. Cost-Effectiveness of Lanadelumab and C1-Inhibitors for Prophylaxis against Acute Attacks of Hereditary Angioedema. Value in Health. 2019;22.
198. Magliano CA, Tura BR, Santos M, Senna K, Costa MG. Cost Effectiveness of Icatibant for Hereditary Angioedema in Brazil: Challenges in the Economic Evaluation of Orphan Drugs. Value in Health. 2019;19(3).
199. Tilden D, Cottrell S, Tocchini L, Jayaram N, R S. A MODELLED ECONOMIC EVALUATION OF FIRAZYR®(ICATIBANT) FOR SYMPTOMATIC TREATMENT OF ACUTEATTACKS OF HEREDITARY ANGIOEDEMA (HAE) IN ADULTSWITH C1-ESTERASE-INHIBITOR (C1-INH) DEFICIENCY. Value in Health. 2011;14(7):1-2.
200. CADTH. Pharmacoeconomic Review Report: Lanadelumab (Takhzyro): (Shire Pharma Canada ULC): Indication: For the routine prevention of attacks of hereditary angioedema in adolescents and adults. 2020.

201. Institute for Clinical and Economic Review. Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value. 2018.
202. CADTH. CADTH. Case Technology Review: Drug Therapies for the Long-Term Prophylaxis of Hereditary Angioedema Attacks. . 2019.
203. National Institute for Health Care and Excellence. Single Technology Appraisal: Lanadelumab for preventing recurrent attacks of hereditary angioedema [ID1268] Appraisal Consultation Document 1st Committee meeting NICE,: NICE, ; 2019.
204. CADTH. CADTH Reimbursement Review
Berotralstat (Orladeyo). Canadian Journal of Health Technologies. 2023;3(4):1-152.
205. All Wales Medicines Strategy Group (AWMSG). AWMSG Secretariat Assessment Report – Limited submission C1 inhibitor (human) (Cinryze®) 500 Units powder and solvent for solution for injection. 2013.
206. Spano R, Di Paola N, Bova M, Barbarino A. Value co-creation in healthcare: evidence from innovative therapeutic alternatives for hereditary angioedema. BMC Health Serv Res. 2018;18(1):571.
207. Sabharwal G, Vernon N, Zbrozek A, Machnig T, Craig TJ. Comparative Economics of On-Demand Treatment Options Approved in the United States for Hereditary Angioedema. Journal of Allergy and Clinical Immunology. 2013;131(2).
208. CADTH. CDR Pharmacoeconomic Review Report for Firazyr 2018.
209. Graham C, Machnig T, Knox H, Supina D, Krishnarajah G. P159 Attacks avoided and cost offsets associated with subcutaneous C1-inhibitor (human) long-term prophylaxis of hereditary angioedema. Annals of Allergy, Asthma & Immunology. 2017;119(5):S40-S1.
210. Federici C, Perego F, Borsoi L, Crosta V, Zanichelli A, Gidaro A, et al. Costs and effects of on-demand treatment of hereditary angioedema in Italy: a prospective cohort study of 167 patients. BMJ Open. 2018;8(7):e022291.
211. Blasco A, Lázaro P, Caballero T, Guilarte M. Social costs of icatibant self-administration vs. health professional-administration in the treatment of hereditary angioedema in Spain. Health Economics Review. 2013;3(2):1-11.
212. Cheng BT, Silverberg JI, Samet JD, Fishbein AB. Burden of emergency department utilization and abdominal imaging for hereditary angioedema. J Allergy Clin Immunol Pract. 2020;8(4):1443-6 e2.
213. Cortes L, Linden S, Baeza M, Baynova K, Guilarte M, Joral A, et al. Study of costs of Hereditary Angioedema in routine clinical practice: economic impact of the disease burden in Spain. 2023.
214. Krishnarajah G, Knox H, Graham C, Christiansen S, B Z. Subcutaneous C1-inhibitor prophylactic treatment for hereditary angioedema: A budget impact model. Journal of Managed Care & Specialty Pharmacy. 2018;24(4):37.
215. Squeglia V, Barbarino A, Di Paola N, Petraroli A, Spanò R, Bova M, et al. COST-MINIMIZATION OF INNOVATIVE C1-INHIBITOR SELF-ADMINISTRATION STRATEGIES IN HEREDITARY ANGIOEDEMA. 2014.
216. Jain G, Neves C, Willis A, Mendivil J, G D. A Budget Impact Model for Lanadelumab Treatment for the Prevention of HAE Attacks Among Patients with Type I or II HAE: Estimates of Yearly Savings for a U.S. Commercial Health Plan. Journal of Managed Care & specialty Pharmacy. 2019;25(3):38.

217. Tutein Nolthenius J, Figueiredo R, Wood S, Whalen DJ, editors. Costs of Treating Hereditary Angioedema (HAE) Attacks with C1 Inhibitors in Five Central and Eastern European Countries. ISPOR Europe; 2022; Vienna, Austria.
218. Javaud N, Bouillet L, Rabetrano H, Bitoun A, Launay D, Lapostolle F, et al. Hereditary angioedema: Clinical presentation and socioeconomic cost of 200 French patients. J Allergy Clin Immunol Pract. 2019;7(1):328-30.
219. Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.
220. Anderson J SD, Mellor J, Connolly H, Wynne-Cattanach K, Earl L, Schultz B, Juethner S, . PHYSICIAN AND PATIENT REPORTED OUTCOMES BY HEREDITARY ANGIOEDEMA TYPE: DATA FROM A REALWORLD STUDY. Ann Allergy Asthma Immunol. 2022;129:S15-S81.
221. Arnaout R, Contreras-Verduzco F, Demuth D, Jain S, Song H, Kang H, editors. Real-world patient burden of hereditary angioedema (HAE) and impact on quality of life (QoL) in regions with limited HAE management options and highest unmet needs. ALLERGY; 2023: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA.
222. Aygören-Pürsün E, Bygum A, Grivcheva-Panovska V, Magerl M, Graff J, Steiner UC, et al. Oral plasma kallikrein inhibitor for prophylaxis in hereditary angioedema. New England Journal of Medicine. 2018;379(4):352-62.
223. Bouillet L B-GI, Launay D, Debord-Peguet S, Lenkei C, Boudjemia K, Du-Thanh A, Fain O, Gobert D, . [No title on this abstract - identifiable as: Allergy: European Journal of Allergy and Clinical Immunology - Volume 75, Issue 0, pp. 87 - published 2020-01-01]. European Journal of Allergy and Clinical Immunology. 2020;75:87.
224. Craig T, Magerl M, Reshef A, Li H, Jacobs J, Bernstein J, et al. Efficacy and Safety of Subcutaneous Garadacimab for the Prophylaxis of Hereditary Angioedema Attacks in Adults and Adolescent Patients with HAE: Results from a Multicenter, Placebo-Controlled Phase 3 Trial. Journal of Allergy and Clinical Immunology. 2023;151(2):AB132.
225. Fain O, Du-Thanh A, Gobert D, Launay D, Inhaber N, Boudjemia K, et al. Long-term prophylaxis with lanadelumab for HAE: authorization for temporary use in France. Allergy, Asthma & Clinical Immunology. 2022;18(1):30.
226. Farkas H, Stobiecki M, Peter J, Kinaciyan T, Maurer M, Aygören-Pürsün E, et al. Long-term safety and effectiveness of berotralstat for hereditary angioedema: The open-label APeX-S study. Clinical and translational allergy. 2021;11(4):e12035.
227. Fijen LM, Klein PC, Cohn DM, Kanters TA. The disease burden and societal costs of hereditary angioedema. The Journal of Allergy and Clinical Immunology: In Practice. 2023;11(8):2468-75. e2.
228. Fijen LM, Riedl MA, Bordone L, Bernstein JA, Raasch J, Tachdjian R, et al. Inhibition of prekallikrein for hereditary angioedema. New England Journal of Medicine. 2022;386(11):1026-33.
229. Grumach A, Zwiener R, Martinez-Saguer I, Simon A, Murphy R, De La Cruz M, et al. Burden of Illness in Adult Patients With Controlled and Poorly Controlled Hereditary Angioedema: Findings From a Multinational Survey. Journal of Allergy and Clinical Immunology. 2024;153(2):AB92.
230. Hahn J, Trainotti S, Wigand MC, Schuler PJ, Hoffmann TK, Greve J. Prospective Analysis in Patients With HAE Under Prophylaxis With Lanadelumab: A Real-life Experience. Journal of Drugs in Dermatology: JDD. 2020;19(10):978-83.

231. Hews-Girard J, Goodyear MD. Psychosocial burden of type 1 and 2 hereditary angioedema: a single-center Canadian cohort study. Allergy, Asthma & Clinical Immunology. 2021;17:1-8.
232. Honda D, Hide M, Fukuda T, Koga K, Morita E, Moriwaki S, et al. Berotralstat for long-term prophylaxis of hereditary angioedema in Japan: Parts 2 and 3 of the randomized APeX-J Phase III trial. World Allergy Organization Journal. 2024;17(3):100882.
233. Johnston D, Banerji A, Riedl M, Soteres D, Bernstein J, Best J, et al. P154 berotralstat improves patient-reported quality of life through 48 weeks in the phase 3 apex-2 trial. Annals of Allergy, Asthma & Immunology. 2020;125(5):S22.
234. Lluncor M, Lamacchia D, Hernanz A, Pedrosa M, Alvez A, Cabañas R, et al. Determinants of health related quality of life (HRQoL) in adult patients with hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE). Journal of Allergy and Clinical Immunology. 2018;141(2):AB266.
235. Lumry WR, Maurer M, Weller K, Riedl MA, Watt M, Yu M, et al. Long-term lanadelumab treatment improves health-related quality of life in patients with hereditary angioedema. Annals of Allergy, Asthma & Immunology. 2023;131(1):101-8. e3.
236. Lumry WR, Weller K, Magerl M, Banerji A, Longhurst HJ, Riedl MA, et al. Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study. Allergy. 2021;76(4):1188-98.
237. Lumry WR, Zuraw B, Cicardi M, Craig T, Anderson J, Banerji A, et al. Long-term health-related quality of life in patients treated with subcutaneous C1-inhibitor replacement therapy for the prevention of hereditary angioedema attacks: findings from the COMPACT open-label extension study. Orphanet journal of rare diseases. 2021;16:1-14.
238. Medina I JD, Berardi A., Cavallo C, Chinigo M, Chorzepa G, Fueyo G, Garcia M, Onetti C, Vazquez D,. Multicenter study on health-related quality of life in patients with Hereditary Angioedema in Argentina: preliminary results. Allergy: European Journal of Allergy and Clinical Immunology. 2023;78:413-4.
239. Mendivil J, Murphy R, de la Cruz M, Janssen E, Boysen HB, Jain G, et al. Clinical characteristics and burden of illness in patients with hereditary angioedema: findings from a multinational patient survey. Orphanet J Rare Dis. 2021;16(1):94.
240. Newman K, Riedl M, Lui C, Bordone L, Alexander V, Schneider E, et al. The Impact of Donidalorsen Taken Every 8 Weeks in Patients With Hereditary Angioedema. Journal of Allergy and Clinical Immunology. 2023;151(2):AB134.
241. Nordenfelt P, Nilsson M, Lindfors A, Wahlgren C-F, Björkander JF, editors. Health-related quality of life in relation to disease activity in adults with hereditary angioedema in Sweden. Allergy and asthma proceedings; 2017: OceanSide Publications.
242. Nuez AL GI, Alvarez-Perea A, Garcia AP, Ochoa De Ocariz MLB,. Hereditary angioedema: Quality of life in 19 patients. Allergy, Asthma and Clinical Immunology. 2019;15:28.
243. Peter JG, Desai B, Tomita D, Collis P, Stobiecki M. Assessment of HAE prophylaxis transition from androgen therapy to berotralstat: A subset analysis of the APeX-S trial. World Allergy Organization Journal. 2023;16(11):100841.
244. Phillips-Angles E, Lluncor M, Pedrosa M, Lamacchia D, Hernanz A, Alvez-Liste A, et al., editors. Determinant factors of disease activity in hereditary angioedema due to C1 inhibitor deficiency. ALLERGY; 2019: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA.

245. Riedl MA, Aygören-Pürsün E, Baker J, Farkas H, Anderson J, Bernstein JA, et al. Evaluation of avoralstat, an oral kallikrein inhibitor, in a Phase 3 hereditary angioedema prophylaxis trial: The OPuS-2 study. Allergy. 2018;73(9):1871-80.
246. ClinicalTrials.gov. Study of C1 Inhibitor (Human) for the Prevention of Angioedema Attacks and Treatment of Breakthrough Attacks in Japanese Subjects With Hereditary Angioedema (HAE) 2021 [Available from: https://clinicaltrials.gov/study/NCT02865720?term=NCT02865720&rank=1.
247. Soteres D, Lumry W, Magerl M, Gagnon R, Desai B, Tomita D, et al. Berotralstat improved quality of life through 96 weeks across multiple subgroups of patients with hereditary angioedema. Journal of Allergy and Clinical Immunology. 2023;151(2):AB139.
248. Watt M, Simon A, Murphy R, De La Cruz M, Romanus D, Zwiener R, et al., editors. Burden of (HAE): Findings from a multinational patient survey in Argentina and Colombia. ALLERGY; 2023: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA.
249. Wedner HJ, Bernstein J, Betschel S, Manning M, Estepan DN, Fei K, et al. Effectiveness, safety, and patient-reported outcomes (PROs) in patients with hereditary angioedema (HAE) from the United States and Canada treated with lanadelumab: 24-month data from the EMPOWER study. Journal of Allergy and Clinical Immunology. 2023;151(2):AB131.
250. Weller K, Maurer M, Fridman M, Supina D, Schranz J, Magerl M, editors. Health-related quality of life with hereditary angioedema following prophylaxis with subcutaneous C1-inhibitor with recombinant hyaluronidase. Allergy & Asthma Proceedings; 2017.
251. Wong JCY, Chiang V, Lam K, Tung E, Au EYL, Lau CS, et al. Prospective Study on the Efficacy and Impact of Cascade Screening and Evaluation of Hereditary Angioedema (CaSE-HAE). J Allergy Clin Immunol Pract. 2022;10(11):2896-903 e2.
252. Zwiener R, Martinez-Saguer I, Grumach A, Simon A, Murphy R, De La Cruz M, et al. Burden of Illness in Female and Male Adult Patients With Hereditary Angioedema: Findings From a Multinational Survey. Journal of Allergy and Clinical Immunology. 2024;153(2):AB93.
253. Braverman J, Chapdelaine H, Sitz K, Katelaris CH, Guilarte M, Longhurst H, et al. Long-term quality-of-life and patient-reported improvements with garadacimab for hereditary angioedema: Phase 3 open-label extension study. Allergologie. 2023;47(9):534 EP - 5.
254. Buttgereit T, Vera Ayala C, Aykanat S, Weller K, Gutsche A, Maurer M, et al. The real life experience goes on: update after 4 years on the first cohort treated with lanadelumab at our center. Frontiers in immunology. 2024;15:1405317.
255. Hioki C, Oda Y, Moriwaki S, Fukunaga A. Effect of lanadelumab on attack frequency and QoL in Japanese patients with hereditary angioedema: Report of five cases. Journal of Dermatology. 2024;51(6):873 EP - 7.
256. Hsu F, Lumry W, Aygoren-Pursun E, Braverman J, Lawo J, Pollen M, et al. BEING ATTACK-FREE WITH GARADACIMAB IMPROVES QUALITY OF LIFE IN PATIENTS WITH HEREDITARY ANGIOEDEMA. Annals of Allergy, Asthma and Immunology. 2024;133(6 Supplement):S33 EP - S4.
257. Itzler R, Lumry WR, Sears J, Braverman J, Li Y, Brennan CJ, et al. An international survey assessing the effects of the duration of attack-free period on health-related quality

of life for patients with hereditary angioedema. Orphanet Journal of Rare Diseases. 2024;19(1):241.
258. Morioke S, Aikyo T, Tanaka A, Matsubara D, Saito R, Iwamoto K, et al. Survey of hereditary angioedema episodes and quality of life impairment through a patient-participatory registry. Journal of Cutaneous Immunology and Allergy. 2024;7:12626.
259. Petersen RS, Bordone L, Riedl MA, Tachdjian R, Craig TJ, Lumry WR, et al. A phase 2 open-label extension study of prekallikrein inhibition with donidalorsen for hereditary angioedema. Allergy: European Journal of Allergy and Clinical Immunology. 2024;79(3):724
EP - 34.
260. Tachdjian R, Riedl M, Bordone L, Newman K, Treadwell S, Lin T, et al. DONIDALORSEN FOR HEREDITARY ANGIOEDEMA: RESULTS FROM THE OASISPLUS OPEN-LABEL EXTENSION STUDY. Annals of Allergy, Asthma and Immunology. 2024;133(6 Supplement):S38.
261. Yarlas A, Riedl M, Bordone L, Treadwell S, Wang S, Newman K, et al. IMPACT OF DONIDALORSEN ON PATIENT-REPORTED OUTCOMES: RESULTS FROM THE PHASE 3 OASIS-HAE STUDY. Annals of Allergy, Asthma and Immunology. 2024;133(6 Supplement):S37.
262. Hide M, Kishimoto M, Kotera I, Oh A, Inoue Y, Yamamoto BA, et al. Analysis of disease burden in patients with hereditary angioedema from Japan by patient-reported outcomes. J Dermatol. 2024.
263. Demir S, Eyice-Karabacak D, Kocaturk E, Unal D, Toprak ID, Korkmaz P, et al. Monitoring recurrent angioedema: Findings from the Turkish angioedema control test validation study. Clin Transl Allergy. 2024;14(3):e12342.
264. Kucharczyk A, Matuszewski T, Kurowski M, Juchacz A, Tomasial-Lozowska M, Trębas-Pietraś E, et al. Real-world Treatment Outcomes of Lanadelumab in the Prevention of Hereditary Angioedema Attacks: an Interim Analysis of a Polish, Prospective, Multicenter, Observational Study (CHOPIN). Journal of Allergy and Clinical Immunology. 2024;153(2):AB9.
265. Troelnikov A, Milburn K, Hissaria P, Thao Le T, Smith W. Hereditary angioedema prevalence and satisfaction with prophylaxis in South Australia. World Allergy Organization Journal. 2024;17(7).
266. Craig TJ, Levy DS, Reshef A, Lumry WR, Martinez-Saguer I, Jacobs JS, et al. Garadacimab for hereditary angioedema attack prevention: long-term efficacy, quality of life, and safety data from a phase 2, randomised, open-label extension study. The Lancet Haematology. 2024;11(6):e436-e47.
267. Manning M, Bordone L, Cohn D, Deng Y, Treadwell S, Newman K, et al. PHASE 2 OPEN-LABEL EXTENSION OF DONIDALORSEN IN PATIENTS WITH HEREDITARY ANGIOEDEMA: A WEEK 197 ANALYSIS. Annals of Allergy, Asthma & Immunology. 2024;133(6):S38.
268. Wedner H, Anderson J, Chapdelaine H, Magerl M, Manning M, Riedl M, et al. PROPHYLACTIC TREATMENT WITH ORAL DEUCRICTIBANT IMPROVES HEREDITARY ANGIOEDEMA DISEASE CONTROL AND HEALTH-RELATED QUALITY OF LIFE. Annals of Allergy, Asthma & Immunology. 2024;133(6):S34-S5.

269. Arce-Ayala YM, Diaz-Algorri Y, Craig T, Ramos-Romey C, editors. Clinical profile and quality of life of Puerto Ricans with hereditary angioedema. Allergy & Asthma Proceedings; 2019.
270. Ayazi M FM, Saghafi S, Mohammadian S, Deshiry SN, Bidad K, Shoormasti RS, Mohammadzadeh I, Bemanian MH, Mahdaviani SA, Pourpak Z,. Quality of life in 41 patients with hereditary angioedema: First report from Iranian National Registry of Hereditary Angioedema. Allergy, Asthma and Clinical Immunology. 2017;13.
271. Devercelli G, Davis K, Brown M, Hollis K, Hunter S, Long J, et al. Burden of Hereditary Angioedema: Findings From a US Patient Survey. Journal of Allergy and Clinical Immunology. 2018;141(2):AB57.
272. Jindal NL, Harniman E, Prior N, Perez-Fernandez E, Caballero T, Betschel S. Hereditary angioedema: health-related quality of life in Canadian patients as measured by the SF-36. Allergy, Asthma & Clinical Immunology. 2017;13:1-5.
273. Liu S, Wang X, Xu Y, Xu Q, Zhi Y. Health-related quality of life and its risk factors in Chinese hereditary angioedema patients. Orphanet Journal of Rare Diseases. 2019;14:1-8.
274. Moreno A, Nunes F, Langer S, Ferriani M, Aragon D, Caballero T, et al. A multidisciplinary intervention resulted in improvement in qualilty of life among patients with hereditary angioedema. Journal of Allergy and Clinical Immunology. 2020;145(2):AB108.
275. Nunes FL, Ferriani MP, Moreno AS, Langer SS, Maia LS, Ferraro MF, et al. Decreasing attacks and improving quality of life through a systematic management program for patients with hereditary angioedema. International Archives of Allergy and Immunology. 2021;182(8):697-708.
276. Wadiwalla SH, Kanani AS. Quality of life evaluation in Hereditary Angioedema patients on home plasma derived C1 inhibitor infusion. Journal of Allergy and Clinical Immunology. 2019;143(2):AB115.
277. Aygören-Pürsün E, Soteres DF, Nieto-Martinez SA, Christensen J, Jacobson KW, Moldovan D, et al. A randomized trial of human C1 inhibitor prophylaxis in children with hereditary angioedema. Pediatric allergy and immunology. 2019;30(5):553-61.
278. Jacobson K, Soteres D, Nieto-Martinez S, Moldovan D, Martinez-Saguer I, Vardi M, et al. C1 inhibitor administration in pediatric patients with hereditary angioedema: patient compliance with intravenous therapy. Annals of Allergy, Asthma & Immunology. 2018;121(5):S36.
279. Lumry WR, Craig T, Zuraw B, Longhurst H, Baker J, Li HH, et al. Health-related quality of life with subcutaneous C1-inhibitor for prevention of attacks of hereditary angioedema. The Journal of Allergy and Clinical Immunology: In Practice. 2018;6(5):1733-41. e3.
280. Martinez-Saguer I SD, Van Leerberghe A, Herrera EM, Devercelli G, Vardi M, Christensen J,. Improved health-related quality of life in pediatric patients with hereditary angioedema (HAE): A phase 3 study of C1 inhibitor for attack prevention. Allergy: European Journal of Allergy and Clinical Immunology. 2018;73:718.
281. Watt M, Maurer M, Lumry W, Li HH, Aygören-Pürsün E, Busse P, et al. Health-related quality of life (Hrqol) in pediatric patients with hereditary angioedema (HAE) receiving Lanadelumab: exploratory results from the spring study. Journal of Allergy and Clinical Immunology. 2023;151(2):AB139.

282. Busse P, Radojicic C, O'Connor M, Craig T, Ulloa J, Danese S, et al. Burden of hereditary angioedema attacks in adolescents. Allergy and Asthma Proceedings. 2024;45(3):212.
283. Park K, Yeich A, Craig T. Evaluating the Impact of Acute Versus Prophylaxis Therapy in Hereditary Angioedema. Journal of Allergy and Clinical Immunology. 2023;151(2):AB135.
284. Castaldo T, Selva C, Johnson P, Hunter AG, Tse J, Martinez A, et al. Comparison of Selected Health and Well Being Characteristics in Seniors with Hereditary Angioedema (HAE) and a Non-HAE Patient Matched Cohort. Journal of Allergy and Clinical Immunology. 2023;151(2):AB136.
285. Craig TJ, Busse P, Christiansen S, O'Connor M, Radojicic C, Ulloa J, et al. Real-World Impact of Treated Hereditary Angioedema Attacks on Patients' Employment and Work Productivity. Value in Health. 2024;27(6):1-2.
286. Ahuja M DA, Bode E, Boulton A, Buckland M, Chee S, Dalley C, Denman S, Ekbote A, Elkhalifa S, El-Shanawany T, Eren E, Garcez T, Ghanta H, Grammatikos A, Grigoriadou S, Herwadkar A, Jain R, Lorenzo L, Moon E, Murng S, Murphy A, Mutlu L, Peters N., Sooriyakumar K, Stroud C, Townsend K, Yong P, Kiani S,. Berotralstat for the prophylaxis of hereditary angioedema -A national survey of patient outcomes in the UK. European Journal of Allergy and Clinical Immunology. 2023;78:413-4.
287. Magerl M, Martinez-Saguer I, Schauf L, Pohl S, Brendel K. The current situation of hereditary angioedema patients in Germany: results of an online survey. Frontiers in Medicine. 2024;10:1274397.
288. Riedl M, Bordone L, Tachdjian R, Newman K, Treadwell S, Lin T, et al. TREATMENT OF HEREDITARY ANGIOEDEMA: SAFETY, EFFICACY, AND PATIENT PREFERENCE AFTER SWITCHING TO DONIDALORSEN (OASISPLUS STUDY). Annals of Allergy, Asthma & Immunology. 2024;133(6):S37.
289. Lee EY, Hsieh J, Borici-Mazi R, Caballero T, Kanani A, Lacuesta G, et al. Quality of life in patients with hereditary angioedema in Canada. Annals of Allergy, Asthma & Immunology. 2021;126(4):394-400. e3.
290. Jacobs J, Aygoren-Pursun E, Sitz K, Tachdjian R, Li H, Best J, et al. P165 BEROTRALSTAT POSITIVELY IMPACTS PATIENT-REPORTED SATISFACTION: RESULTS FROM THE PHASE 3 APEX-2 TRIAL. Annals of Allergy, Asthma & Immunology. 2020;125(5):S25.
291. Aabom A, Nguyen D, Fisker N, Bygum A. Health-related quality of life in Danish children with hereditary angioedema. Allergy & Asthma Proceedings. 2017;38(6):440-6.
292. Lumry W, Davis-Lorton M, Soteres D, Hall J, Earl L, Connolly H, et al., editors. Clinical outcomes and quality of life in patients with HAE receiving lanadelumab long-term prophylaxis: Interim analysis of 3-year real-world data. ALLERGY; 2023: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA.
293. Farkas H, Aygoeren-Puersuen E, Kanani A, Psarros F, Ebo D, Bara N, et al., editors. Real-world burden of illness in patients with hereditary angioedema (HAE) type I and II. ALLERGY; 2023: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA.
294. Boursiquot JN, Chapdelaine H, St-Pierre C, Hebert J. The Disease Burden of Hereditary Angioedema: Insights from a Survey in French-Canadians from Quebec. J Immunol Res. 2024;2024:3028617.

295. Giavina-Bianchi P, Giavina-Bianchi M, Oliveira Martins R, Cristina Fortunato M, Guersoni AC. Unmet needs in the management of hereditary angioedema from the perspective of Brazilian patients. World Allergy Organ J. 2024;17(11):100992.
296. Ritter AMV, Silva S, de Paula R, Senra J, Carvalho F, Ribeiro T, et al. A real-world study of hereditary angioedema patients due to C1 inhibitor deficiency treated with danazol in the Brazilian Public Health System. Front Med (Lausanne). 2024;11:1343547.
297. S C, Lopez-Gonzalez L, MacKnight S, Laliberté F, Boudreau J, Nestler-Parr S, et al. Health care resource utilization among patients initiating berotralstat for the long-term prophylaxis of hereditary angioedema in the United States. Managed Care & Specialty Pharmacy. 2024;30(10):1-168.
298. Gehlen CT, Mazzeu JF, Veronez CL, Mendes AR, Bertoli AF, Grumach AS, et al. The Burden of Hereditary Angioedema in a Large Family in Brazil. Int Arch Allergy Immunol. 2024;185(12):1207-15.
299. Kutrieb E, Weycker D, Llonch MV, Zbrosek Aea. DRUG PATTERNS, CLINICAL OUTCOMES, AND ECONOMIC COSTS AMONG HEREDITARY ANGIOEDEMA PATIENTS INITIATING LONG-TERM PROPHYLAXIS. Ann Allergy Asthma Immunol. 2024;133:S2-100.
300. Shah C, Princic N, Evans K, Schultz B. Real-world changes in costs over time among patients in the United States with hereditary angioedema on long-term prophylaxis with lanadelumab. Journal of Medical Economics. 2023;26(1):871-7.
301. Sánchez P, Gallardo M, Delgado M, Molina M, de Ceano-Vivas la Calle M. Pediatric Emergency Department Management of C1 Inhibitor Deficiency. Pediatric Emergency Care. 2022;38(2):844-8.
302. Cosme J, Spinola A, Ferreira MB, Barbosa MP. Hospitalizations due to Angioedema without Urticaria in a Portuguese Center: Five Year Retrospective Study. Acta Med Port. 2019;32(11):714-20.
303. Petraroli A, Squeglia V, Di Paola N, Barbarino A, Bova M, Spano R, et al. Home Therapy with Plasma-Derived C1 Inhibitor: A Strategy to Improve Clinical Outcomes and Costs in Hereditary Angioedema. Int Arch Allergy Immunol. 2015;166(4):259-66.
304. Arora NS, Nelson B, Carpenter L, Wettenstein RP, Hashmi M, Selva CN, et al. Consequences of Insurance Coverage Delays and Denials for Patients With Hereditary Angioedema. J Allergy Clin Immunol Pract. 2023;11(8):2432-8 e1.
305. Barbosa A, De Oliveira Martins RR, Martins R, Grumach AS. Assessment on hereditary angioedema burden of illness in Brazil: A patient perspective. Allergy Asthma Proc. 2019;40(3):193-7.
306. Mendivil J, DerSarkissian M, Banerji A, Diwakar L, Katelaris CH, Keith PK, et al. A multicenter chart review of patient characteristics, treatment, and outcomes in hereditary angioedema: unmet need for more effective long-term prophylaxis. Allergy Asthma Clin Immunol. 2023;19(1):48.
307. Javaud N, Gompel A, Bouillet L, Boccon-Gibod I, Cantin D, Smaiti N, et al. Factors associated with hospital admission in hereditary angioedema attacks: a multicenter prospective study. Ann Allergy Asthma Immunol. 2015;114(6):499-503.
308. Javaud N, Fain O, Durand-Zaleski I, Launay D, Bouillet L, Gompel A, et al. Specialist Advice Support for Management of Severe Hereditary Angioedema Attacks: A Multicenter Cluster-Randomized Controlled Trial. Ann Emerg Med. 2018;72(2):194-203 e1.

309. Riedl MA, Banerji A, Manning ME, Burrell E, Joshi N, Patel D, et al. Treatment patterns and healthcare resource utilization among patients with hereditary angioedema in the United States. Orphanet J Rare Dis. 2018;13(1):180.
310. Mullins RJ, Wainstein BK, Barnes EH, Campbell DE. Angioedema in Australia: hospital admission rates and fatalities, 2000-2013. Med J Aust. 2018;208(7):308.
311. Javaud N, Altar A, Fain O, Reuter PG, Desmaizieres M, Petrovic T, et al. Hereditary angioedema, emergency management of attacks by a call center. Eur J Intern Med. 2019;67:42-6.
312. Rasmussen ER, Aagaard L, Bygum A. Real-life experience with long-term prophylactic C1 inhibitor concentrate treatment of patients with hereditary angioedema: Effectiveness and cost. Ann Allergy Asthma Immunol. 2016;116(5):476-7.
313. Riedl MA, Hinds DR, Prince PM, Alvord TM, Dosenovic S, Abdelhadi JF, et al. Healthcare utilization of patients with hereditary angioedema treated with lanadelumab and subcutaneous C1-inhibitor concentrate. Allergy Asthma Proc. 2023;44(4):275-82.
314. Fragnan N, Tolentino ALN, Borba GB, Oliveira AC, Simoes JA, Palma SMU, et al. Hereditary angioedema with C1 inhibitor (C1-INH) deficit: the strength of recognition (51 cases). Braz J Med Biol Res. 2018;51(12):e7813.
315. Iwamoto K, Yamamoto B, Ohsawa I, Honda D, Horiuchi T, Tanaka A, et al. The diagnosis and treatment of hereditary angioedema patients in Japan: A patient reported outcome survey. Allergol Int. 2021;70(2):235-43.
316. Ohsawa I, Honda D, Nagamachi S, Hisada A, Shimamoto M, Inoshita H, et al. Clinical manifestations, diagnosis, and treatment of hereditary angioedema: survey data from 94 physicians in Japan. Ann Allergy Asthma Immunol. 2015;114(6):492-8.
317. Wentzel N, Panieri A, Ayazi M, Ntshalintshali SD, Pourpak Z, Hawarden D, et al. Fresh frozen plasma for on-demand hereditary angioedema treatment in South Africa and Iran. World Allergy Organ J. 2019;12(9):100049.
318. Rosado-Quiñones A, Zaragoza-Urdaz R. Hereditary Angioedema: An Updated Experience with Patients with Angioedema in Puerto Rico. Puerto Rico Health Sciences Journal. 2019;38(4):248-54.
319. Yamamoto B, Honda D, Ohsawa I, Iwamoto K, Horiuchi T, Fukunaga A, et al. Burden of illness seen in hereditary angioedema in Japanese patients: Results from a patient reported outcome survey. Intractable Rare Dis Res. 2023;12(1):35-44.
320. Christiansen SC, Wilmot J, Castaldo AJ, Zuraw BL. The US Hereditary Angioedema Association Scientific Registry: hereditary angioedema demographics, disease severity, and comorbidities. Ann Allergy Asthma Immunol. 2023;131(6):766-74 e8.
321. Banerji A, Li Y, Busse P, Riedl MA, Holtzman NS, Li HH, et al. Hereditary angioedema from the patient's perspective: A follow-up patient survey. Allergy Asthma Proc. 2018;39(3):212-23.
322. Riedl MA, Banerji A, Gower R. Current medical management of hereditary angioedema: Follow-up survey of US physicians. Ann Allergy Asthma Immunol. 2021;126(3):264-72.
323. Nieto S, Madrigal I, Contreras F, Vargas ME. Real-world experience of hereditary angioedema (HAE) in Mexico: A mixed-methods approach to describe epidemiology, diagnosis, and treatment patterns. World Allergy Organ J. 2023;16(9):100812.

324. Tachdjian R, Johnson KE, Casso D, Oliveria SA, Devercelli G, Jain G. Real-world cohort study of adult and pediatric patients treated for hereditary angioedema in the United States. Allergy Asthma Proc. 2020;41(3):172-82.
325. Moran K, Juethner S, Mellor J, Hatchell N, Earl L. RWD47 Understanding Patient Characteristics and Healthcare Resource Utilization in HAE Patients Currently Prescribed Prophylactic Treatment. Value in Health. 2022;25(7).
326. Palma SMU, Pimenta FMCA, Costa VA, Melo AKB, Aoki AL, Wandalsen NF, et al. Hereditary angioedema with C1 inhibitor deficiency: experience of a new reference center. World Allergy Organization Journal. 2015;8.
327. Watson DJ, Riedl MA, Banerji A, Manning ME, Burrell E, Joshi N, et al. Use Of Central Venous Access Devices (CVAD) And Associated Outcomes In Hereditary Angioedema (HAE) Patients: Findings From A Large United States (US) Claims Database. Journal of Allergy and Clinical Immunology. 2018;141(2).
328. Badiou J, Rowe A, Cooper M, Roberts K, Dumbrille D, Bick R, et al. Real World Data of Canadian Adults Living with Angioedema: Part 4 - Health Economic Burden. Journal of Allergy and Clinical Immunology. 2021;147(2).
329. Badiou J, Dumbrille D, Cooper M, Kelly S, Keith P, Lacuesta G, et al. Emergency room visits by patients with HAE based on data from the Canadian 2020 national survey. Journal of Allergy and Clinical Immunology. 2023;151(2).
330. Aggarwal S, Kumar S, Topaloglu O, editors. PSY60- Trends in Hospitalization Lenght of Stay and Costs in Patients with Hereditary Angioedema: Analysis of US National In-Patient Data for 2015. Value in Health; 2018: Value in Health
331. Slade C, DerSarkissian M, Katelaris C, Devercelli G, Smith W. P61: Patient Characteristics, Treatment, and Outcomes of Hereditary Angioedema in Australia: Findings from a Chart Review Study. Internal Medicine Journal. 2021;51(S4):22-3.
332. Zaragoza-Urdaz RH. Hereditary vs Acquired Angioedema: An Actualized Experience with Patients in Puerto Rico. Journal of Allergy and Clinical Immunology. 2017;139(2).
333. Lumry W, Li H, Milligan S, Raasch J, Riedl M. Attack location and severity/ resolution in patients with hereditary angioedema (HAE); observations from community immunology. Annals of Allergy, Asthma & Immunology. 2022;129:31.
334. Katelaris C, Perram F, Burton P. Hereditary angioedema attack prophylaxis management in Australian patients. Internal Medicine journal. 2017;47:27.
335. Roe C, Frew A, Cottingham R, Tarzi M. Specialist management of C1 inhibitor deficient patients has improved patient outcomes and reduced emergency hospital attendances in Brighton & Hove, United Kingdom. Allergy. 2015;70(S101):393-408.
336. Anderson J, Craig T, Mellor J, Earl L, Connolly H, Wynne-Cattanach K, et al. Comparison of Hereditary Angioedema Among Patients of Different Races and Ethnicities in the United States: Data From a Real-World Study. Journal of Allergy and Clinical Immunology. 2023;151(2).
337. Monte Boquet E, José C, Brugueras M, Escobar Oblitas A, Caballero Molina M, Smith Flotz S. Hereditary Angioedema: Impact of the Burden of Disease in Spain. Eur J Hosp Pharm. 2023;30:1.
338. Josviack D, Fantini C, Vazquez D, I M. Clinical characteristics and geographical distribution of a cohort of patients with Hereditary Angioedema (HAE) seen by physicians

belonging to the HAE scientific committee of the AAAeIC. Allergy. 2018;73 Suppl 105(Suppl 105):370-702.
339. Tachdjian R, Soteres D, Anderson J, Mellor J, Connolly H, Wynne-Cattanach K, et al. Disease Burden and Physician-Reported Outcomes in Pediatric Patients With Hereditary Angioedema: Data From A Real-World Study. Journal of Allergy and Clinical Immunology. 2023;151(2).
340. Tutein Nolthenius J, Figueiredo R, Wood S, Whalen DJ, editors. Costs of Treating Hereditary Angioedema (HAE) Attacks with C1 Inhibitors in Four European Countries. ISPOR; 2022.
341. Mendivil J, Murphy R, Janssen E, Aygoeren-Puersuen E, Devercelli G, HB B. Clinical and demographic characteristics of patients with hereditary angioedema in eight countries in Europe, North America, and Australia. Allergy. 2019;74(S106):130-331.
342. Liu S, Zhi Y. The economic and humanistic burden of hereditary angioedema in China. Allergy. 2018;73:370-96.
343. Hakl R, Kuklinek P, Krcmova I, Kralickova P, Hanzlikova J, Vachova M, et al. P165 Hereditary angioedema laryngeal attacks treated with recombinant C1-INH: report from the Czech National Registry. Annals of Allergy, Asthma & Immunology. 2017;119(5).
344. Viegas LP, Soares JB, Ferreira MB, Spinola A, Barbosa MP. Hereditary angioedema: burden of emergency department visits. Journal of allergy and clinical immunology. 2013;68:189–336.
345. Bernstein JA, Nanda MK, Singh U, Wilmot J. A cross-sectional questionnaire assessing patient and physician use of short-term prophylaxis for hereditary angioedema. Ann Allergy Asthma Immunol. 2014;113(2):198-203.
346. Garcia JFB, Takejima P, Aun MV, Kalil J, Motta AA, Giavina-Bianchi P. Gender Influence on Hereditary Angioedema with C1-inhibitor Deficiency. Journal of Allergy and Clinical Immunology. 2017;139(2).
347. Christiansen S, Lopez-Gonzalez L, MacKnight SD, Laliberté F, Spencer C, Nestler-Parr S, et al., editors. Reductions in real-world healthcare resource utilization among United States hereditary angioedema patients following berotralstat initiation. International Society for Pharmacoeconomics and Outcomes Research; 2024; Atlanta, GA, USA.
348. Bowen K, Sahli B, Gleason PP. Hereditary Angioedema (HAE) Real-World Prophylactic and On-demand Treatment Cost in a 15 Million Commercially Insured Population: Comparison of C-1 Inhibitor (Haegarda®) versus Lanadelumab (Takhzyro®) Treated Members. 2020.
349. Poquette C, Starner C, Hall S, P G. Hereditary angioedema drug utilization and spend: A medical and pharmacy integrated analysis. Managed Care & Specialty Pharmacy. 2015;21(4):18.
350. Helbert M, Holbrook T, MacCulloch A, Mannan A. Exploring the cost and burden of illness
of hereditary angioedema in England. Allergy. 2014;69(s99):454-572.
351. Vande Walle SE, Starner CI, Gleason PP. Hereditary Angioedema: A Comprehensive Integrated Medical and Pharmacy Claims Analysis of Utilization and Costs Among 15 Million Commercially Insured Members. 2018.
352. Vegh AB, Park N, Cantwell T. Recombinant human C1-esterase inhibitor for the prevention of acute hereditary angioedema attacks: a case report. Journal of Drug Assessment. 2018;7(sup1):15-.

353. Tachdjian R, Soteres D, Chang R, Mohan M, Pinaire M, DerSarkissian M, et al., editors. Healthcare Costs Among Commercially-Insured Patients with Hereditary Angioedema Managed with Long-Term Prophylaxis: A Retrospective US Claims Database Analysis. ISPOR Annual Meeting; 2024; Atlanta, GA.
354. KalVista. [KVD900-201 Phase 2 CSR report] A randomized, double-blind, placebo-controlled, phase II, cross over clinical trial evaluating the efficacy and safety of KVD900, an oral plasma kallikrein inhibitor, in the on-demand treatment of angioedema attacks in adult subjects with hereditary angioedema type I or II. 2021 16 November 2021.
355. Cicardi M, Levy RJ, McNeil DL, Li HH, Sheffer AL, Campion M, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. N Engl J Med. 2010;363(6):523-31.
356. Signorovitch JE, Sikirica V, Erder MH, Xie J, Lu M, Hodgkins PS, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value Health. 2012;15(6):940-7.
357. Pharming Healthcare Inc. RUCONEST Prescribing information. 2020 [Available from: https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf.
358. Petersen RS, Fijen LM, Apfelbacher C, Magerl M, Weller K, Aberer W, et al. A Core Outcome Set for Efficacy of Acute Treatment of Hereditary Angioedema. J Allergy Clin Immunol Pract. 2024;12(6):1614-21.
359. Longhurst HJ, Cancian M, Grivcheva-Panovska V, Koleilat M, Magerl M, Savic S, et al. Hereditary Angioedema Attacks in Patients Receiving Long-Term Prophylaxis: A Systematic Review. Clin Rev Allergy Immunol. 2024;67(1-3):83-95.
360. Wang H, Rowen DL, Brazier JE, Jiang L. Discrete Choice Experiments in Health State Valuation: A Systematic Review of Progress and New Trends. Applied Health Economics and Health Policy 2023;21.
361. Mulhern B, Norman R, Street DJ, Viney R. One Method, Many Methodological Choices: A Structured Review of Discrete-Choice Experiments for Health State Valuation. PharmacoEconomics. 2019;37:29-43.
362. Matza LS, Howell TA, Chounta V, van de Velde N. Patient preferences and health state utilities associated with the treatment process of antiretroviral therapy for people living with HIV. Quality of Life Research. 2022;32:531–41.
363. Matza LS, Deger KA, Vo P, Maniyar F, Goadsby PJ. Health state utilities associated with attributes of migraine preventive treatments based on patient and general population preferences. Quality of Life Research. 2019;28:2359–72.
364. Matza LS, Cutts KN, Stewart KD, Norrbacka K, Garcia-Perez LE, Boye KS. Health state utilities associated with treatment process for oral and injectable GLP-1 receptor agonists for type 2 diabetes. Quality of Life Research. 2021;30:2033–43.
365. Shingler SL, Swinburn P, Ali S, Perard R, Lloyd A. A discrete choice experiment to determine patient preferences for injection devices in multiple sclerosis. Journal of Medical Economics. 2013;16(8):1036-42.
366. Lloyd A, Hodgkins PS, Dewilde S, Susane R, Falconer S. Methylphenidate delivery mechanisms for the treatment of children with attention deficit hyperactivity disorder: Heterogeneity in parent preferences. International Journal of Technology Assessment in Health Care. 2011;27(3):215-23.

367. Lo S, Gorni K, Sutherland CS, Marti Y, Lloyd A, Paracha N. Preferences and Utilities for Treatment Attributes in Type 2 and Non-ambulatory Type 3 Spinal Muscular Atrophy in the United Kingdom. PharmacoEconomics. 2022;40:91–102.
368. Danner M, Hummel JM, Volz F, van Manen JG, Wiegard B, Dintsios CM, et al. Integrating patients' views into health technology assessment: Analytic hierarchy process (AHP) as a method to elicit patient preferences. International Journal of Technology Assessment in Health Care. 2011;27(4):369-75.
369. Sain N, Willems D, Charokopou M, Hiligsmann M. The importance of understanding patient and physician preferences for psoriasis treatment characteristics: a systematic review of discrete-choice experiments. Current Medical Research and Opinion. 2020;36(8):1257–75.
370. Ho MP, Gonzalez JM, Lerner HP, Neuland CY, Whang JM, McMurry-Heath M, et al. Incorporating patient-preference evidence into regulatory decision making. Surgical Endoscopy. 2015;29:2984–93.
371. National Institute for Health and Care Excellence. Migalastat for treating Fabry disease [HST4]. 2017.
372. Webb EJ, O'Dwyer J, Meads D, Kind P, Wright P. Transforming discrete choice experiment latent scale values for EQ-5D-3L using the visual analogue scale. The European Journal of Health Economics. 2020;21:787–800.
373. Bahrampour M, Byrnes J, Norman R. Discrete choice experiments to generate utility values for multi-attribute utility instruments: a systematic review of methods. Eur J Health Econ. 2020;21.
374. Bansback N, Hole AR, Mulhern B, Tsuchiya A. Testing a discrete choice experiment including duration to value health states for large descriptive systems: Addressing design and sampling issues. Social Science and Medicine. 2014;114:38-48.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over [ID6284]

Summary of Information for Patients (SIP)

May 2025

File name	Version	Contains confidential information	Date
ID6284 Sebetralstat KalVista_SIP_Final 23.5.25	Final	No	23 May 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Response:
Sebetralstat (brand name: Ekterly®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response:
People aged 12 years and older with hereditary angioedema (HAE)

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response:
Marketing authorisation for sebetralstat is pending. Please see the evidence section 1.2 of the evidence submission for details of the anticipated dates for marketing authorisation.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:

HAE UK

- An unrestricted grant of £10,000 was provided to HAE UK in December 2024.

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:

Hereditary angioedema (HAE) is a chronic (life-long) rare genetic disorder. It causes sudden, repeat, painful and potentially life-threatening episodes of swelling (attacks) that can affect any area of the body. (1) There are two main subtypes of HAE, Type I and Type II. Type I HAE is the most common and accounts for 85% of HAE cases.(2)

A recent UK-based study based on data collected in 2023 estimated that 1 in 59,000 people in the UK have HAE Type I or II.(3) This estimate is similar to the British Society for Immunology's estimate that HAE affects approximately 1 in 50,000 of the population and does not show ethnic variation in frequency.(4)

HAE attacks usually cause painful swelling in subcutaneous tissue or mucous membranes in areas such as the limbs, face, trunk (chest, back and abdomen), genitals, and the gastro-intestinal (GI) tract.(5) Swelling in the mouth is less common (under 10% of cases), and it's very rare in the brain, joints, or abdominal organs. (6) Symptoms vary depending on the attack location. Severe pain is a major symptom of HAE attacks, specifically those affecting the abdomen. Swelling within the GI tract can be extremely painful and disruptive, causing symptoms such as nausea, vomiting, diarrhoea and abdominal pain.(7) Swelling in the throat (laryngeal swelling) affects up to 50% of people with HAE and can be life-threatening because it can block the airways, leading to loss of consciousness or death from suffocation.(8, 9) Laryngeal attacks account for the very significant lifetime mortality reported in HAE patients.(8, 10, 11)

Various factors can trigger HAE attacks, including physical trauma, mental stress, infections, surgical or dental procedures, hormonal changes (menstruation, pregnancy), and certain medications.(12) Despite these known triggers, patients often do not know when attacks will happen and attacks can occur at any point in time.

People with HAE have a lower quality of life compared to healthy individuals, with higher rates of depression and anxiety. A recent burden of treatment study found that nearly half (45.6%) of UK patients with HAE experienced moderate to severe anxiety (with 13.0%, n=6/46 reporting being 'moderately anxious' and 32.6% (n=15/46 reporting being 'extremely anxious').(13) The unpredictability of HAE attacks impacts daily life, leading many to avoid travelling, hobbies, or social events. It also affects personal decisions, including relationships and decisions on whether to have children.(14-16)

Caring for HAE patients can be demanding, especially during attacks when quick treatment, on-demand treatment through injection, is needed. Caregivers, often family members, help manage these attacks and are trained to give urgent treatments. A study in Spain, Germany, and Denmark found that over half of HAE patients relied on caregivers during their last attack.(17) Caregivers spent more time helping when the patient's pain was severe, losing about 2 days of time compared to 1 day for mild cases, with missed time increasing as the pain worsened.(17) Many caregivers experience stress and anxiety, often as a result of their responsibilities in disease management, which includes locating suitable veins and timely administration of on-demand treatments.(18) Emotionally, caregivers highlight the psychological impact of witnessing the individual they care for in pain or distress following an attack.(18)

One carer for a HAE patient said:
"I had to leave work or erm .. er, yeah and I would have to go home and give him an injection so that definitely was sort of you know, as you never know when it will happen, it could be any day, you know? Any time of the day, it could be at night." UK Caregiver to child with HAE

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response:

Doctors usually start suspecting HAE when patients have recurring swelling, abdominal pain, vomiting, or throat swelling, especially if there's a family history of the condition.(19) Diagnosis is confirmed through laboratory tests showing low levels or poor function of a protein called C1 esterase inhibitor or low levels of C4 protein.(20) In the UK, most patients are referred by GPs to specialist centres where immunologists oversee treatment. Specialist nurses and gastro-enterologists also play a role in managing the condition.

There are no additional diagnostic tests required for the new treatment of sebetralstat.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

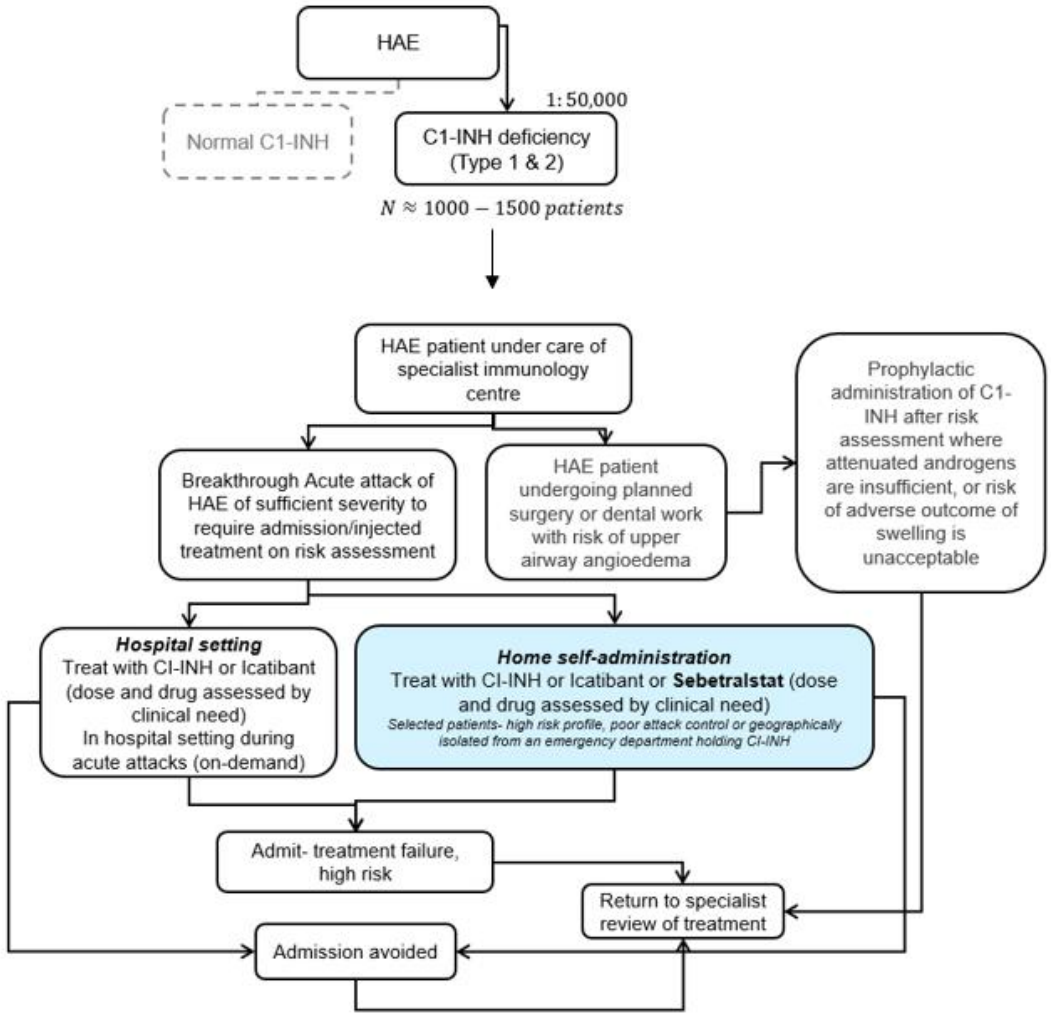
Response:

HAE treatment includes managing acute attacks (on-demand treatment; i.e. once an attack has started), short-term prophylactic (preventive) treatments, and long-term preventive treatments. Common on-demand treatments for HAE include icatibant and C1-protein inhibitors (C1-INHs).(3) Short term preventative treatments used in the UK include C1-INHs, attenuated androgens or antifibrinolytics.(21) Treatments for long-term prevention of HAE include attenuated androgens, lanadelumab, berotralstat, C1-INHs, and anti-fibrinolytics.

Sebetralstat is an investigational on-demand oral tablet treatment for acute HAE attacks. Figure 1 below shows the positioning of sebetralstat in the UK HAE treatment pathway. Sebetralstat is intended for self-administration use outside of the hospital setting (i.e. it can be taken at home or when a patient is out and about, without help from a healthcare professional to administer sebetralstat treatment).

Of note, sebetralstat is currently being offered to patients with high unmet need as part of an Early Access to Medicines Scheme (EAMS) that was approved by the MHRA in March 2025.(22)

Figure 1: Positioning of Sebetralstat in the HAE UK Treatment Pathway (adapted from Adapted from NHS commissioning Board Policy report)(6)



Recent international clinical guidelines for HAE treatment recommend all that attacks (irrespective of location or severity) are considered for on-demand treatment and that treatment should begin as early as possible to stop progression. Earlier administration of on-demand treatment provides a better treatment response, with shorter time to symptom relief and attack resolution. The guidelines also note all patients should have sufficient medication for on-demand treatment of two attacks and carry on-demand medication at all times.(21) Sebetralstat's positioning as an on-demand oral treatment for self-administration at home would help patients to more easily follow these treatment guidelines and improve their health outcomes.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for

collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

Studies have shown that patients with HAE experience symptoms that affect their quality of life.

Severe pain is a major symptom of HAE attacks, specifically those affecting the abdomen. A retrospective observation of 33,671 abdominal attacks in 153 HAE patients conducted by Bork et al. (2006) reported that up to 87% of HAE patients describe the pain during abdominal attacks as excruciating or severely painful, often leading them to seek medical attention.(23)

HAE affects all aspects of a patient's life, causing significant social, education and work disability. A European study on the socioeconomic burden of HAE found that over half (56%) of patients reported missing school or work during their most recent attack, highlighting the disorder's disruptive nature on education and employment.(17)

HAE patients report significantly worse health-related quality-of-life (HRQoL) outcomes compared to healthy individuals, including increased rates of depression. A recent multinational survey of 242 HAE patients from 8 countries (including the UK), reported that 38% of patients experienced moderate to severe anxiety, and 17.4% suffered from depression.(24) Additionally, in a recent burden of treatment study, nearly half (45.6%) of UK patients with HAE report that they experience moderate to severe anxiety.(13) A US-based patient survey by Banerji et al (2020) found 24.8% of patients rated their general health status as "poor" or "fair," and 34.2% reported that their physical health or emotional problems interfered with their ability to participate in social activities at least some of the time during the past week.(25)

Laryngeal swellings occur in up to 50% of HAE patients and are potentially life threatening since they can lead to the obstruction of airways, loss of consciousness and death due to asphyxiation.(8, 26) Studies show that laryngeal attacks account for the very significant lifetime mortality reported in HAE patients (11, 27).

Patient quotes

One patient said "*I go to bed every night and at the back of my mind is the thought I might wake up with a swelling – or not wake up*". NICE 2024 (28)

"**Having this disease has taken my life; my education, my prospect of a career, having a family**" (UK HAE patient).(NICE 2021) (28)

Quote shared by a patient with KalVista, related to judgement from others:
"I had to leave, go back to inject… you can't just carry all these boxes with you, you certainly get them out on a table in a restaurant or, and start mixing vials of powder and water and dealing with needles and .. people would just, nobody would understand, you know?" UK Adult with HAE.

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

Sebetralstat is a small molecule (a simple chemical structure) that works by stopping a protein called plasma kallikrein from making bradykinin protein. Bradykinin causes swelling in the body and so by stopping its production, sebetralstat works to halt HAE attacks.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / **No**

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response:

Sebetralstat is not intended to be used in combination with any other treatments.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Response:

Sebetralstat tablets can be self-administered by the patient (i.e. it does not require caregiver or healthcare professional support to administer) as it can be swallowed by the patient at home or outside of home. Patients should take sebetralstat once they sense a swelling attack is happening or beginning. The dose is a 300 mg sebetralstat tablet which is enough to stop or reduce an attack. An additional dose of sebetralstat may be taken if needed. Sebetralstat can be taken with or without food.

An oral treatment option for the on-demand treatment of hereditary angioedema can help to improve compliance with HAE treatment guidelines and avoid adverse drug reactions related to current treatment options that are injectables or intravenous infusions. International treatment guidelines recommend that all people living with hereditary angioedema, including those who

receive long-term prophylaxis, should 1) consider the treatment of all attacks, irrespective of location or severity; 2) have ready access to and carry an effective on-demand medication for the treatment of at least two attacks, and 3) treat attacks as early as possible to arrest progression. Sebetralstat will provide a much-anticipated solution to this area of unmet need.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

Completed trials

There are three completed trials of sebetralstat in adults and adolescents with HAE Type I and II.

Phase 1: KVD900-101 NCT04349800(29)

Title: A phase I randomised, double-blind, placebo-controlled, single ascending dose study of the safety, tolerability, and pharmacokinetics of sebetralstat followed by crossover sub-studies of sebetralstat formulations, and food effect in healthy male volunteers.

Patient group size: 98 participants.

Study completion date: 2018-09-10.

Locations: Wales, UK.

Brief description of trial design:

Sebetralstat was administered in 2 phase I clinical studies. In the first study, healthy adult men received single ascending doses (5-600 mg) of sebetralstat capsule or placebo, single 100 mg doses of sebetralstat tablet and sebetralstat capsule (crossover), and single 600 mg doses of sebetralstat (6 x 100 mg tablets) under fed and fasting conditions (crossover). In a second study, 3 cohorts of healthy adults were provided 600 mg of KVD900 tablets at 8-, 4, and 2-hour intervals.

Key inclusion criteria:

Patients could enrol if they were healthy male subjects between 18 and 55 years of age, with a body mass index (BMI) of 18-32 kg/m^2 and no clinically significant history of previous allergy or sensitivity to sebetralstat. Participants also had to have no clinically significant abnormal serum biochemistry, haematology, clotting profiles, and urine examination values within 28 days before the first dose of sebetralstat and no special food restrictions that would hinder ability to consume the high fat breakfast provided during study Part C; such as lactose intolerance , vegan, low-fat, low sodium, etc.

Key exclusion criteria:

Patients were not allowed to take part if they had a clinically significant history of gastrointestinal disorder likely to influence sebetralstat's absorption or evidence of renal, hepatic, central nervous system, respiratory, cardiovascular (no history of syncope or vasovagal events), metabolic dysfunction or a history of clotting abnormalities.

Phase 2: KVD900-201 study NCT04208412 (30, 31)

Title: A phase II, cross-over clinical trial evaluating the efficacy and safety of sebetralstat in the on-demand treatment of angioedema attacks in adult subjects with hereditary angioedema type I or II.

Patient group size: 84 participants.

Study completion date: 2020-12-08.

Locations: 25 Study Centres in 10 countries (1 in Austria, 3 in Czech Republic, 3 in Germany, 1 in Hungary, 3 in Italy, 1 in Macedonia, 2 in Poland, 1 in the Netherlands, 4 in the United Kingdom and 6 in the United States of America [USA]).

Brief description of trial design:

- A two-part, randomised, double-blind, crossover phase 2 trial comparing sebetralstat versus placebo in patients with HAE type I or II.
- In part 1 of the trial, participants were given a single 600 mg open-label oral dose of sebetralstat to assess safety, pharmacokinetics, and pharmacodynamics of the dose.
- Part 2 was a randomised, double-blind, placebo-controlled, two-sequence, two-period (2 × 2) crossover trial; participants were randomly assigned (1:1) to either sequence 1, in which they were given a single dose of 600 mg of sebetralstat to treat the first eligible attack and a second dose of placebo to treat the second eligible attack, or sequence 2, in which they were given placebo to treat the first eligible attack and then 600 mg of sebetralstat to treat the second eligible attack. Participants and investigators were masked to treatment assignment.(31)

Key inclusion criteria:

Individuals were eligible if they were male of female adults (aged 18 years or older) and had experienced at least three hereditary angioedema attacks in the past 93 days, were not on prophylactic therapy, and had access to and the ability to self-administer conventional attack treatment.(31)

Key exclusion criteria:

- Patients were not allowed to take part if they had any diagnosis of another form of chronic angioedema, such as acquired C1 inhibitor (C1-INH) deficiency, HAE with normal C1-INH (also known as HAE type III), idiopathic angioedema, or angioedema associated with urticaria. Patients using C1INH, androgens, or tranexamic acid for HAE prophylaxis were also not allowed to take part as well as any patients using angiotensin-converting enzyme (ACE) inhibitors or any oestrogen-containing medications within 93 days prior to initial study treatment.
- Use of androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) or antifibrinolytics within 30 days prior to initial study treatment and use of lanadelumab within 10 weeks prior to initial study treatment were also not allowed.

Phase 3: KONFIDENT trial [KVD900-301 study] NCT05259917 (32)

Title: The pivotal KONFIDENT [KVD900-301] study is a randomised, double-blind, placebo-controlled, phase 3, three-way crossover trial that evaluates the efficacy and safety of two dose levels of sebetralstat (300mg and 600mg), for on-demand treatment of angioedema attacks in adolescent and adult patients with hereditary angioedema type I or II.

Patient group size: 136 participants.

Study completion date: 2023-12-31.

Locations: US, Australia, Bulgaria, Canada, France, Germany, Greece, Hungary, Israel, Italy, Japan, Netherlands, New Zealand, North Macedonia, Poland, Portugal, Puerto Rico, Romania, Slovakia, Spain, United Kingdom (5 UK sites included).

Brief description of trial design:

A phase 3, double-blind, three-way crossover trial, participants at least 12 years of age with type 1 or type 2 hereditary angioedema were randomly assigned to take up to two oral doses of sebetralstat (300 mg or 600 mg) or placebo for an angioedema attack.

Primary endpoint: time to beginning of symptom relief (Patient Global Impression of Change rating of at least "A Little Better" two time points in a row) within 12 hours. Key secondary endpoints: time to first decrease in severity from attack onset (≥1 level decrease on Patient Global Impression of Severity [PGI-S] two time points in a row) within 12 hours and time to attack resolution (PGI-S rating of "None") within 24 hours.(33)

Key inclusion criteria:

Individuals were eligible if they were male of female (aged 12 years or older) and had at least 2 documented HAE attacks within 3 months prior to screening or randomisation; or is a completer of the KVD824-201 trial within 3 months prior to randomisation and meets all other entry criteria to enroll in KVD900-301. If a patient was receiving long-term prophylactic treatment with one of the protocol-allowed therapies, they must be on a stable dose and regimen for at least 3 months prior to the Screening Visit.

Key exclusion Criteria:

Individuals were not allowed to participate if they had a diagnosis of other forms of chronic angioedema, including acquired C1-INH deficiency, HAE with normal C1-INH, idiopathic angioedema, or angioedema associated with urticaria. Patients were also excluded if they use angiotensin-converting enzyme inhibitors after the screening visit or within 7 days prior to randomisation or used any oestrogen-containing medications with systemic absorption within 7 days prior to the screening visit or during the trial. Patients using strong cytochrome P450 3A4 inhibitors and inducers during participation in the trial starting at the screening visit were also excluded as were any pregnant or breastfeeding patients.(34) Attenuated androgens, antifibrinolytic agents, and other investigational long-term prophylactic agents were not permitted in most countries.(35)

Ongoing trial

There is one ongoing trial of sebetralstat in adults and adolescents with HAE Type I and II. The patient recruitment stage of this study is now complete and participants are now actively participating in this trial (no further patients can enter the study).

KONFIDENT-S open-label extension trial: [KVD900-302 study] NCT05505916 (36)

Patient group size: up to 150 patients.

Locations: Total of 72 trial sites. Australia (1 site), Austria (1 site), Bulgaria (1 site), Canada (1 site), France (4 sites), Germany (4 sites), Greece (2 sites), Hungary (1 site), Israel (4 sites), Italy (4 sites), Japan (9 sites), Netherlands (1 site), New Zealand (1 site), North Macedonia (1 site), Poland (2 sites), Portugal (1 site), Romania (1 site), Saudi Arabia (1 site), Slovakia (1 site), South Africa (1 site), Spain (3 sites), United Kingdom (7 sites), United States (20 sites).

Brief description of trial design:

The KONFIDENT-S trial is an open label extension study evaluating the long-term safety of 600 mg sebetralstat for on-demand treatment of HAE attacks in adolescent and adult Patients (≥12 years) patients with HAE Type I or Type II. Rollover patients are patients who were randomised in the KVD900-301 trial. Non-rollover patients include patients who were randomised in the KVD900-201 trial (Phase 2) or sebetralstat naïve patients.

The trial is also evaluating sebetralstat for use as a short-term prophylaxis treatment prior to medical procedures.(37)

Key inclusion criteria: (36)

Individuals were eligible if they were male of female (aged 12 years or older) and has had at least 2 documented HAE attacks within 3 months prior to the Enrollment Visit. If a patient is receiving long-term prophylactic treatment with one of the protocol-allowed therapies, they must have been on a stable dose and regimen for at least 3 months prior to the Enrollment Visit (except for danazol, which requires a stable dose and regimen for at least 6 months prior to the Enrollment Visit).

Similar exclusion criteria apply as with the phase 3 and 2 trials.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

Phase 1 trial results:
Results from the phase 1 trial showed sebetralstat was generally safe and well tolerated. All adverse events (AEs) were mild, except for a single moderate AE (headache).(38)

Phase 2 trial results:
Results from the phase 2 trial showed sebetralstat was rapidly absorbed and there was a rapid onset of symptom relief and significant reduction in the use of rescue medication showing patients could confidently take sebetralstat at the earliest signs of an attack and avoid the burden and discomfort of injections.(39)

In addition to achieving the trial's primary endpoint, with sebetralstat significantly increasing time to use of conventional therapy within 12 h versus placebo ($p = 0.001$), sebetralstat resulted in earlier symptom relief than placebo, with a median time to symptom relief using the Patient Global Impression of Change (PGI-C) (defined as a rating of at least "A Little Better" for two consecutive time points within 12 h) of 1.6 h (95% CI: 1.5–3.0) with sebetralstat versus 9.0 h (95% CI: 4.0–17.2) with placebo ($p < 0.0001$) and median time to symptom relief using the composite VAS (defined as 50% reduction from baseline for three consecutive time points) of 6.0 h (95% CI: 3.0–9.0) with sebetralstat versus > 12 h (95% CI: not evaluable-not evaluable) with placebo ($p < 0.0001$).

Furthermore, patients who received sebetralstat reported a lower proportion of attacks with symptom worsening on the PGI-S (21% vs. 45%; $p = 0.0045$) within 12 h and a greater proportion of attacks that achieved resolution on the PGI-S (53% vs. 26%; $p = 0.012$) within 24 h than those who received placebo.

KONFIDENT Phase 3 trial results:
Results from the phase 3 KONFIDENT trial show oral sebetralstat provided faster times to the beginning of symptom relief, reduction in attack severity, and complete attack resolution than placebo.

The time to the beginning of symptom relief with the 300 mg dose and the 600 mg dose was faster than with placebo ($P<0.001$ and $P=0.001$ for the two comparisons, respectively), with median times of 1.61 hours (interquartile range, 0.78 to 7.04), 1.79 hours (1.02 to 3.79), and 6.72 hours (1.34 to >12), respectively.

The time to reduction in the attack severity with the 300 mg dose and the 600 mg dose was faster than with placebo ($P=0.004$ and $P=0.003$), with median times of 9.27 hours (interquartile range, 1.53 to >12), 7.75 hours (2.19 to >12), and more than 12 hours (6.23 to >12).

The time to complete resolution was faster with the 300 mg and 600 mg doses than with placebo (P=0.002 and P<0.001). The percentage of attacks with complete resolution within 24 hours was 42.5% with the 300 mg dose, 49.5% with the 600 mg dose, and 27.4% with placebo. Sebetralstat and placebo had similar safety profiles; no serious adverse events related to the trial agents were reported.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Response:

In the sebetralstat clinical trials, patient reported outcome (PRO) measures were used to capture the patients' state at varying time points of the trial to assess their symptom relief, disease severity, reduction of pain and swelling. These PROs provide representation of sebetralstat's ability to treat/resolve HAE symptoms and attacks (i.e. improve clinical outcomes) and thereby improve patient quality of life.

The PROs captured in the Phase 2 and 3 sebetralstat trials included the following key scales: (31, 33)

- **The 7-point Patient Global Impression of Change (PGI-C) scale** was used to record the effect of treatment and onset of symptom relief by patients selecting on of the 7 scores: Very much improved, much improved, minimally improved, no change, minimally worse, much worse or very much worse to show changes in how they felt after treatment with sebetralstat.
    - In the phase 2 trial: PGI-C scoring showed the median time to sebetralstat treated attacks getting better was significantly shorter (5 hrs) than those treated with placebo (12 hrs) and the median time to symptom relief was 1.6 hrs with sebetralstat versus 9.0 hrs with placebo.
    - In the phase 3 trial: the beginning of symptom relief (the primary endpoint in the trial) was reached faster with the 300 mg and 600 mg doses of sebetralstat than with placebo.

- **The 5-point Patient Global Impression of Severity (PGI-S) scale** was used to measure attack severity using a 5-point scale (ratings range from "none" to "very severe")
    - In the phase 2 trial: PGI-S showed the time to conventional attack treatment use or worsening in severity was significantly longer after treatment with sebetralstat than after treatment with placebo. PGI-S scoring also showed the median time to attack resolution was significantly shorter with sebetralstat than with placebo (18 hrs with sebetralstat vs 24 hrs with placebo) and the proportion of attacks that resolved (ended) was significantly with sebetralstat than with placebo at 24 hrs.
    - In the phase 3 trial: The median time to a reduction in attack severity was 9.27 hours with 300 mg sebetralstat, 7.75 hours with 600 mg sebetralstat and more than 12 hours with placebo.

- PGI-S was also used to show time to HAE attack resolution defined as “none” on the PGI-S scale within 24 hours of the first sebetralstat administration: results show sebetralstat led to faster resolution of attacks vs placebo.(33)

- **Another PRO used in the phase 2 and 3 trials was the 100-mm visual analogue scale (VAS)** that assesses abdominal pain, skin pain, and skin swelling.
  - In the phase 2 trial, VAS scoring showed that more attacks treated with sebetralstat had symptom relief than with placebo and the median time to symptom relief was 6.0 hrs after sebetralstat treatment and was not calculable for the placebo group because fewer than 50% of attacks resulted in the endpoint.
  - In the phase 3 trial, composite VAS was used to measure time to ≥50% decrease from baseline in VAS for 3 consecutive timepoints within 12 and 24 hours of study drug administration. (34) Note: results are not publicly available for this measure.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

In the phase 3 trial, the safety of sebetralstat at both doses (300 mg and 600 mg) was no different than placebo. There were no patient withdrawals due to any adverse events and no treatment-related serious adverse events (SAEs) or treatment-related deaths were observed. Very small numbers of patients experienced side effects occurring within 3 days of treatment including dyspepsia (upset stomach), nausea, fatigue, headache, dysgeusia (taste disorder), irregular menstruation and rash. (33)

Similarly, in the phase 2 trial, no serious or life-threatening adverse events, deaths, or treatment discontinuations due to adverse events occurred. Side effects noted in this trial included abdominal pain, anal incontinence, nausea, dizziness, flushing and headache. (31)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Response:

- Sebetralstat is the first orally administered therapy for the on-demand treatment of HAE. Currently, not all patients follow international treatment guidelines that all attacks are

considered for on-demand treatment and that patients should carry on-demand treatment at all times to enable treatment to begin as early as possible to arrest attack progression. The earlier treatment of HAE attacks is directly associated with better outcomes: "*Early treatment is associated with a shorter time to resolution of symptoms and shorter total attack duration regardless of attack severity*" WAO/EAACI treatment guidelines, 2022.(21)

- Sebetralstat would make it possible for patients to achieve these guidelines, and thereby optimise outcomes, as it can easily be carried at all times and swallowed in tablet form, as soon as required. This is an advantage over current injectable on-demand treatments which require more preparation and training to use. A time to treatment analysis from the KONFIDENT study showed that attacks that were treated earlier were more likely to be mild (than attacks treated later) and attack resolution was also reached faster.(40)
- Furthermore some patients have expressed a fear of needles and that current treatments are painful and hard to carry discreetly since they are bulky. Sebetralstat does not have these issues and is expected to enable faster time to treatment and attack resolution.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

Nothing to highlight.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

KalVista (the manufacturer of sebetralstat) has built an economic model in Microsoft Excel to explore the cost-effectiveness of sebetralstat when compared with other currently available on-demand options for the treatment of HAE attacks (subcutaneous icatibant and intravenous C1-INHs: Ruconest, Berinert and Cinryze).

The economic model shows the different ways in which a patient's health can change with treatment of their HAE attack. It compares the total costs (e.g. drugs including rescue therapy, hospitalisation, healthcare resource use) generated by sebetralstat and the other treatments; a review of the quality of life change due to treatment on sebetralstat over a lifetime time horizon produces a result called the quality-adjusted life year (QALY). One QALY is equal to one year of life in perfect health. The economic model can calculate the QALY change due to treatment with sebetralstat compared to its comparators.

The model uses data from the KONFIDENT phase 3 trial. A key trial input is the time to administration (TTA) and time to attack resolution (TTR). The model also includes key factors such as disutility associated with an acute HAE attack as well as comparator injectable treatments and side effects.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

Sebetralstat represents a 'step change' in treatment as it will be the first oral on-demand treatment for HAE attacks and able to be self-administered by the patient at home or out and about with ease. Furthermore, as mentioned previously, an oral treatment option for the on-demand treatment of HAE can ultimately help patients to follow treatment guidelines to arrest attack progression and optimise patient outcomes, since sebetralstat can easily be carried at all times and swallowed in tablet form, as soon as required, whilst avoiding adverse drug reactions related to current on-demand treatment options that are all injectables or intravenous infusions.

Sebetralstat will also enable patients with HAE and their carers (who may be involved in treatment administration) to live out more normal lives. However, of note, the impact on loved ones/carers is not included in the model base case.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Response:

There are no equality issues to highlight for this appraisal.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Response:

Phase 1 trial: Study Details | A Single Dose Safety, Tolerability, Pharmacokinetic and Food Effect Study of KVD900 in Healthy Volunteers | ClinicalTrials.gov

Phase 2 trial: Study Details | A Phase II, Cross-over Clinical Trial Evaluating the Efficacy and Safety of KVD900 in the On-demand Treatment of Angioedema Attacks in Adult Subjects With Hereditary Angioedema Type I or II | ClinicalTrials.gov

Phase 2 published results: An investigational oral plasma kallikrein inhibitor for on-demand treatment of hereditary angioedema: a two-part, randomised, double-blind, placebo-controlled, crossover phase 2 trial - The Lancet

Phase 3 trial (KONFIDENT): Study Details | A Phase III, Crossover Trial Evaluating the Efficacy and Safety of KVD900 for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients With Hereditary Angioedema (HAE) | ClinicalTrials.gov

Phase 3 (KONFIDENT) published results: Oral Sebetralstat for On-Demand Treatment of Hereditary Angioedema Attacks - PubMed

Open-label extension trial (KONFIDENT-S): Study Details | An Open-label Extension Trial to Evaluate the Long-term Safety of KVD900 for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients With Hereditary Angioedema (HAE) | ClinicalTrials.gov

HAE UK: HAE UK - Living for today… Planning for tomorrow

British Society Immunology, HAE: Hereditary angioedema | British Society for Immunology

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/

- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

HAE: *hereditary angioedema.*

HRQoL: Health related quality of life.

Abdomen: the area of the body between the chest and the pelvis.

Chronic: long-lasting. A chronic illness is generally defined as one that lasts at least 3 months.

Placebo: a 'dummy' medication that looks identical to a real medication and is taken in the same way.

QALY: quality adjusted life year. A measure of how well a treatment improves or lengthens a patient's life. One QALY is equal to one year of life in perfect health.

Patient reported outcomes: questionnaires that patients complete to provide information about their health status.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

1. Ghazi A, Grant JA. Hereditary angioedema: epidemiology, management, and role of icatibant. Biologics. 2013;7:103-13.
2. Farkas H, Martinez-Saguer I, Bork K, Bowen T, Craig T, Frank M, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. Allergy. 2017;72(2):300-13.
3. Yong PFK, Coulter T, El-Shanawany T, Garcez T, Hackett S, Jain R, et al. A National Survey of Hereditary Angioedema and Acquired C1 Inhibitor Deficiency in the United Kingdom. J Allergy Clin Immunol Pract. 2023;11(8):2476-83.
4. El-Shanawany T. Hereditary angioedema https://www.immunology.org/public-information/bitesized-immunology/immune-dysfunction/hereditary-angioedema.2024 [Available

from: https://www.immunology.org/public-information/bitesized-immunology/immune-dysfunction/hereditary-angioedema.
5. Nordenfelt P, Dawson S, Wahlgren CF, Lindfors A, Mallbris L, Bjorkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. Allergy Asthma Proc. 2014;35(2):185-90.
6. NHS. Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angiodema (Adult). 2013.
7. Staller K, Lembo A, Banerji A, Bernstein JA, Shah ED, Riedl MA. Consider Hereditary Angioedema in the Differential Diagnosis for Unexplained Recurring Abdominal Pain. J Clin Gastroenterol. 2022;56(9):740-7.
8. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol. 2012;130(3):692-7.
9. Li HH. Self-administered C1 esterase inhibitor concentrates for the management of hereditary angioedema: usability and patient acceptance. Patient Prefer Adherence. 2016;10:1727-37.
10. Agostoni A, M C. Hereditary and Acquired C1-Inhibitor Deficiency: Biological and Clinical Characteristics in 235 Patients. Medicine. 1992.
11. Bork K, Siedlecki K, Bosch S, Schopf RE, Kreuz W. Asphyxiation by laryngeal edema in patients with hereditary angioedema. Mayo Clin Proc. 2000;75(4):349-54.
12. Zotter Z, Csuka D, Szabo E, Czaller I, Nebenfuhrer Z, Temesszentandrasi G, et al. The influence of trigger factors on hereditary angioedema due to C1-inhibitor deficiency. Orphanet J Rare Dis. 2014;9:44.
13. Yong PFK, El-Shanawany T, Gurugama P, Jain G, Danese S, Ulloa J, et al. [EAACI 2024 Burden of Treatment poster] Anxiety Associated with On-Demand Treatment for Hereditary Angioedema (HAE) Attacks. EAACI (European Academy of Allergy and Clinical Immunology) 2024; June 2024; Valencia, Spain. 2024.
14. Caballero T, Sala-Cunill A, Cancian M, Craig TJ, Neri S, Keith PK, et al. Current status of implementation of self-administration training in various regions of Europe, Canada and the USA in the management of hereditary angioedema. Int Arch Allergy Immunol. 2013;161 Suppl 1:10-6.
15. Tuncel O, Gokmen N, Demir E, Gulbahar O, Pirildar s. The impact of hereditary angioedema on quality of life and family planning decisions. The International Journal of Psychiatry in Medicine. 2019.
16. Savarese L, Mormile I, Bova M, Petraroli A, Maiello A, Spadaro G, et al. Psychology and hereditary angioedema: A systematic review. Allergy Asthma Proc. 2021;42(1):e1-e7.
17. Aygören-Pürsün E, Bygym A, Beusterien K, Hautamai E. Socioeconomic burden of hereditary angioedema:
results from the hereditary angioedema burden
of illness study in Europe. Orphanet Journal of Rare Diseases. 2014.
18. Bygum A, Aygoren-Pursun E, Beusterien K, Hautamaki E, Sisic Z, Wait S, et al. Burden of Illness in Hereditary Angioedema: A Conceptual Model. Acta Derm Venereol. 2015;95(6):706-10.
19. Bowen T, Cicardi M, Farkas H. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy, Asthma & Clinical Immunology. 2010;6.
20. Sinnathamby ES, Issa PP, Roberts L, Norwood H, Malone K, Vemulapalli H, et al. Hereditary Angioedema: Diagnosis, Clinical Implications, and Pathophysiology. Adv Ther. 2023;40(3):814-27.
21. Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygoren-Pursun E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. Allergy. 2022;77(7):1961-90.
22. Gov.uk website. Decision: Sebetralstat in the treatment of hereditary angioedema (HAE) attacks Gov.uk: Gov.uk; 2025 [Available from:

https://www.gov.uk/government/publications/sebetralstat-in-the-treatment-of-hereditary-angioedema-hae-attacks.
23. Bork K, Staubach P, Eckardt AJ, Hardt J. Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. Am J Gastroenterol. 2006;101(3):619-27.
24. Chong-Neto HJ. A narrative review of recent literature of the quality of life in hereditary angioedema patients. World Allergy Organ J. 2023;16(3):100758.
25. Banerji A, Davis KH, Brown TM, Hollis K, Hunter SM, Long J, et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States. Ann Allergy Asthma Immunol. 2020;124(6):600-7.
26. Li H. Self-administered C1 esterase inhibitor concentrates for the management of hereditary angioedema: usability and patient acceptance. Patient Preference and Adherence. 2016;Volume 10:1727-37.
27. Agostoni A, Cicardi M. Hereditary and Acquird C1-Inhibitor Deficinecy: Biological and Clinical Characteristics in 235 patients. Medicine (Baltimore). 1992;71(4).
28. NICE. [NICE TA738] Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]. Public observer slides- redacted. https://www.nice.org.uk/guidance/ta738/documents/1: National Institute for Health and Care Excellence; 2021 2021.
29. ClinicalTrials.gov. A Single Dose Safety, Tolerability, Pharmacokinetic and Food Effect Study of KVD900 in Healthy Volunteers ClinicalTrials.gov2020 [Available from: https://clinicaltrials.gov/study/NCT04349800?intr=NCT04349800&rank=1.
30. ClinicalTrials.gov. A Phase II, Cross-over Clinical Trial Evaluating the Efficacy and Safety of KVD900 in the On-demand Treatment of Angioedema Attacks in Adult Subjects With Hereditary Angioedema Type I or II: KalVista; 2023 [Available from: https://clinicaltrials.gov/study/NCT04208412?intr=NCT04208412&rank=1.
31. Aygören-Pürsün E, Zanichelli A, Cohn D, Cancian M. An investigational oral plasma kallikrein inhibitor for
on-demand treatment of hereditary angioedema:
a two-part, randomised, double-blind, placebo-controlled,
crossover phase 2 trial. Lancet. 2023;401.
32. ClinicalTrials.gov. A Phase III, Crossover Trial Evaluating the Efficacy and Safety of KVD900 for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients With Hereditary Angioedema (HAE) ClinicalTrials.gov: KalVista 2024 [Available from: https://clinicaltrials.gov/study/NCT05259917?intr=NCT05259917&rank=1.
33. Riedl MA, Farkas H, Aygoren-Pursun E, Psarros F, Soteres DF, Staevska M, et al. Oral Sebetralstat for On-Demand Treatment of Hereditary Angioedema Attacks. N Engl J Med. 2024;391(1):32-43.
34. Lumry WR, Aygoren-Pursun E, Zanichelli A, Cohn D. KONFIDENT Phase 3 Trial Design for Sebetralstat (KVD900), a Novel Investigational Oral Plasma Kallikrein Inhibitor for the On-Demand Treatment of Hereditary Angioedema Attacks. 2022.
35. Riedl MA, Farkas H, Aygören-Pürsün E, Psarros F, Soteres DF, Staevska M, et al. [NEJM Supplementary Appendix] Oral Sebetralstat for On-Demand Treatment of Hereditary Angioedema Attacks. N Engl J Med. 2024;391(1):32-43.
36. ClinicalTrials.gov. An Open-label Extension Trial to Evaluate the Long-term Safety of KVD900 for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients With Hereditary Angioedema (HAE) ClinicalTrials.gov: KalVista; 2024 [Available from: https://clinicaltrials.gov/study/NCT05505916?a=3.
37. KalVista Pharmaceuticals. KalVista Pharmaceuticals Announces New England Journal of Medicine Publishes Oral Sebetralstat Phase 3 Data Demonstrating its Potential to Transform the Treatment Landscape for People with Hereditary Angioedema 2024 [Available from:

https://ir.kalvista.com/news-releases/news-release-details/kalvista-pharmaceuticals-announces-new-england-journal-medicine.
38. Maetzel A, Smith MD, Duckworth EJ, Hampton SL, De Donatis GM, Murugesan N, et al. KVD900, an oral on-demand treatment for hereditary angioedema: Phase 1 study results. J Allergy Clin Immunol. 2022;149(6):2034-42.
39. KalVista Pharmaceuticals. KalVista Pharmaceuticals Reports Positive Results for KVD900 Phase 2 Demonstrating Statistically and Clinically Significant Responses Across All Endpoints as an Oral On-Demand Treatment for HAE Attacks 2021 [Available from: https://ir.kalvista.com/news-releases/news-release-details/kalvista-pharmaceuticals-reports-positive-results-kvd900-phase-2.
40. Craig T, Bernstein JA, Longhurst H, Hao J, Smith MD, Audhya PK, et al. [ACAAI 2024 Time to Treatment Phase 3 poster] Correlation of Time to Treatment with Attack Duration in the Sebetralstat KONFIDENT Phase 3 Trial. ACAAI (American College of Allergy, Asthma & Immunology) 2024; October 2024; Boston, USA2024.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over [ID6284]

Clarification questions

June-July 2025

File name	Version	Contains confidential information	Date
ID6284 Sebetralstat clarification response_ Updated 16.9.25 [CON]	Final	Yes	Updated: 16 September 2025

Section A: Clarification on effectiveness data

Literature searches

A1. Appendix B, page 18 states that MEDLINE, Embase and the Cochrane Database of Systematic Reviews (CDSR) were searched to identify relevant clinical effectiveness systematic reviews and meta-analyses. Please provide details of the strategies used.

Company response: The primary objective of the clinical SLR was to synthesize the clinical evidence from randomized controlled trials in Hereditarily Angioedema (HAE).

To ensure all relevant evidence was captured, a combination of applicable medical subject headings and free text terms were used to retrieve all relevant publications. MEDLINE and EMBASE databases were searched to identify studies and the Cochrane database was used to identify relevant SLRs and meta-analyses.

Initial searches were conducted on 12th February 2024 and updated searches were run on 15th November 2024. The following tables of the CS Appendix provide the search strategies for the relevant databases:

- CS Appendix Table 38 MEDLINE initial search
- CS Appendix Table 39 Embase initial search
- CS Appendix Table 40 Cochrane initial search
- CS Appendix Table 41 MEDLINE update search
- CS Appendix Table 42 Embase update search
- CS Appendix Table 43 Cochrane update search.

A2. The strategies provided in Appendix E for MEDLINE and Embase do not include details of the date range/segment searched (e.g. 1946 to February 12,

2024 for MEDLINE). Please confirm the date ranges searched for each of these resources.

Company response: Apologies for this oversight, we can confirm that the MEDLINE search date range is 1946 to March 15, 2024. The Embase search date range is 1974 to 2024 March 15. We also want to clarify that the clinical SLR search end date was 12 February 2024 but the economic SLR search end date was 15 March 2024.

A3. There appears to be a discrepancy between the numbers found by the database searches in the PRISMA flow diagram (Appendix E, Figure 8) and the numbers recorded in the MEDLINE and Embase searches (Tables 23-24). Please correct or explain this discrepancy.

Company response: Thank you for your question. We can supply the correct MEDLINE and Embase search strategies below. These searches were run on the 15th March 2024 and relate to the PRISMA in Appendix E, Figure 8.

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to March 15, 2024>
Search Strategy:

1 Economics/ (27527)
2 "costs and cost analysis"/ (51865)
3 Cost allocation/ (2019)
4 Cost-benefit analysis/ (94231)
5 Cost control/ (21681)
6 Cost savings/ (12789)
7 Cost of illness/ (32094)
8 Cost sharing/ (2775)
9 "deductibles and coinsurance"/ (1874)
10 Medical savings accounts/ (549)
11 Health care costs/ (44784)
12 Direct service costs/ (1217)
13 Drug costs/ (17553)
14 Employer health costs/ (1098)
15 Hospital costs/ (12017)
16 Health expenditures/ (24590)
17 Capital expenditures/ (2003)
18 Value of life/ (5824)
19 exp economics, hospital/ (25802)
20 exp economics, medical/ (14426)
21 Economics, nursing/ (4013)
22 Economics, pharmaceutical/ (3128)
23 exp "fees and charges"/ (31424)
24 exp budgets/ (14188)
25 (low adj cost).mp. (93525)
26 (high adj cost).mp. (21031)
27 (health?care adj cost$).mp. (17920)
28 (fiscal or funding or financial or finance).tw. (211314)

29 (cost adj estimate$).mp. (2837)
30 (cost adj variable).mp. (53)
31 (unit adj cost$).mp. (3219)
32 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (432129)
33 or/1-32 (975392)
34 Economics.mp. (505730)
35 Price.mp. (37989)
36 Pricing.mp. (7822)
37 Cost.mp. (689333)
38 Cost Analysis.mp. (59522)
39 Economics, Dental.mp. (1924)
40 Economics, Hospital.mp. (11295)
41 Economics, Medical.mp. (9351)
42 Economics, Nursing.mp. (4016)
43 Economics, Pharmaceutical.mp. (3154)
44 Pharmacoeconomics.mp. (1878)
45 Value for Money.mp. (2223)
46 Budget.mp. (26514)
47 Health Economics.mp. (7875)
48 Economic Evaluation.mp. (13883)
49 Health Care cost.mp. (2662)
50 Economic analysis.mp. (7300)
51 Cost effectiveness analysis.mp. (14483)
52 Cost utility analysis.mp. (3635)
53 Cost benefit analysis.mp. (96782)
54 (cost$ adj1 (util$ or effective$ or efficac$ or benefit$ or consequence$ or analy$)).ti,ab. (209076)
55 or/34-54 (1037761)
56 standard gamble*.tw. (912)
57 (rate adj3 consultation).tw. (692)
58 (((hospital or length or duration*) adj2 stay) or hospitali*).ti,ab,kw,kf. (506643)
59 exp Hospitalization/ (299030)
60 exp "Length of Stay"/ (104004)
61 ((healthcare or health care or treatment*) adj3 (cost or economic* or expenditure* or expenc*)).ti,ab,kw,kf. (49661)
62 ((healthcare or health care or health service*) adj3 ("use" or utili*)).ti,ab,kw,kf. (62962)
63 exp "Facilities and Services Utilization"/ (1399)
64 (employment adj3 rate*).ti,ab,kw,kf. (1945)
65 (productiv* or efficiency).ti,ab,kw,kf. (744395)
66 exp Efficiency/ (37937)
67 or/56-66 (1490129)
68 Cost effectiveness.mp. (79668)
69 Cost effectiveness ratio.mp. (9696)
70 Incremental cost effectiveness ratio.mp. (8224)
71 Cost effectiveness plane.mp. (141)
72 Cost effectiveness acceptability curve.mp. (239)
73 Quality adjusted life years.mp. (22107)
74 Net monetary benefit.mp. (659)
75 (ICER or CEAC or QALY or NMB).af. (17144)
76 or/68-75 (90636)
77 33 or 55 or 67 or 76 (2722879)
78 Life years.mp. (27685)
79 (((angioedema* or angioneurotic edema* or angioneurotic oedema* or hea or heas) adj2 (estrogen sensitive or estrogen related or type iii)) or ((angioneurotic edema* or angioneurotic oedema* or hea or heas) adj4 (normal c1 inhibit or normal c1 inhibitor))).tw. (30)
80 ((c1 esterase inhibitor adj2 deficien*) or (c1 inhibitor adj2 deficien*) or hereditary angioedema* or hereditary angioneurotic edema* or hereditary angioneurotic oedema* or hea or heas).tw. (4926)
81 angioedema/ (5549)
82 angioedemas, hereditary/ (1424)
83 hereditary angioedema type iii/ (33)
84 "hereditary angioedema types i and ii"/ (176)

85 (acute circumscribed edema* or acute circumscribed oedema* or acute essential edema* or acute essential oedema* or angio oedema* or angio-oedema* or angioedematous urticaria or angioneurotic oedema* or angioneurotic edema* or angioneurotic swelling* or angioneurotic syndrome* or angioneurotic urticaria or angioedema* or giant hives or giant urtica or giant urticaria or hereditary angioedema* or hereditary angioedema* or hereditary angioneurotic edema* or hereditary angioneurotic oedema* or hereditary angiooedema* or milton urticaria or neurogenic edema* or neurogenic oedema* or Quincke edema* or Quincke oedema* or urtica gigantea or urticaria edematosa or urticaria gigantea or urticaria oedematose or wandering edema or wandering oedema).tw. (8811)
86 (estrogen sensitive or estrogen related or "type iii" or hereditary or "normal c1 inhibit*" or "normal c1 inhibitor*").tw. (132769)
87 85 and 86 (3274)
88 or/79-84,87 (9294)
89 77 and 88 (548)

EMBASE
Database: Embase <1974 to 2024 March 15>
Search Strategy:
1 Socioeconomics/ (165690)
2 Cost benefit analysis/ (96395)
3 Cost effectiveness analysis/ (188305)
4 Cost of illness/ (21588)
5 Economic aspect/ (127106)
6 Financial management/ (123349)
7 Health care cost/ (233125)
8 Health care financing/ (14067)
9 Health economics/ (36347)
10 Hospital cost/ (26056)
11 (fiscal or financial or finance or funding).tw. (316343)
12 Cost minimization analysis/ (4097)
13 (cost adj estimate$).mp. (4300)
14 (cost adj variable$).mp. (333)
15 (unit adj cost$).mp. (5675)
16 Standard gable/ or standard gamble*.tw. (1208)
17 (rate adj3 consultation).ti,ab,kw,kf. (921)
18 (((hospital or length or duration*) adj2 stay) or hospitali*).ti,ab,kw,kf. or hospitalization/ or "length of stay"/ (1076532)
19 ((healthcare or health care or treatment*) adj3 (cost or economic* or expenditure* or expenc*)).ti,ab,kw,kf. (77214)
20 Health care utilization/ or ((healthcare or health care or health service*) adj3 ("use" or utili*)).ti,ab,kw,kf. (150462)
21 (employment adj3 rate*).ti,ab,kw,kf. (2627)
22 (productiv* or efficiency).ti,ab,kw,kf. or productivity/ (866821)
23 (Budget impact adj3 (model* or analys*)).tw. (3804)
24 exp Economics/ (250289)
25 exp Price/ (7234)
26 exp Pricing/ (1276)
27 exp Cost/ (415320)
28 exp Cost Analysis/ (96426)
29 exp Economics, Dental/ (1063093)
30 exp Economics, Hospital/ (1063093)
31 exp Economics, Medical/ (1063093)
32 exp Economics, Nursing/ (1063093)
33 exp Economics, Pharmaceutical/ (239618)
34 exp Pharmacoeconomics/ (239618)
35 "value for money".ti,ab,kw,kf. (3069)
36 exp Budget/ (34430)
37 exp Health Economics/ (1063093)
38 exp Economic Evaluation/ (365101)

39 exp Health Care cost/ (350056)
40 exp "cost effectiveness analysis"/ (188305)
41 exp Cost utility analysis/ (12798)
42 exp Cost benefit analysis/ (96426)
43 (cost$ adj1 (util$ or effective$ or efficac$ or benefit$ or consequence$ or analy$)).ti,ab,kw,kf. (293504)
44 exp Cost effectiveness/ (188305)
45 exp Cost effectiveness ratio/ (188305)
46 cost effectiveness ratio*.ti,ab,kw,kf. (21714)
47 Cost effectiveness plane.ti,ab,kw,kf. (257)
48 Cost effectiveness acceptability curve*.ti,ab,kw,kf. (1027)
49 exp Quality adjusted life years/ (36928)
50 life year*.ti,ab,kw,kf. (40938)
51 Net monetary benefit*.ti,ab,kw,kf. (1211)
52 (ICER or CEAC or QALY or NMB).ti,ab,kw,kf. (30460)
53 or/1-52 (3657010)
54 (((angioedema* or angioneurotic edema* or angioneurotic oedema* or hea or heas) adj2 (estrogen sensitive or estrogen related or type iii)) or ((angioneurotic edema* or angioneurotic oedema* or hea or heas) adj4 (normal c1 inhibit or normal c1 inhibitor))).tw. (84)
55 ((c1 esterase inhibitor adj2 deficien*) or (c1 inhibitor adj2 deficien*) or hereditary angioedema* or hereditary angioneurotic edema* or hereditary angioneurotic oedema* or hea or heas).tw. (7464)
56 exp *angioneurotic edema/ (9385)
57 (acute circumscribed edema* or acute circumscribed oedema* or acute essential edema* or acute essential oedema* or angio oedema* or angio-oedema* or angioedematous urticaria or angioneurotic oedema* or angioneurotic edema* or angioneurotic swelling* or angioneurotic syndrome* or angioneurotic urticaria or angioedema* or giant hives or giant urtica or giant urticaria or hereditary angioedema* or hereditary angioedema* or hereditary angioneurotic edema* or hereditary angioneurotic oedema* or hereditary angiooedema* or milton urticaria or neurogenic edema* or neurogenic oedema* or Quincke edema* or Quincke oedema* or urtica gigantea or urticaria edematosa or urticaria gigantea or urticaria oedematose or wandering edema or wandering oedema).tw. (16351)
58 (estrogen sensitive or estrogen related or "type iii" or hereditary or "normal c1 inhibit*" or "normal c1 inhibitor*").tw. (175320)
59 57 and 58 (5862)
60 54 or 55 or 56 or 59 (12176)
61 53 and 60 (1057)

Decision problem

A4. Priority question: It is noted that the population in the decision problem addressed in the company submission is aligned with the NICE Final Scope, specifically "people with hereditary angioedema (HAE) having an acute attack." However, the company also mentions that "a third much rarer subtype of HAE exists and presents with normal C1-INH (HAE-nC1-INH; previously classified as HAE type III)."

a) **Please clarify whether HAE type III (HAE-nC1-INH) has been considered in the company submission (CS).**

Company response: No, we can confirm that the HAE-nC1-INH subtype of HAE has not been considered in the CS. The sebetralstat submission relates to HAE Type I and II.

b) If it has not been included, please explain the rationale for its exclusion and describe the potential implications of this exclusion on the clinical effectiveness assessment and cost-effectiveness assessment.

Company response: As described on page 16 of the CS, Type I and Type II are the two main subtypes of HAE with Type I accounting for approximately 85% of HAE cases and Type II accounting for approximately 15% of HAE cases. Type I is caused by a **deficiency** in C1-esterase inhibitor (C1-INH) protein whilst Type II is caused by **dysfunction** in C1-INH. In both these types, the deficiency (Type I) and dysfunction (Type II) in C1-INH protein, due to a mutation in the SERPING1 gene, leads to subsequent uncontrolled activation of the kallikrein-kinin system (KKS) and produces swellings associated with HAE attacks. Sebetralstat works by targeting the KKS cascade, selectively inhibiting plasma kallikrein and its uncontrolled activity that drive HAE attacks.

The third subtype of HAE that presents with normal C1-INH and function (HAE-nC1-INH; previously classified as HAE type III), exists but is extremely rare with genetic mutations that result in a very small percentage of patients affected within a country – UK prevalence is estimated at around 1:3,000,000.(1) HAE-nC1-INH is understood to be caused by a variety of genetic mutations for example in factor XII, angiopoietin-1, plasminogen, and kininogen genes. This third type of HAE and how resultant swellings occur, has a different biochemical pathway from HAE Types I and II.

The focus within sebetralstat's clinical programme has been on Types I and II where much is understood about the biochemical pathway and sebetralstat's action to reduce HAE swellings. The focus on only these two subtypes within the sebetralstat clinical programme helped to ensure a relatively homogeneous study population within the trials to limit any inherent unknowns related to the HAE-nC1-INH subtype.

Theoretically, sebetralstat could potentially work to reduce swellings in patients with the HAE-nC1-INH subtype. Plasminogen and kallikrein are involved in separate but related proteolytic cascades in the body. These pathways are being elucidated, however, and further basic and clinical research is warranted in order to predict sebetralstat's action on patients with HAE-nC1-INH.

Please note that the focus on Types I and II alone was also the case with the two previous NICE appraisals for long-term prevention of HAE attacks (NICE TA606 lanadelumab and NICE TA738 berotralstat). We do not expect any impact on the sebetralstat cost-effectiveness assessment.

Systematic review

A5. Please describe how disagreements were resolved between the two reviewers when no consensus could be reached.

Company response: There were limited instances where disagreements were unresolvable between the two reviewers. On these occasions, the reviewers would engage with the project lead to seek her input.

A6. Please describe how many reviewers conducted quality appraisals of the included studies and how data was checked or disagreements between reviewers resolved.

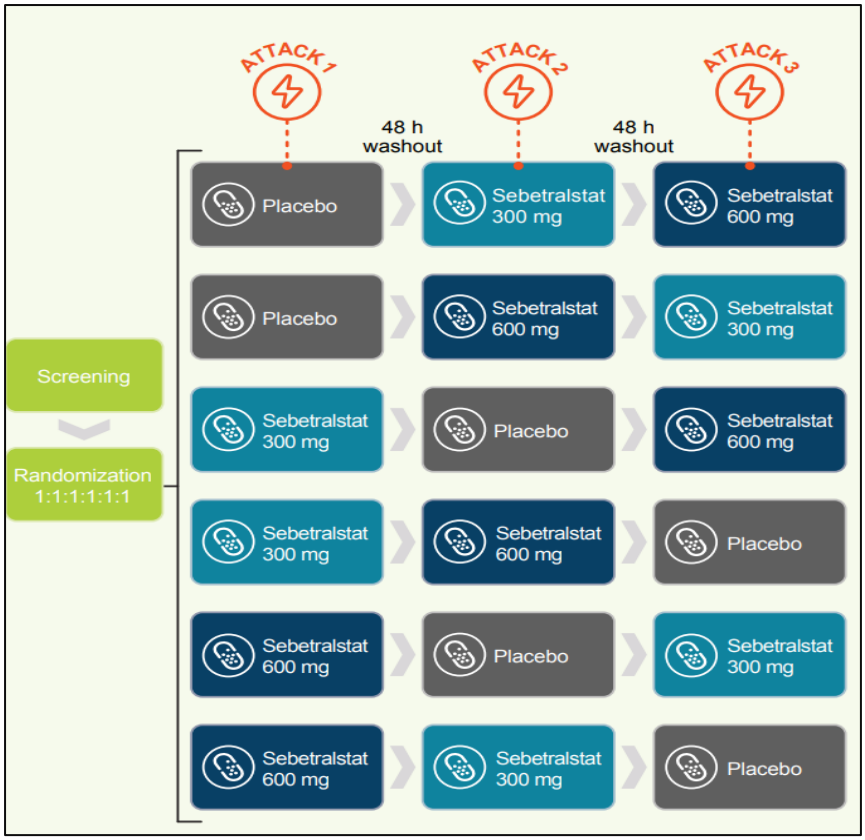
Company response: Two reviewers conducted the quality appraisals and would consider any disagreements. The project lead was engaged whenever her input was required.

Clinical effectiveness evidence

A7. Priority question: Please clarify how treatment switching was dealt with in the analysis of the KONFIDENT (Phase 3) trial.

Company response: The purpose of the crossover design was to enable the randomised evaluation of effect of the 3 different options (i.e. placebo and the 2 doses of sebetralstat) on the same individuals, essentially including each participant as their own control and maximizing data collection in patients with a rare disease. This type of trial design helps to minimise the impact of individual variability between participants and to ensure sufficient number of attacks were available for analysis.

[CS Figure 3] KONFIDENT Phase 3 trial design



h, hour.
Patients will be randomised to treat 3 eligible attacks with sebetralstat 300 mg, sebetralstat 600 mg, or placebo in a 3-way crossover design using 1 of 6 treatment sequences
Source: Lumry et al. (2022)(2)

In any crossover trial, carryover effects should be considered. For the KONFIDENT trial, a minimum washout was required to ensure drug concentrations were eliminated by the end of the data collection period. The half-life of sebetralstat is approximately 3 hours. Because of the intermittent nature of attack frequency, median attacks actually occurred approximately every 21 days. The period and sequence were included in the primary analysis as a fixed effect to control for these effects, if any, and patients were nested within sequence as a random effect.

A8. Priority question: The key clinical trial (KONFIDENT, Phase 3) excluded patients with HAE Type III (HAE-nC1-INH). Please clarify whether the trial population is representative of patients treated in UK clinical practice. If not, please discuss the relevance of the trial population to UK clinical practice.

Company response: As mentioned in Question A4, the third subtype of HAE (HAE-nC1-INH) is extremely rare and the resultant swellings follow a different biochemical pathway from the common Type I and II swellings. Therefore, the inclusion of HAE Types I and II in the KONFIDENT trial is representative of the UK patients that would receive sebetralstat.

A9. Priority question: The key clinical trial (KONFIDENT, Phase 3) is a three-way crossover trial. Please clarify whether this trial design is reflective of treatment pathways in UK clinical practice. If not aligned, please discuss the potential impact on the generalisability of the trial results to NHS patients.

Company response: The KONFIDENT study was a phase 3 double-blind, randomised, placebo-controlled, three-way crossover trial that was conducted to evaluate the efficacy and safety of sebetralstat (300 mg or 600 mg) as compared with placebo for the on-demand treatment of HAE attacks. The results of the KONFIDENT trial have demonstrated the effectiveness of sebetralstat 300mg in providing faster times to the beginning of symptom relief, reduction in attack severity and complete attack resolution than placebo.(3) Additionally, the trial findings also demonstrated equivalence between the sebetralstat 300 mg and 600 mg doses.(3)

As mentioned in Question A7, the crossover trial design helps to minimise the impact of individual variability between participants by essentially including each participant as their own control, to ensure sufficient number of attacks were available for analysis and to maximise data in patients with a rare disease. Importantly, the crossover trial design does not reflect the treatment pathway and how patients would be treated in clinical practice (i.e. patients would not systematically switch between sebetralstat doses nor placebo in the real-life clinical setting). However, since the KONFIDENT results represent the treatment effect of sebetralstat in treating an acute HAE attack, the efficacy and safety findings from the trial are considered

generalisable to NHS clinical practice, even though the crossover trial design does not reflect the NHS treatment pathway.

Of note, UK clinical experts engaged during the development of the submission validated the generalisability of the KONFIDENT findings to clinical practice. They highlighted that the proportion of patients receiving long-term prophylaxis (in addition to on-demand treatment) in clinical practice would likely be higher than the 21.8% in the KONFIDENT trial, however, they added that this would not affect the sebetralstat clinical findings.(4)

Please be aware that unlike previous on-demand treatment trials in HAE, the KONFIDENT trial design was designed with the aim to be more reflective of clinical practice and consistent with expert HAE guidelines. This includes consideration of patient demographics, inclusion/exclusion criteria, concomitant medications, primary and secondary endpoints (e.g. assessment of time to attack symptom relief and attack resolution, additional dosing requirements, attack locality, etc).

This trial enrolled all eligible patients aged 12 years and older including patients from UK, North America, Europe, Israel and Japan. The trial allowed patients using long-term prophylactic HAE therapy to enrol who met attack criterion (i.e. sufficient number of breakthrough attacks). Patients were allowed to make a determination to use sebetralstat, including the use of a second dose if needed, without verification from a clinician as is currently done with standard of care. No minimum severity or location was required for treatment with the only exclusion being life-threatening/ severe laryngeal attacks which should not ethically be treated with placebo. Indeed, patients were encouraged, consistent with guidelines, to treat the attack as soon as the start of the attack was recognised. The endpoints used patient-friendly language and reflected important clinical milestones such as symptom relief and attack resolution which patients indicate are clinically meaningful to them.

Indirect treatment comparison (ITC)

A10. Priority question: The company stated in Appendix L that the indirect treatment comparison (ITC) used propensity score weighting (PSW) to

enhance the comparability between included trials. Please clarify which baseline characteristics were used to estimate the PS. Please also provide a table showing which baseline characteristics were included from the systematic review, which were identified by clinical experts and which were available in the individual patient data (IPD) for the ITC. Please also provide a list of prognostic variables (which were identified via systematic review and/or by clinical experts) that were not adjusted for in the matching-adjusted indirect comparisons (MAIC) analysis.

Company response: The company has conducted a systematic literature review and found no evidence suggesting potential treatment effect modifiers for HAE on-demand therapies. In the best effort to evaluate potential confounders, we assessed the list of potential prognostic factors outlined in a recent publication on the indirect comparison of HAE prophylactic treatments (Table 1), in addition to data availability in KONFIDENT. Two scenarios were considered with regarding to the matching variables:

- Scenario 1: match on disease severity, measured by the baseline visual analogue scale (VAS)
- Scenario 2: match on baseline disease severity and selected demographic variables (age, sex, race).

Table 1: Potential prognostic factors, confounders and/or treatment effect modifiers

Potential prognostic factors, confounders and/or treatment effect modifiers	Watt et al (2024) (5)	Available in KONFIDENT IPD (individual patient data)	Used for matching
Disease severity	✓	✓	✓ (Scenario 1 & 2)
Age	✓	✓	✓ (Scenario 2 only)
Sex	✓	✓	✓ (Scenario 2 only)
Race (white/Caucasian vs. other)	✓	✓	✓ (Scenario 2 only)
HAE type (Type I vs Type II)	✓	✓	

Presence of family history	✓		
Comorbidity categories	✓		
Route of administration	✓		
Follow-up time	✓	✓	
Baseline attack frequency	✓		
Smoking habit	✓		
Alcohol consumption	✓		

The remaining potential prognostic factors, confounders and/or treatment effect modifiers could not be adjusted for because either they were not available in the KONFIDENT IPD and/or not reported in the Ruconest studies.

A11. Priority question: Please provide the mean and standard deviation of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm before matching. Please provide the sample size for each arm. Please also provide standardised mean difference for the comparison of the intervention arm and the comparator arm before matching.

Company response: Please see the requested information in Table 2 below.

Table 2: Mean and standard deviation of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm before matching, and standardised mean difference

Baseline variables	KONFIDENT (N = 169)	Riedl 2014 (6) (N = 75)	Standardised mean difference
Attack severity, VAS mean (SD)	46.6 (25.4)	75.1 (13.5)	-1.401
Age, mean (SD)	37.5 (14.9)	40.2 (15.1)	-0.180
Female sex, n (%)	107 (63.3%)	47 (63.3%)	0.000
White race, n (%)	144 (85.2%)	72 (95.8%)	-0.368

Abbreviations: SD: standard deviation, VAS: visual analogue scale

A12. Priority question: Please provide mean and standard deviation of the covariates which were adjusted for in the MAIC analysis for the intervention

arm and the comparator arm after matching. Please provide the effective sample size for each arm. Please also provide the standardised mean difference for the comparison of the intervention arm and the comparator arm after matching.

Company response: Please see the requested information in Table 3 below.

Table 3: Mean and standard deviation of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm after matching, and standardised mean difference

Scenario 1	Used for matching	Baseline variables	KONFIDENT (ESS = 62)	Riedl 2014 (6) (N = 75)	Standardised mean difference
	Yes	Severity, VAS mean (SD)	75.1 (21.1)	75.1 (13.5)	**0.000**
	No	Age, mean (SD)	37.8 (15.2)	40.2 (15.1)	-0.158
	No	Female sex, n (%)	39 (62.4%)	47 (63.3%)	-0.019
	No	White race, n (%)	54 (86.7%)	72 (95.8%)	-0.326
Scenario 2	**Used for matching**	**Baseline variables**	**KONFIDENT (ESS = 58)**	**Riedl 2014 (N = 75)**	**Standardised mean difference**
	Yes	Severity, VAS mean (SD)	75.1 (20.7)	75.1 (13.5)	**0.000**
	Yes	Age, mean (SD)	40.2 (13.6)	40.2 (15.1)	**0.000**
	Yes	Female sex, n (%)	37 (63.3%)	47 (63.3%)	**0.000**
	Yes	White race, n (%)	56 (95.8%)	72 (95.8%)	**0.000**

Abbreviations: ESS: effective sample size, SD: standard deviation, VAS: visual analogue scale

A13. The company submission provided results of a recently published ITC (based on two conference abstracts)[1],[2] with the objective of demonstrating the method-of-administration comparability between an oral on-demand treatment with an intravenous treatment (page 68 of CS). However, the EAG noted that a recent paper relating to this ITC was not included in the company submission.[3]

[1] Li HH, Magerl M, Craig T, Manning ME, Hummel N, Wang A, et al. R083. Indirect treatment comparison of oral sebetralstat and intravenous rhC1-INH as on-demand treatments for hereditary angioedema [Poster]. In: American Academy of Allergy, Asthma & Immunology 2024; Boston, USA, 2024. Available from: https://www.kalvista.com/wp-content/uploads/2024/10/ITC_Sebetralstat_vs_rhC1-INH_Poster_ACAAI-2024_10Oct2024_FINAL.pdf

[2] Wang A, Li H, Magerl M, Craig TJ, Manning M, Hummel N, et al. Indirect treatment comparison of oral sebetralstat and intravenous RHC1-INH as on-demand treatments for hereditary angioedema. Ann Allergy Asthma Immunol 2024; 133(Suppl):S28-S29

[3] Li HH, Aygören-Pürsün E, Magerl M, Craig TJ, Manning ME, Hummel N, et al. Indirect treatment comparison of oral sebetralstat and intravenous recombinant human C1 esterase inhibitor for on-demand treatment of hereditary angioedema attacks. Allergy Asthma Clin Immunol 2025; 21(1):10

Please provide an explanation why this recent paper relating to the ITC was not included in the company submission.

Company response: Thank you for highlighting this oversight. The Li et al. (2025) manuscript that you mention is the full publication for the same body of work as the Li et al. 2024 (ACAAI 2024 poster) and Wang et al. 2024 (ACAAI 2024) conference abstract. The submission's Appendix L content is a detailed write up of the ITC based on the Li et al. (2025) manuscript, which was a draft (unpublished) item at the time of submission development, so the omission of Li et al. (2025) as a final reference in the submission was an oversight for which we apologise.

Section B: Clarification on cost-effectiveness data

Population

B1. Priority question: In the description of the decision problem (Table 1 of the CS), it is noted that the population in the CS is aligned with the population in the NICE Final Scope, specifically "*people with hereditary angioedema (HAE) having an acute attack*". However, in the the economic evaluation the population is defined as "patients 12 years and over with type I and type II HAE".

a) Please explain the discrepancy in the description of the target population of interest.

Company response: Apologies for any confusion regarding the patient population. To clarify, the NICE scope states a population of "*People 12 years and over with hereditary angioedema having an acute attack*." The economic evaluation is aligned to this population in the NICE scope but we had also further specified that the patients were also "*with Type I and Type II HAE*" which is accurate in the analyses since Type I and Type II HAE make up 65% and 35% of HAE cases, respectively, and the KONFIDENT study trial population only comprised Type I and Type II HAE patients.

b) On page 102 of the CS, it is mentioned that "*since there are no differences in the clinical and economic outcomes between type I and type II HAE patients, these sub-types are assumed homogenous and are not separately modelled*". If there are no differences in terms of clinical and economic outcomes between type I and type II patients, please describe what is the real distinction between these patient sub-populations.

Company response: As mentioned in Question A4 part b, Type I is caused by a **deficiency** in C1-INH protein whilst Type II is caused by **dysfunction** in C1-INH. In both these types, the deficiency (Type I) and dysfunction (Type II) in C1-INH protein, due to a mutation in the SERPING1 gene, leads to subsequent uncontrolled activation of the kallikrein-kinin system (KKS) and produces swellings associated with HAE attacks. Sebetralstat works by targeting the KKS cascade, selectively inhibiting plasma kallikrein and its uncontrolled activity that drive HAE attacks. This mode of action is the same for both Type I and II HAE attacks and therefore the two types can be considered homogeneous and do not require separate modelling.

c) The baseline patient characteristics in the model are informed from the KONFIDENT Phase III and open-label extension (OLE) trials, as mentioned on page 102 of the CS. Please explain if these patients are representative of the patient population in the UK.

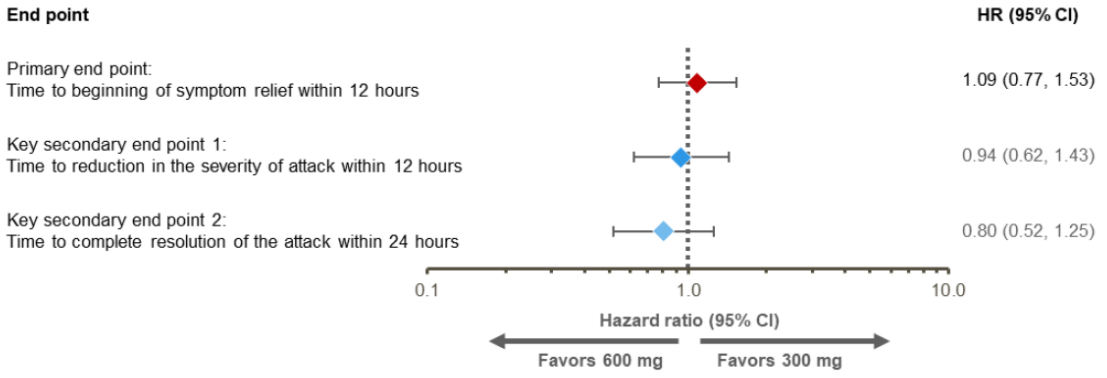
Company response: As mentioned in CS page 94 the participants in the KONFIDENT study were considered generally representative of the overall worldwide population with HAE.(7) Additionally, UK clinical experts engaged during the development of this submission informed us that the proportion of patients receiving long-term prophylaxis (LTP) in addition to on-demand treatment in clinical practice would likely be higher than the 21.8% in the KONFIDENT trial, however, they added that this would not affect the sebetralstat clinical findings.(4) Of note, the KONFIDENT-S OLE trial patient demographics were similar to the KONFIDENT study and therefore also considered representative of the UK patient population.

Intervention and comparators

B2. Priority question. The intervention in the health economic (HE) model is sebetralstat 300 mg, but in the KONFIDENT trial the intervention is defined as a sequence of treatments including sebetralstat 300 mg, 600 mg and placebo. Please justify that the data informing the efficacy parameters in the HE model sourced from the KONFIDENT trial are appropriate even though the intervention in the trial and in the model is not the same.

Company response: Please refer to page 92 of the CS for a summary of the equivalence between the sebetralstat 300 mg dose and the 600 mg dose. Essentially, pharmacokinetic evidence from the evidence base demonstrates the two doses to be equivalent in terms of both efficacy and safety. In the phase 3 KONFIDENT study, there was no statistical difference demonstrated between the 300 mg and 600 mg dose as shown by hazard ratios for the primary and key secondary endpoints.

[CS Figure 11] KONFIDENT study: Hazard ratios of sebetralstat 300mg and 600mg doses for primary or key secondary endpoints



HR: hazard ratio
Source: Figure S5 from Riedl *et al.* 2024 supplementary appendix (7)

Furthermore, the demonstration of dose equivalence in the KONFIDENT study led to the KONFIDENT-S open-label extension study implementing a dose change from the original 600 mg dose to the 300 mg dose from January 2025. Clinical experts consulted as part of submission development were in agreement of the dose equivalence and the suitability of trial data (including 600 mg dose in the

KONFIDENT-S) to be used to represent the intended-license dose of 300 mg that features in the cost-effectiveness model.

B3. Priority question: In Table 2 of the CS, it is mentioned that "The recommended dose of sebetralstat is a 1 x 300 mg tablet to be taken orally by patients at the earliest recognition of a HAE attack. An additional dose may be taken if needed". Please explain the reasons for needing an additional dose. Is the patient assessing the need for a second dose or a health-care professional (HCP)? Is one additional dose the maximum or is it possible for a patient taking more than one?

Company response: HAE attack resolution is achieved with sufficient kallikrein inhibition. Most attacks can resolve within one dose but sometimes more inhibition is required (through an additional dose) to help achieve the appropriate level of kallikrein inhibition. It cannot be assumed that a patient's attack will resolve in the same way each time, indeed requiring an additional dose for an attack does not imply that the next attack will require the same. This is due to the heterogeneity of HAE as a condition whereby attacks are impacted by ever-changing factors in the same individual's health, wellbeing and circumstances. The heterogeneity in HAE attacks is the same for all on-demand treatments and is not unique to sebetralstat as an investigational oral on-demand treatment for HAE. Trials and real-world clinical practice report additional dosing for all the currently available on-demand treatment options. Furthermore, it is reasonable to expect that over time with market, physician and patient education and treatment experience, trust in sebetralstat's efficacy will grow and thus the occurrences of patients taking a second dose will decrease further in practice.

The decision to take an additional dose during the KONFIDENT and KONFIDENT-S trials was at the patient's own discretion and no reasons were provided. The majority of HAE attacks can be resolved through one single dose of sebetralstat, however, patients may have taken an additional dose because it was available to them during the clinical trial. Indeed, ad hoc efficacy data from the KONFIDENT study demonstrated that the majority of patients go onto achieve HAE attack resolution without the need of a second dose of sebetralstat (see pages 65–66 of the CS).

B4. Priority question. Please justify the definition of standard of care (SoC) as a basket of treatment options and whether this is in line with NICE methods. In addition, the base case comparator treatments included in the basket of SoC are icatibant, ruconest, and berinert (see page 113 of the CS). However, the final scope by NICE in Table 1 states that C1-esterase inhibitors should also include cinryze. Please justify why cinryze is not part of the SoC in the UK.

Company response: In general, NICE methods encourage for economic models to reflect clinical practice. Specifically, regarding the use of a basket comparator, for example, section 4.2.17 of the NICE Methods Guide also explicitly states that "… *if the technologies form part of a class of treatments, and evidence is available to support their clinical equivalence, estimates of QALYs gained for the class as a whole can be shown*." While on-demand (OD) HAE treatments can differ in mechanism of action, all treatments are functionally substitutable. Differentiation between treatment efficacy is largely driven by the TTA of treatment. As stated in our CS, OD treatments are most effective when administered during the start of an attack before swelling has peaked. OD treatments can only halt the attack and prevent additional swelling and do not directly reverse or eliminate swelling that has already occurred. The relationship between TTA and TTAR is a direct result of the pathophysiology of HAE and treatment pharmacodynamics, demonstrated across contemporary OD treatments (8-14).

NICE appraisal of basket comparators has precedence. For example, in NICE TA1051, the company submission provided pairwise comparisons with treatments deemed most likely to be replaced by the intervention. However, this was flagged as a key issue by the EAG, and the company was requested by committee to present results using a basket of current comparator treatments. A basket comparator was also submitted in TA1054, TA995 and TA757. In TA1054, the EAG did not raise major objections towards the use of a basket comparator. In TA995 and TA757, the EAGs were mostly critical about the costs included in the basket.

While the basket comparator is more reflective of NHS clinical practice, we have provided the functionality in the model for pairwise comparisons. The omission of Cinryze from the basket comparator is due to the fact that market share data was

used to inform the proportions of comparator treatments, however, Cinryze data was provided as a single unit (i.e. the data did not distinguish between on-demand or long-term prophylaxis usage). Anecdotal feedback from UK clinical experts is that Cinryze's use as an on-demand treatment is very limited to not used at all. For completeness, and in follow up to this clarification question, we have now added a nominal 1% share of Cinryze in the model to capture this very limited to no usage. Please note that all cost-effectiveness results reported from hereon include this nominal 1% Cinryze share.

B5. Priority question: Please define rescue therapy, its purpose, frequency and if it is the same for intervention and comparators. Please clarify if it is provided by HCP or if it can be self-administered, and in what proportion.

Company response: Rescue therapy is an alternative therapy used by patients if there is inadequate response to their first OD treatment. The use of an alternative OD treatment, i.e. rescue therapy, is determined by the patient and is used after the primary OD treatment. To provide a clear example, if a patient's primary OD treatment is typically icatibant, the patient first administers a single dose, but may take additional doses of icatibant every 6 hours if there is inadequate response. However, if there is inadequate response, the patient can also opt to use an alternative OD treatment, such as Berinert or Ruconest, after the first dose of the primary OD treatment.

The cost of rescue therapy is applied to both intervention and comparators, based on the proportion of patients requiring rescue therapy per attack, specific to each initial OD treatment. Rescue therapy can be provided by either HCP or self-administered. The proportion of HCP or self-administered is defined by the distribution of patients who require HCP or self-administer. Please refer to section 3.5 and Table 32 in the CS for detailed discussion. Please see the CS model, columns 'Life Table and Age HRQoL'!R:Z, for the functions used to calculate the weight-dependent cost of rescue therapy.

Model structure and assumptions

B6. On page 15 of the CS, it is mentioned that patients may experience simultaneous swellings at more than one site. Please explain whether this has been included in the economic model or not and why.

Company response: The model assumes 3 mutually exclusive areas of the body where an attack occurs. The 'Neck and Above' area assumes to include laryngeal and other areas from the neck and above. The 'Abdominal' area is specifically attacks occurring around the abdomen. The 'Other' area is the largest area, which includes areas such as the arms, legs, hands, and feet. Moreover, while patients can experience swelling across several locations, it is most common for a patient to experience swelling at and around a specific area of the body. For instance, IOS data of six European countries report that 90.1% of attacks occurred at a single anatomical site.(15)

While the model does not capture the minority of attacks that occur at multiple sites, it is a reasonable compromise given the available utility data for modelling HAE. Available utility data estimate the impact of an attack at specific locations or levels of severity. However, these data do not estimate the HRQoL impact of an attack occurring at multiple locations. Additionally, due to the paucity of attacks that cause swelling at multiple locations, it is particularly difficult to estimate reliable HRQoL data while avoiding issues of double counting.

B7. Please explain under what circumstances patients would receive treatment in an hospital setting (as opposed to home setting). How frequent do patients receive treatment at the hospital compared to at home? In addition, on page 24 of the CS, it is mentioned that "half of patients self-administer their C1-INH on-demand treatment, 13% require carer administration, and over one-third require administration by healthcare professionals (38%) within the secondary care setting". Please clarify why these patients would require carer or health-care professional administration.

Company response: Typical reasons for receiving on-demand treatment in a hospital setting include:

- If the attack is laryngeal and therefore it is considered a severe attack – patients are advised to go to the hospital for treatment
- Patient choice
- Icatibant on-demand treatment has not worked so patients visit the hospital for further treatment
- After failure of self/carer administration
- Attacks are infrequent and so patients are not sufficiently confident to maintain their self-treating/IV cannulation skills at home
- Patient is a child (the parent/carer of the patient is not sufficiently confident to deliver the on-demand treatment)
- Poor venous access – patient/carer/parent finds it hard/awkward to do and therefore seeks HCP support.

Of note, carer administration typically relates to HAE patients that are children/adolescents.

B8. On page 18 of the CS, it is mentioned that UK clinical experts reported that roughly 5-10% of patients have an accident and emergency (A&E) visit per year. Please explain whether this has been included in the economic model or not.

Company response: This is included in the model, see 'Clinical Inputs'!E169:E170. We acknowledge that the wording may be confusing since the input is named 'Hospitalization Risk'.

Generally, HAE patients typically only require observation at the A&E for a period of up to 24 hours. The inputs in cells 'Clinical Inputs'!E169:E170 represent the risk of an A&E visit for patients in England. As noted in the original submission, the risk is dependent on whether treatment is self-administered or administered by a healthcare professional. This implicitly assumes that HCP-assisted administration

has a greater delay in treatment administration and thus carries a higher risk of hospitalisation due to delayed treatment. This assumption is uncertain given the limited evidence of hospitalisation rates between treatments, but it was applied in NICE TA606. The input has a minor impact on cost-effectiveness. When the risk of hospitalisation (A&E visit) is set to 0% for all treatments, the submitted base case ICER changes by [redacted]%.

B9. Priority question: On page 111 of the CS, it is stated that "The adjusted TTAR of each treatment is assumed to include adjustment for the TTA of the first dose, any additional doses, and rescue therapy use." Please comment on the implications of this assumption. For instance, would the benefit of sebetralstat be overestimated [in terms of health-related quality of life (HRQoL) improvement and potentially costs] if a patient receives sebetralstat as a first dose and as an additional dose, but then still needs another on demand (OD) treatment as a rescue therapy? Please explain.

Company response: This is largely a limitation of the available data. The KONFIDENT trial protocol censors time to resolution when rescue therapy is used, and the TTAR is reported as the endpoint time period, e.g. 12, 24 or 48 hours. Therefore, the TTAR after rescue therapy use is not accurately reported. Therefore, applying the use of rescue therapy as a covariate in the Cox model leads to convergence issues due to perfect correlation between the use of rescue therapy and the response variable.

Given the current time constraints, and considering the above, KalVista have run a subgroup analysis that excludes patients who used rescue therapy. This analysis results in a minor decrease in the hazard ratios between TTA and TTAR, resulting in a ratio of [redacted] (vs. [redacted]). When applying a hazard ratio [redacted] for the association between TTA and TTAR, the submitted base case ICER changes by [redacted]%. We will provide updated R code of this analysis alongside our additional responses to B14.

B10. Priority question: Please clarify what is meant with the following statement on page 112 of the CS: "It is important to acknowledge that, in the absence of appropriate data on the conditional use of rescue therapy, i.e., differentiating between patients not taking additional doses or taking additional doses prior to use of rescue therapy, the proportions of patients requiring additional doses and using rescue therapy are modelled independently." What are the implications of this approach? How did the company examine the impact of this approach on the cost-effectiveness outcomes?

Company response: There is no sufficient direct or indirect data providing the conditional probability of using rescue therapy before or after taking additional doses. While this can be calculated using the KONFIDENT data, comparator data on the conditional use of rescue therapy is largely absent or inconsistently reported. Therefore, an assumption of independence was applied. KalVista acknowledge the limitations of this assumption and that if, for example, additional dosing reduces the need for rescue therapy use, independence may overestimate the total use of rescue therapies (and thus the associated costs). KalVista have, however, performed extensive sensitivity analyses. In both DSA and PSA, the proportion of patients requiring additional doses and using rescue therapy are varied.

B11. On page 109 of the CS, it is mentioned that in the base case model, attack location categories are preferred to severity categories—an assumption supported by clinical expert feedback. Please provide the source of this expert opinion.

Company response: This is based on discussions and subsequent model validation with clinicians during conceptual modelling. Please see details on slide 9 of the submitted data on file provided at the time of submission: 6. [data on file] Sebetralstat KoL Validation Exec Summary_v1.0.

B12. Priority question: Please discuss the validity of the assumption that inputs for additional dosing and rescue therapy do not adjust time to attack

resolution (TTAR). For example, is it unreasonable to expect that if an additional dose is needed, this is because the first dose has not worked as it should and then then TTAR would be longer? In addition, would the risk of hospitalisation be also conditional on having a second dose and/or rescue therapy?

Company response: As mentioned in our response to Question B3, HAE attacks are heterogeneous in their onset, manner and resolution even in the same individual. If an additional dose or rescue remedy is needed, it could be down to the attack requiring more kallikrein inhibition on that occasion, and it does not necessarily indicate that TTAR would be longer. The additional dose of sebetralstat, in essence, completes the full inhibition required in the uncommon cases where this is necessary. There is no risk of hospitalisation associated with additional dose or rescue therapy requirements.

As also mentioned in our response to Question B3, the decision to take an additional dose during the KONFIDENT was at the patient's own discretion and no reasons were collected from the patients for doing so. Analysis of additional dosing required in the KONFIDENT study showed that the majority of patients achieved HAE attack resolution without the need of a second dose of sebetralstat (see pages 65–66 of the CS), however, patients in the KONFIDENT study may have taken an additional dose because it was available to them during the trial setting and also the risk of placebo may have increased the rate of second dose use.

The estimates in the cost-effectiveness analysis likely overestimate the additional dosing requirements for sebetralstat in clinical practice. We have already seen lower rates of additional dosing required in the KONFIDENT-S open-label study (22.3% in the latest datacut[4]) compared with the phase 3 KONFIDENT study, and expect that with greater familiarity, experience, and confidence, that additional dosing rates with sebetralstat would likely further decline in the real-world clinical practice setting. Interestingly, rates of rescue therapy also reduced in the KONFIDENT-S open-label study (5.2% in the latest datacut[4]) compared to KONFIDENT.(16)

[4] The latest KONFIDENT-S data was presented as a conference poster by Riedl et al. (2025) at the WSAAI (Western Society of Allergy, Asthma & Immunology) annual meeting in February 2025.

B13. Please provide evidence to justify the assumption that the cohort attack rate is time homogenous and does not change from the baseline attack rate and that OD treatments do not impact long-term attack rates. In the absence of evidence, please clarify if this was validated by clinical experts and how.

Company response: This is due to the significant heterogeneity in attack frequency. Moreover, sufficient evidence is absent to reliably extrapolate attack variation over a patient's lifetime. The assumption therefore favours simplicity. During conceptual validation, clinicians noted that attack frequency is highly variable, but observed OD patients having between 1-3 attacks every 3-4 months. Moreover, clinicians reported that, within the UK, patients on lanadelumab experience hardly any attacks. However, patients on lanadelumab comprise roughly <10% of LTP + OD patients due to its restrictions. For patients on berotralstat, clinicians reported that patients experience at least 1 attack every 1-2 months. Please see details on slide 4 of the submitted data on file that was provided at the time of submission: 6. [data on file] Sebetralstat KoL Validation Exec Summary_v1.0.

Clinical effectiveness parameters and assumptions

B14. Priority question: Please include in the HE model the results of the ITC reported by Li et al. 2025. When doing so, please consider including all reported ITCs including MAICs. The model should be able to accommodate both the company and Li et al. 2025 approaches and explore the impact on scenario analyses and probabilistic sensitivity analyses (PSA).

Company response [provided 10 July 2025]: We appreciate the EAG's interest in assessing the impact of the recently published Li et al. (2025) ITC in the cost-effectiveness analysis. As highlighted in CS Section 2.10 and written up in submission Appendix L, please be aware that the Li et al. ITC was conducted in collaboration with KalVista, with the aim to explore the **method of administration** comparability between an **oral** on-demand treatment with an **intravenous** treatment. This ITC was based on the primary endpoint ('time to beginning of symptom relief')

and safety outcomes, and the results demonstrated no significant differences in these outcomes between oral sebetralstat and intravenous rhC1-INH.

Li et al. (2025) cannot inform the economic analyses because the ITC endpoints are not the outcomes of interest in the cost-effectiveness model. Due to the absence of robust and feasible ITCs to appropriately capture comparative effectiveness between sebetralstat and its comparators, the model considers that earlier on-demand treatment administration is associated with a shorter total attack duration. The model incorporates a statistical sub-model to estimate the effect moderation of TTA (time to treatment administration) on TTAR, to obtain an adjusted TTAR (time to attack resolution) for each treatment.

Although the current CEM cannot be updated to include the Li et al. ITC, we appreciate the EAG's interest to explore an alternative comparative effectiveness approach. Therefore, we have conducted additional analyses to provide you with alternative models.

In addition to the cluster Cox model presented in the CS, we have explored several hierarchical random effects models.

Hierarchical random effects models were fitted under different distributional assumptions for the time-to-event data, including Cox (semi-parametric) and fully parametric models based on the Exponential, Weibull and Log-Normal probability density functions. Each model incorporated group-level (random) effects to account for clustering and unobserved heterogeneity within and between participants. While the Cox and Exponential hierarchical models exhibited acceptable convergence and model diagnostic behaviour, the Weibull and Log-Normal models exhibited clear divergence issues in the Markov chain Monte Carlo simulations – especially the Log-Normal model. These issues were not ameliorated by re-parameterisation or applying informative priors. An attempt was made to also explore the application of spline models, but data sparsity led to poor model performance and nonsensical results.

While Watanabe-Akaike Information Criterion (WAIC) and Leave-One-Out Cross-Validation (LOO-CV) indicated preference for the Weibull model over the Exponential and Cox, KalVista determined that the comparative convergence stability of these

models provided a stronger signal for internal model validity. We do not provide a full statistical report due to time constraints. Therefore, for technical details and replicable analyses, please see the submitted data on file “KalVista 2025_DoF_Updated TTA-TTAR analysis”.(17)

In general, the hierarchical random effects models affirmed consistency in the patterns of association between the response and explanatory variables observed in the original CS cluster Cox model. Thus, all models indicated that longer TTA leads to delayed TTAR, which aligns with the relationships reported in literature.

KalVista reiterate the strength of the original CS cluster Cox model. Its ability to accommodate variable baseline hazards, produce very similar signals to more complex models, while enabling easier interpretation and greater transparency without increasing model complexity, is desirable.

Given the above, we have updated functionality in the CEM to include the hazards between TTA and TTAR predicted by the Cox, Exponential, and Weibull hierarchical random effects models. This is provided in the updated CEM model with the filename “ID6284 Sebetralstat KalVista_CEM_Clarification_10.7.25 [CON]”.

Please note that in response to Clarification question B23, we have also provided functionality to include pre- and post-COVID lifetables.

Background and rationale for current model

As highlighted during the clarification call on 26 June 2025, early scientific advice was sought for sebetralstat during which the challenges of heterogeneity between on-demand HAE treatment clinical trials was thoroughly discussed.

Pages 69–71 and 110–111 of the CS describe the comparative effectiveness challenges for on-demand HAE treatments due to the heterogeneity in trial designs and outcomes. Key points include:

- Design of the sebetralstat KONFIDENT phase 3 study had evolved to reflect the considerable recent changes in treatment guidelines and real-world clinical practice (including eligible population, timing of treatment administration, efficacy endpoints).

- Previous on-demand treatments undertaken in the early 2000s were generally limited to individuals with moderate-to-severe attacks.(18-23)
- All currently approved on-demand treatments were originally studied using HCP administration. The pivotal trials required patients to report to healthcare professionals within 4 to 12 hours of attack onset or of attacks becoming moderate to severe in intensity.
- KONFIDENT captured time to treatment administration but this was not an outcome captured in comparator trials (FAST-3 was the only comparator trial to report time to treatment).(24)
- Results of a systematic review of 13 on-demand treatment trials revealed the use of 72 different standardised efficacy outcome terms, none of which was reported consistently across all trials. There are no standard patient-reported outcome measures for HAE attacks in clinical trials. Early trial patient-reported outcomes lacked granularity,(25) icatibant trials captured treatment response using VAS scores,(18, 24) rhC1INH trial used TEQ (treatment effect questionnaire),(6) sebetralstat's KONFIDENT study and the ongoing RAPIDe-3 trial of investigational deucrictibant used PGI-C and PGI-S to capture treatment response.(3, 26)

- As summarised in CS page 70, previous attempts at indirect comparison of on-demand treatments have included Bork et al. (2016) for laryngeal attacks and Helbert et al. (2012).(27, 28)

In summary, due to differences in attack characteristics (e.g. location and severity), timing of treatment administration (early vs. within 4–12 hours of attack onset/moderate to severe intensity), and efficacy evaluations, cross-trial comparisons of the different approved/investigational on-demand treatments have not been feasible to date.

Despite the limited comparative evidence for TTAR (the model's outcome of interest), there is, nevertheless, clear evidence that earlier on-demand treatment administration is associated with a shorter total attack duration.(29, 30). Please also

see section 3.3 of the CS for further studies discussing the observed relationship between earlier TTA and faster TTAR. It is important to emphasise that WAO/EAACI clinical guidelines explicitly recommend treating attacks as early as possible as current clinical evidence strongly indicates that delayed TTA results in delayed TTAR.(29)

B15. On page 102 of the CS, it is mentioned that of the modelled cohort, 45% of patients are on a combination of long-term prophylaxis and on-demand (LTP + OD) treatment; 55% are on on-demand only (OD only) treatment.

> **a) Please explain whether this is assumed for all treatments included in the model (i.e., both sebetralstat and the comparators) and therefore whether it has an impact on the incremental results. It was noted that increasing the percentage of patients using the combination of LTP+OD treatment improves the incremental cost-effectiveness ratio (ICER) of sebetralstat versus SoC. Please provide a detailed explanation for this outcome.**

Company response: This is assumed for all treatments in the model. However, this variable has an impact on the cost-effectiveness results: the total average cost per attack is inflated by the proportion of patients using additional doses and rescue therapy.

> **b) In addition, please clarify whether treatment effect on acute attacks is dependent on patients being on prophylaxis treatment or not.**

Company response: Patients taking LTP in addition to on-demand (LTP+OD) experience less attacks overall than patients who do not receive LTP (i.e. OD only) since it is the objective of LTP to reduce the number of attacks that patients experience. In the KONFIDENT study, around 78% of on-demand only patients experienced HAE attacks compared with around 19% of LTP+OD patients.(7)

Importantly, when it comes to sebetralstat's treatment effect, there is no link between a patient's LTP treatment approach status and the overall treatment effect of

sebetralstat. As reported in Riedl et al. (2024), the efficacy results with sebetralstat were consistent across the LTP+OD and OD only treatment approach subgroups (Table 4).(7)

Table 4: Median time to primary and key secondary endpoints by participant haracteristics (by diagnosis and by treatment approach)

Group	End Point	Sebetralstat 300 mg		Sebetralstat 600 mg		Placebo	
		Attacks, no. (%)	Median, h (IQR)	Attacks, no. (%)	Median, h (IQR)	Attacks, no. (%)	Median, h (IQR)
All attacks	Time to beginning of symptom relief within 12 hours	87 (100%)	1.61 (0.78-7.04)	93 (100%)	1.79 (1.02-3.79)	84 (100%)	6.72 (1.34->12)
	Time to reduction in severity within 12 hours		9.27 (1.53->12)		7.75 (2.19->12)		>12 (6.23->12)
	Time to complete attack resolution within 24 hours		>24 (8.58->24)		24.00 (7.54->24)		>24 (22.78->24)
By diagnosis							
HAE Type 1	Time to beginning of symptom relief within 12 hours	79 (91%)	1.70 (0.79-6.54)	87 (94%)	1.77 (0.98-3.40)	79 (94%)	5.90 (1.33->12)
	Time to reduction in severity within 12 hours		9.32 (1.53->12)		6.53 (2.19->12)		>12 (5.57->12)
	Time to complete attack resolution within 24 hours		>24 (7.52->24)		21.46 (7.29->24)		>24 (22.78->24)
HAE Type 2	Time to beginning of symptom relief within 12 hours	8 (9%)	1.28 (0.78->12)	6 (6%)	2.80 (1.49->12)	5 (6%)	>12 (>12->12)
	Time to reduction in severity within 12 hours		4.76 (1.33->12)		>12.00 (2.23->12)		>12 (>12->12)
	Time to complete attack resolution within 24 hours		24.00 (13.33->24)		>24 (7.69->24)		>24 (>24->24)
By treatment approach							
On-demand only	Time to beginning of symptom relief within 12 hours	68 (78%)	1.35 (0.78-6.54)	72 (77%)	1.77 (1.02-3.79)	66 (79%)	>12 (1.32->12)
	Time to reduction in severity within 12 hours		8.45 (1.35->12)		8.15 (2.10->12)		>12 (6.81->12)
	Time to complete attack resolution within 24 hours		>24 (5.60->24)		>24 (7.54->24)		>24 (>24->24)
On-demand + LTP	Time to beginning of symptom relief within 12 hours	19 (22%)	1.85 (0.79-10.12)	21 (23%)	2.03 (0.78-3.89)	18 (21%)	4.71 (2.28->12)
	Time to reduction in severity within 12 hours		9.27 (1.79->12)		5.53 (2.27->12)		>12.00 (5.57->12)
	Time to complete attack resolution within 24 hours		17.05 (10.55->24)		19.24 (5.28->24)		16.49 (7.46->24)

Source: Riedl et al. (2024) supplementary appendix, Table S6.(7)

B16. On page 102, it is also reported that "the distribution of different treatment strategies is specified in the model to calculate an average cohort attack rate", when describing the 45% of patients assumed to be on LTP+OD treatment and the 55% of patients assumed to be on OD-only treatment. Based on this, it is mentioned that the cohort average attack rate per year was calculated at 14.7.

a) Please provide a detailed description of the calculations used to estimate the cohort average attack rate based on the LTP+OD and OD-only patient populations. Please also explain if the input describing the average attack rate per year has been included in the deterministic sensitivity analyses (DSA) and PSA. Finally, please describe where this input can be adjusted in the electronic model.

Company response: The average cohort attack rate is calculated based on a weighted average. This is based on the expected attack rates of OD only and LTP + OD treatments and the respective proportion of patients on each treatment strategy.

For example:

$$Average\ Attack\ rate\ =\ 11\ \times 45\%\ +\ 17.74\ \times 55\%\ =\ 14.71$$

Please see Settings!G58:G61 in the model to adjust these respective inputs. The user can also simply adjust the average cohort attack rate in cell Settings!G62. Lastly, the input of the average cohort attack rate is included in the PSA and DSA.

b) Furthermore, in the PBAC study there were 5.49 treated attacks per patient per year as reported in Table 24. This means that the attack rate in the electronic model is about 3 times higher (14.7 vs 5.49). Please comment on the differences in the attack rate used in this submission compared to the PBAC study and comment on the validity of these inputs.

Company response: Given the limited reporting of the PBAC study, we are unable to comment reliably on the observed differences. However, differences may be due to variation in the attack rate between and within each patient, thus resulting in large differences observed across different populations and periods of longitudinal data. There may also be variations due to differences in the proportion of patients on LTP in Australia versus England, since patients on LTP are expected to have a lower attack frequency. Nevertheless, the model can incorporate scenarios analyses with varying attack rates.

c) Figure 13 distinguishes between HAE attacks and treated HAE attacks. Please clarify if in the HE model 14.7 refers to treated attacks only (as mentioned in page 109 of the CS). Please explain what is the reason to provide a distinction between treated and untreated attacks in Figure 13. Please also explain the reason that the percentage of treated

and untreated attacks per treatment are included in the HE model if in the end those are not used.

Company response: The submitted base case model only refers to treated attacks. This is because WAO guidelines stipulate that all HAE attacks must be treated. Thus, CS Figure 13 represents the pathways applied in CS base case for England. The functionality to include treated vs. non-treated attacks was incorporated during the conceptual modelling phase solely to ensure model flexibility.

d) As the HE model employs a lifetime time horizon, the attack rate per patient per year is assumed to be stable over patients' lifetime. Please comment on the validity of this assumption.

Company response: The model is a cohort Markov model, representing the expected outcomes of the average HAE patient. During the conceptual modelling phase, clinicians highlighted significant uncertainty in determining whether a patient's attack rate will increase or decrease over time. Therefore, the choice to apply a stable attack rate was driven by the trade-off of increasing model complexity without reliable improvements in predictive accuracy. Nevertheless, the average attack rate is incorporated in both the PSA and DSA. KalVista consider that the PSA adequately captures this uncertainty.

e) Related to the previous sub-question: On page 113 it is mentioned that "There is limited evidence demonstrating predictable changes in HAE attack rates over time, based on, for example, a patient's age or other characteristics. Since OD treatments do not impact long-term attack rates, this assumption is reasonable", when referring to the "homogenous over time" cohort attack rate. However, the patient population in the HE model does not only receive OD therapy because 45% of the patient population is assumed to receive LTP+OD therapy. Would the assumption on constant attack rate be reasonable then? Please explain how LTP therapy influences the attack rate over time. Please also comment on the uncertainty of this parameter. Specifically,

how is the percentage of patients using LTP treatment changing over time in the UK? Is LTP expected to be used more often? Please run scenario analyses to assess the robustness of the model to changes on this assumption.

Company response: The model assumes a constant distribution, and thus the effect of LTP on attack frequency is fixed. KalVista acknowledge the limitations of this approach. However please note that the future treatment landscape and future efficacy of LTP treatment is unknown. Most treatments are appraised in HTA based on the current treatment landscape, modelled using a fixed market over a lifetime horizon. Extrapolating uptake or changes in LTP efficacy over an extended period is highly uncertain. Moreover, increases in LTP uptake have been relatively constant, fluctuating between [redacted] units per year since late 2023 (see Figure 1).

Figure 1: Units of LTP treatments dispensed over time

Source: KalVista data on file (HAE UK monthly market data)

Nonetheless, we provide cost-effectiveness results from two scenarios: 1) using attack rate between for LTP + OD (11 per year) as the average cohort attack rate and 2) using the attack rate reported in the PBAC study (5.49 per year). Since the cost of treatment is estimated per attack, reductions in the attack rate impact cost-effectiveness. Please see Table 5 and Table 6.

Please note that a new PAS price of [redacted] per tablet of sebetralstat was submitted to PASLU during NICE clarification. All the cost-effectiveness results in this response document reflect the newly submitted PAS price.

Table 5: Cost-effectiveness results using the LTP + OD attack rate of 11 per year

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	Net Monetary Benefit @£30k WTP
Sebetralstat	[redacted]	22.01	18.40	-	-	-	-
SoC	£404,516	22.01	18.29	[redacted]	0.10	[redacted]	[redacted]

Table 6: Cost-effectiveness results using the PBAC study attack rate of 5.49 per year

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	Net Monetary Benefit @£30k WTP
Sebetralstat	[redacted]	22.01	18.47	-	-	-	-
SoC	£201,890	22.01	18.38	[redacted]	0.09	[redacted]	[redacted]

B17. Priority question: The HE model assumes that different time to treatment administration (TTA) between OD treatments lead to different response in TTAR. Please justify why data from Christian et al. 2024 (a patient survey) were used to inform the TTA inputs for all intravenous (IV) OD treatments. The economic analysis assumed ~3.8 hours (or: 228 minutes) for receiving subcutaneous (SC)/IV OD treatments, based on data from Christian et al. 2024 (reference 69 in the CS). Please explain what is meant by this being a conservative assumption (page 114 of the CS). Furthermore, Christian et al. 2024 shows that patients had a mean of ~1.6 hours for receiving SC/IV OD treatments, when the attack was affecting the face, which is less than half of the TTA used in the analysis. Considering that attacks in neck and above are usually more severe, followed by abdominal attacks, would it be expected that

the time to OD treatment administration would vary according to the location of the attack? Please provide alternative scenario analyses that allow for different TTA based on attack location and severity.

Company response: Data from Christian et al. (2024) are likely a conservative assumption because it includes the TTA of patients prescribed icatibant. Icatibant is generally, on average, administered faster than IV treatments.

The Cox model controls for attack location and severity and these covariates are included in the function applied in the economic model as they are expected to meaningfully influence the marginal effect of TTA on TTAR. Please see section 3.3 of the CS for a detailed discussion. Please see our responses to Questions B18.c and B18.e for further discussion on the impact of location on the expected TTAR. While the impact of TTA may not vary by location, the marginal effect of TTA on TTAR is adjusted for differences in location.

B18. Priority question: Please answer the following questions regarding the Cox regression model (Table 28).

a) Please provide justification for the proportional hazards (PH) assumption.

Company response: The assumption for proportional hazards (PH) was tested via standard visual inspection of residuals and statistical tests. A formal test for the proportional hazards (the Grambsch and Therneau test) indicates moderate concerns for violating the assumption. Please see Table 7.

Table 7: Proportional hazards test

Covariate	Chi-Square Test	Degrees of freedom	p-value
Treatment sequence	[redacted]	[redacted]	[redacted]
Baseline attack severity	[redacted]	[redacted]	[redacted]
Attack location	[redacted]	[redacted]	[redacted]
Time to administration	[redacted]	[redacted]	[redacted]

Global	[redacted]	[redacted]	[redacted]

However, deviation is likely attributable to the limited sample size and sparsity in certain strata, especially the categorical variables, thus reducing test reliability. Visual inspection of the PH test for the ttdose_h covariate suggests that violation of PH is negligible. Schoenfeld plots (see Figure 2) do not reveal consistent trends over time, particularly in the case of ttdose_h, which is the primary covariate effect of interest. Moreover, delta-beta residuals do not indicate any influential observations (see Figure 3).

Importantly, the concordance statistic (C = 0.639) and D statistic (~0.96) indicated reliable discrimination, suggesting the model captures a meaningful and consistent relationship between the included covariates and the hazard.

Figure 2: Cox model Schoenfeld residuals

Figure 3: Cox model delta-beta residuals

b) Please discuss the goodness of fit of the Cox regression model.

Company response: Please see our response to Question B18.a.

c) Please explain how to interpret the coefficient of “Neck and Above” in Table 28.

Company response: The 'Neck and Above' location covariate indicates that time to attack resolution is reduced relative to attacks occurring at the location 'Other'. More precisely, it is the controlled effect of an attack occurring in the 'Neck and Above' area relative to the 'Other' location, when treatment sequence, attack number, and baseline attack severity are held fixed at a given level. However, KalVista would like to emphasise that this coefficient should not be interpreted casually – its aim is to isolate the effect of time to administration by accounting for location-based differences.

d) Please present the results of the random effects (RE) Cox model as well, and allow the HE model to include both fixed effects (FE) and RE estimates for the base-case and PSA.

Company response: Please see Table 8 below, tabulating the results of the RE Cox model. Given the results below, and as stated in the original CS, there is no predictive gain from using a RE model. Please see data submitted as on file in the CS, 5. KalVista 2025_Data on file_Cox model.

Table 8: Cox model RE results

Explanatory Variable	ln(HR)	95% CI	SE	p-value
Treatment Sequence (ref. group 6)				
6	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
HAE Attack Number (ref. group 3)				
3	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Attack Severity (ref. group None or Mild)				
None or Mild	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe or Very Severe	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Attack Location (ref. group Other)				
Other	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal	[redacted]	[redacted]	[redacted]	[redacted]
Neck and Above	[redacted]	[redacted]	[redacted]	[redacted]
Time to Administration (TTA)	[redacted]	[redacted]		[redacted]
Subject (frailty)	[redacted]	[redacted]	[redacted]	[redacted]

e) Please provide justification for covariates included in the Cox model, with explicit definitions of them (e.g., treatment sequence). If the only predictor for TTAR is effectively TTA, please clarify why all the other covariates are included in the equation. Please discuss the role of severity and location since these have been assumed to be mutually exclusive in the HE model. Please explain if it would be more consistent to have two separated Cox models, one based on location and one on severity?

Company response: The covariates treatment sequence (TRTSEQPN) and attack number (HAEATTN) were included in the Cox model to ensure adequate control for potential bias from treatment sequence and attack position. In other words, the aim is to helps isolate the true effect of treatment from the effect of sequence position and attack number. KalVista note that the attack number is not estimable due to data sparsity. As a result, the covariate can be dropped from the model; it was included at submission with the aim of ensuring transparency in our approach.

Baseline attack severity (SEV) and location (CELOCA3) is then included to control for baseline attack severity and location whilst estimating the effect of time to administration (ttdose_h) on time to attack resolution.

In summary, the aim is to estimate the change in hazard associated with earlier administration while holding constant the influence of attack characteristics and trial structure.

f) The model assumes sebetralstat 300 mg only as interventions, therefore please discuss the role of "sequences" in the Cox regression model.

Company response: In the Cox model, data were filtered to only include patients receiving the 300 mg dose. Nevertheless, given, for example, the potential for learning effects, the covariate is included in the model to ensure adequate control for systematic differences across treatment sequences.

g) The Cox model includes the number of attacks as a covariate. However, the coefficients of this covariate are reported to be not estimated (NE) in Table 28. Please explain the reason behind this output (i.e., is it related to the variation of the levels, model convergence or another issue?) Also, please explain why this was included as covariate in the Cox model since number of attacks is not included in the HE model.

Company response: Please see our response to B18.e. The attack number is not estimable due to data sparsity, where some combinations of categories have very few or no observations when filtered according to attack number. Please see the motivation to include this covariate in B18.e.

h) Please provide alternative predictions of fixed and random effects models that address the issues described above.

Company response: Due to time constraints and, most importantly, because there are no differences between results of the clustered and RE models, KalVista will not provide the functionality to include the RE model in the economic model.

i) Furthermore, it is stated that the formula $exp(-\beta_k)$ is used to estimate the hazard ratio from the Cox model outcomes. Please explain why this is not $exp(\beta_k)$, so for the TTA variable this should be [redacted] instead of [redacted]. Please also explain what the value of [redacted] represents in the example of TTAR estimation on page 118 of the CS. Is it the average time of treatment administration in the specific area of attacks (Neck and above)?

Company response: $exp(-\beta_k)$ is equivalent to $\underline{exp(-1 \times -[redacted]) = exp(\beta_k)}$. We apply the reciprocal of the hazard ratio to estimate the appropriate outcome. Using the direct hazard output of [redacted] is interpreted as: for each 1-hour increase in TTA, the hazard of resolution decreases by ≈ [redacted]%, i.e. resolution becomes slower. However, in the economic model, we want to estimate by how much TTA delays

TTAR. Thus, using the reciprocal, we interpret the result as: for each 1-unit less of TTA increases the hazard of resolution by ~[redacted]%.

The value of [redacted] is the mean TTA of the data used to inform the Cox model. This is used to standardise the TTA across treatments, i.e. to centre the expected TTA in the economic model function. Thus, this value is applied to all locations and severities.

j) Please explain how the formula's for TTAR_adjusted on pages 117 and 118 of the CS were derived. Why is it not based on all the covariates used in the Cox model? Should these not be aligned?

Company response: The function was derived by applying a standard additive linear function to estimate TTAR based on the relevant covariates. Baseline severity and location were included in the linear predictor as these covariates are clinically relevant to adjustments in the expected TTAR given a specific TTA. Covariates like treatment sequence and attack number were included in the Cox model to ensure adequate control to estimate the marginal effect of TTA on TTAR.

k) Please clarify how the baseline TTAR was estimated.

Company response: Baseline TTAR was estimated using the mean time-to-event from the data applied in the Cox model. This is assumed to represent the baseline efficacy, prior to additive effects from TTA.

l) To adjust TTAR per location, please clarify if the equation should use 1 or 0 to calculate the TTAR per location, and then use the percentage to calculate the average TTAR across all locations?

Company response: Yes, the equation should use an indicator variable for each TTAR per location, and then use the percentage to calculate the average across all locations.

m) Please provide a full report based on the R code used to conduct the Cox regression analysis. This could be presented for example in the form of an R-Markdown file, but please also include an associated Word or pdf file in case the EAG is unable to run the R code.

Company response: These items were submitted as data on file in the original CS reference pack. Please see 5. KalVista 2025_Data on file_Cox model.

B19. Priority question: The model assumes that "the proportion of attacks requiring additional dosing per cycle is fixed and does not change over time, but it is specific to each treatment" (page 120 of the CS). Please comment on the validity of this assumption. Please comment on the impact of this assumption on model outcomes.

Company response: KalVista acknowledge the limitations of this assumption. However, given the limited available data, we reiterate that the uncertainty of this assumption is adequately captured and reflected by the DSA and PSA. KalVista would also like to emphasise that the uncertainty associated with additional dosing and rescue therapy use is not unique to the sebetralstat model.

Regarding the impact on model outcomes, variations in the proportion of attacks requiring additional dosing and rescue therapy will lead to variations in the overall cost of an attack.

B20. Priority question: Table 30 presents additional clinical inputs, including the percentage of patients requiring additional dosage and rescue therapy for each of the alternative OD treatment options. For icatibant, the percentage of patients requiring additional dosage per attack was set at 12.70, referring to Longhurst et al. (2018). However, Longhurst et al. (2018) mention that "C1-INH was used as rescue medication in 12.7% of icatibant-treated attacks (48/378 attacks)". Please confirm if this is a mistake in the report and the HE model and update the model results and report accordingly. Please explain why the

12.7% from Longhurst et al. (2018) is not preferred over the 16.67% from Circadi et al. (2010) as an estimate for icatibant-treated attacks that required rescue medication.

Company response: This is an error caused by misinterpretation of the wording found in Longhurst et al. (2018). Accordingly, we have substituted the data from Cicardi et al. (2010) with Longhurst et al. (2018) as an estimate for icatibant-treated attacks that require rescue medication.

Additionally, we apply data from Aberer et al. (2017) (17) to estimate the proportion of icatibant-treated attacks requiring additional dosing. We have used Aberer at al. (2017) because it clearly distinguishes between attacks requiring additional dosing and attacks requiring rescue therapy.

We use the data reported for LTP + OD (95/973 attacks) and OD only (221/2255 attacks) patients, and apply a weighted average to calculate the expected proportion of patients requiring additional doses as follows:

$$\%\ icatibant\ treated\ attacks\ using\ rescue\ therapy\ = \frac{95}{973} \times \%\ on\ LTP\ and\ OD\ + \frac{221}{2255} \times \%\ on\ OD\ only$$

Please note that all cost-effectiveness results reported in this response document apply these changes to the model. We have also updated the additional dosing and rescue therapy use proportions for sebetralstat, based on an interim analysis of KONFIDENT-S OLE data. The updated input values for sebetralstat, based on the latest datacut, are 22.25% (85/382) of attacks requiring additional dosing and 5.25% (20/382) requiring rescue therapy.(16)

B21. The mean TTA for sebetralstat is sourced from KONFIDENT OLE trial, whereas for icatibant, this was sourced from Longhurst et al. 2018, which is a real-world study. Christian et al. 2024 (a patient survey) are used to inform the TTA inputs for all intravenous OD treatments. Please discuss the possibility that for sebetralstat, given that TTA is measured in a trial setting, TTA is likely to be shorter than in daily practice.

Company response: Thank you for your question. The possibility of TTA being shorter in the KONFIDENT-S OLE study than in daily practice and/or the highlighted comparator studies is as an unlikely possibility.

In the sebetralstat studies, the protocol for sebetralstat required patients to follow multiple procedural steps (including unpacking medication, scanning QR codes, and answering trial-related questionnaires) before administering treatment. The resulting time from onset of the first attack to the first IMP administration was 41 minutes (N=330) (median data point) (Table 9). This trial-specific protocol likely overestimates the TTA that would be seen in routine clinical practice and real-world studies, where such administrative steps are absent.

Supporting this, data from the KONFIDENT-S OLE trial, where patients were more familiar with the medication and procedural burdens were reduced, showed a substantially shorter median time from onset of attack to the first IMP administration of [redacted] (Table 10).

Importantly, the mean TTA from the OLE was used. However, the mean of [redacted] is highly skewed by outliers, while the median data is the better statistical representation of the expected TTA. Therefore, the TTA in the cost-effectiveness model is an overestimate of TTA and was only used because a mean value is the standard input for cohort Markov models.

In summary, we would expect that for real-world practice, the TTA for sebetralstat would likely be much shorter than what has been observed in the trials, as patients would be able to self-administer the oral therapy promptly at attack onset without trial protocol related delays. Furthermore, commercial packaging will be smaller and easier to carry and access than those used in the clinical trial setting; further supporting shorter TTA in real-world practice.

Table 9: KONFIDENT summary of the baseline characteristics of the IMP-treated HAE attacks. Full Analysis Set

	300 mg KVD900 (N=110)	**600 mg KVD900 (N=110)**	**Placebo (N=110)**	**Total (N=330)**
Time from onset of the first attack to the first IMP administration (minutes)				

n	86	93	84	263
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	35.0	41.0	51.0	41.0

Source: KONFIDENT phase 3 CSR report May 2024. KalVista, data on file. Table 14.2.6.1 (18) and Riedl et al. (2024) (3)

Table 10: KONFIDENT-S OLE summary of time to first dose by rollover status. Full Analysis Set

	Rollover Attack=828	**Non Rollover Attack=878**	**Overall Attack=1706**
Time (minutes) from onset of attack to the first IMP administration			
Number of IMP records	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]

Source: KONFIDENT-OLE CSR report. KalVista, data on file. Table A302-4. Data cutoff date: 2024-09-14 (19)

Adverse events

B22. Please clarify which criteria were used to include adverse events (AEs) in the HE model and justify the assumptions for considering (or not) AE-related costs and HRQoL decrements. Please clarify also whether adverse events and side effects are used as synonyms or not. On page 109 of the CS, it is mentioned that utilities and costs related to HAE attacks include side effects/adverse events. However, for side effects, these events are assumed to resolve without additional costs to the NHS. Please explain this assumption. How are AEs assumed to be managed?

Company response: No serious adverse events have been observed across contemporary C1-INH and icatibant OD treatments. The side effects included in the model were based on consultation with clinical experts. For example, all clinicians raised the fact that the majority, if not all, their patients experience the burning associated with icatibant injections – as the histamine-inducing inflammatory response generated by icatibant causes pain, a flare response at the injection site, including erythema (redness). Please see data on file that was provided at submission: 6. [data on file] Sebetralstat KoL Validation Exec Summary_v1.0. The adverse events included in the model are applied to reflect the frequent side effects

experienced by patients on each OD treatment. These events are expected to resolve without additional costs to the NHS as it is assumed that these are managed with over-the-counter medication, such as paracetamol.

Mortality

B23. Please clarify if the risk of mortality derived from UK general population lifetables is pre or post COVID. If post-COVID were used, please include the other option in the HE model.

Company response: The UK general population lifetables applied in the submitted base case model are post-COVID. KalVista will provide the functionality for pre-COVID lifetables alongside other additions to the model in our response to B14.

Health-related Quality of Life

B24. Priority question: Please estimate the appropriate utility per age group using the coefficients and their standard errors of the model estimated by Hernández-Alava et al. 2022

Company response: KalVista will provide an updated age- and gender-adjusted utility distribution using the Hernández-Alava et al. 2022 model in our response to B14.

B25. Please explain how caregiver burden has been implemented in the model (explain also the assumptions, not only the implementation) when this option is selected for the cost-effectiveness analysis.

Company response: The disutility associated with caregiver burden is not included in the CS base case model. However, the disutility of caregiver burden can be included by selecting 'Yes' or 'No' in cell Settings!G96. In addition to this input selection, the user must edit the maximum age of a patient up until caregiver disutility is applied, in cell 'HRQoL Inputs'!E113.

When caregiver disutility is applied in the model, the disutility of caregiver burden is an annual value adjusted to a per cycle period. The values for caregiver burden are dependent upon route of administration. The current scenario available in the model assumes an annual disutility value of -0.02, applied to both SC and IV treatments. It is assumed that the disutility of caregiver burden is driven by route of administration and the burden associated with assisting with a patient's treatment. Therefore, no caregiver disutility is applied to the sebetralstat cohort.

B26. On page 25 of the CS, it is mentioned that for participants receiving subcutaneous treatment, the most common reasons for anxiety were related to concerns about treatment efficacy. Please explain exactly what these efficacy concerns are and whether the same concerns would apply to oral treatments or not. Also, on the same page, it is mentioned that one clinician noted that treatment delay could also be due to patients not wanting to waste their medication supply. Please explain whether the same would apply to oral treatments or not.

Company response: Thank you for your question. The specific efficacy concerns identified for on-demand subcutaneous (SC) treatment as reported by Cancian et al. at the 14th C1-inhibitor Deficiency & Angioedema Workshop (Budapest, June 2025) are:(20)

- Uncertainty about how long the treatment would take to begin (36% of respondents)
- Uncertainty about whether the treatment would work (24% of respondents)
- Worry about a rebound attack after the first treatment (26% of respondents).

These concerns are primarily related to the mode of administration and the logistics involved with SC injections. These specific efficacy concerns are less likely to apply to sebetralstat as an oral on-demand treatments for the following reasons:

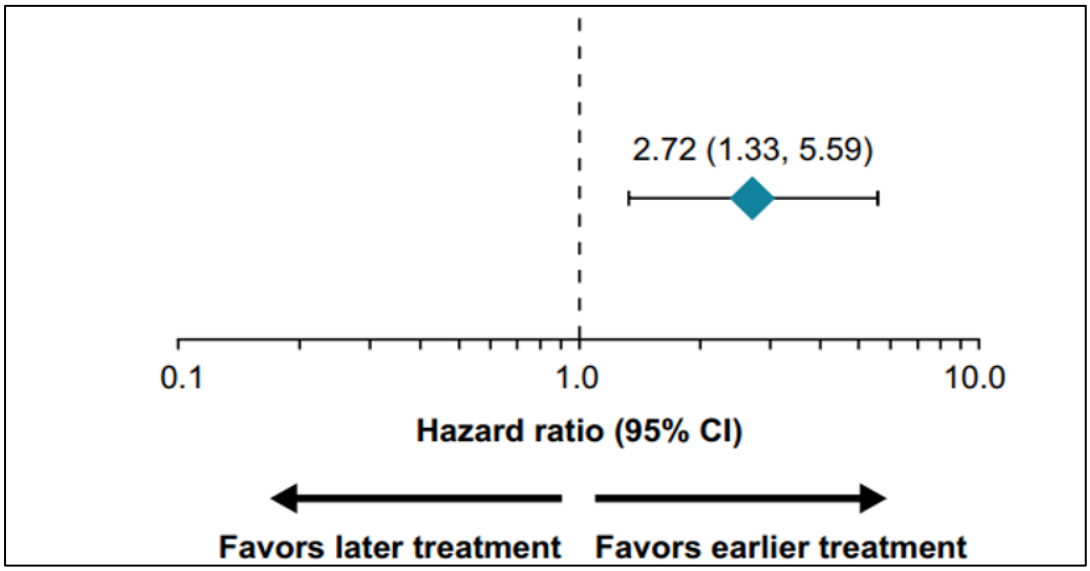
- As an oral on-demand treatment, sebetralstat can be administered immediately at the onset of an attack without the logistical and psychological delays

associated with preparing injections including finding a suitable location, overcoming needle phobia or fear of injection site reactions.(12, 20)

- Sebetralstat's immediacy of treatment administration can reduce uncertainty about onset of action and improve patient confidence in timely symptom control.

Supporting this, an analysis of the KONFIDENT phase 3 trial on correlation of the time to treatment with attack duration showed the probability for shorter attack duration was higher when attacks were treated earlier versus later in KONFIDENT (see CS Figure 7). Thus, attacks that were treated earlier were more likely to be mild than attacks treated later.

[CS Figure 7] Probability for faster complete attack resolution



H, hours; HR, Hazard ratio; IQR, interquartile range.
Source: Craig *et al.* 2024 (21)

For SC on-demand treatment delays, the submission also states "*one clinician also noted that treatment delay could also be due to patients not wanting to waste their medication supply*".

The concern about patients delaying treatment to avoid wasting medication reflects an outdated mindset that was more prevalent in the UK a decade ago, it was raised by one clinical expert during submission development as a past issue that has been overturned by better patient education. Importantly, the most recent international HAE guidelines (Maurer et al. (2022) WAO/EAACI)(22) strongly recommend treating attacks as soon as they are clearly recognised, regardless of their location or severity. The guidance states "*early treatment is associated with a shorter time to resolution of*

symptoms and shorter total attack duration regardless of attack severity". This guidance supports immediate treatment and reinforces that delaying therapy (whether due to concerns about medication wastage or other factors) is not in line with recommended clinical practice.

We note that in the UK (unlike some other markets), there are no restrictions to patients on access to HAE medication such as quantity limits on supply, so this is not expected to be a current barrier to medication usage by patients.

B27. On page 109 of the CS, it is mentioned that in the base-case analysis, attack location categories are preferred to severity categories mostly because severity is strongly influenced by subjective responses to the circumstance of the attack, duration of attack, previous experiences of attacks, anxiety, and the experienced functional deficit. Attack location is therefore a more reliable and consistent indicator for the impact of an attack on patient HRQoL. This assumption was supported by expert clinical opinion. Please clarify where the opinion of the clinical expert can be found.

Company response: The source of this expert opinion is from discussions during model validation with clinicians, during conceptual modelling. Please see details on slide 9 of the submitted data on file that was provided at submission: 6. [data on file] Sebetralstat KoL Validation Exec Summary_v1.0.

B28. On page 126 of the CS, it is reported that the preference utility between subcutaneous and oral treatment is not applied in the model base case, due to non-significant differences from the discrete choice elicitation (DCE) data, which is supported by clinical expert opinion. Please clarify where the opinion of the clinical expert can be found. Please explain if that means that oral OD treatments would lead to a similar HRQoL as SC OD treatments for patients with HAE.

Company response: The decision to not apply the non-significant subcutaneous (SC) utility value for SC treatment was based on feedback from the methods experts who conducted the commissioned DCE studies considering two key factors:

1. Handling of non-significant treatment-related utility values in a recent NICE technology appraisal of atogepant for preventing migraine (TA973) where the ERG removed a disutility for monthly SC injection (compared to oral medicine) due to non-significance in the supporting study.

2. Qualitative evidence from patients during the qualitative development phase suggesting a benefit of oral administration: during the qualitative interview phase of the commissioned DCE study, patients described the HRQoL impacts injectable treatments had on their life.(23, 24) Interviews were conducted with 17 patients (11 US, 6 UK) using a semi-structured interview guide. All patients reported at least one HRQoL impact associated with their current injectable OD treatment. This included psychological impacts such as anxiety due to self-administration (n=6), limitations to daily or leisure activities (n=10) or work/education (n=7) due to the disruption caused by administering treatments (e.g. having to return home or go to the hospital to take their treatment) and impacts of relationships with others (n=5).

KalVista would like to clarify that the DCE utility results still indicate that HRQoL between SC and oral on-demand treatments is expected to differ for patients due to injection-related side effects (e.g. injection site reactions, painful or stinging sensations when medication is administered). Qualitative feedback from patients during the development phase of the study indicated that while fear or dislike of needles was a factor for some, fear and dislike of the pain or discomfort associated with injection was more commonly reported as impacting HRQoL particularly due to anxiety.

In a roundtable discussion with three UK clinical experts to discuss the face validity of the DCE findings, the clinical experts indicated the non-significant SC utility value was unexpected based on their discussions with patients. Clinical experts believed there is a HRQoL burden associated with SC on-demand treatments which was most present at the time of attacks but also present day-to-day between attacks. Clinicians

highlighted there was a mismatch between DCE patient participants not associating SC administration with a significant disutility but believing there is a disutility associated with injection-related side effects which may be caused by familiarity with injectable treatments compared to an oral treatment which would be hypothetical to almost all of the participants at the time of the DCE study.

Additionally, the rescaled utility values using the VAS approach also indicate that patients have a significant preference for oral administration over SC administration. However, these impacts on HRQoL and preference to avoid SC administration did not appear to translate into a significant utility value under the QALY framework, once administration-related side effects were accounted for.

Finally, the notions of patient-reported preferences for, and HRQoL benefits of oral compared to SC administration are well supported by the literature across multiple disease or therapeutic areas including migraine,(25) inflammatory bowel disease,(26) diabetes(27) and cancer.(28)

B29. The cost-effectiveness (CE) analysis accounts for utility decrements for OD treatments that are administered via self-infusion into the vein or HCP-administered infusion into the vein, which were estimated from a commissioned DCE study (values reported in Table 31 of the CS). Please comment on how these values compare to utility decrements for other treatments administered via HCP or via self-administration.

Company response: Based on our best knowledge, we are not aware of any published studies which directly compare self-administered versus HCP-administered IV administration. However, published evidence relating to the following topics support the finding that patients associate HCP-administered IV infusion with a greater utility decrement than self-administered IV infusion:

- Preference for home-based care compared to hospital-based care: Patient preferences for home-based care versus hospital care have been documented in a variety of conditions.(29-31) In a systematic review investigating long-term injectable biologic therapies in multiple disease areas

(irritable bowel disease, rheumatoid arthritis, psoriasis), a statistically significant difference between patients preferring administering SC at home vs. IV infusions in a hospital inpatient or outpatient setting was observed.(31) This burden has also been quantified using utility values, for example a TTO study with the general population found SC injections at home were associated with a small utility gain compared to the SC injections at a hospital (0.011).(32) Additionally, a survey study of 59 HAE patients also found self-administration at home associated with increased patient satisfaction and treatment adherence.(33)

- Preference for SC injection or oral administration compared to IV infusion: Several utility studies across disease areas have demonstrated that IV administration is associated with a greater utility decrement compared to SC and/or oral administration, suggesting it is less preferred.(32, 34) In the context of HAE, the NICE evaluation of lanadelumab (TA606) for prophylactic treatment of HAE utilised evidence from a TTO study with the general public (relating to biologic administration) to demonstrate the utility gains of switching from IV to SC treatment. This study estimated a utility gain of 0.024 (based on the difference between two utility estimates: oral treatment versus SC injection (0.0151) and oral versus IV infusion (0.0304)).(32)

- Feasibility of self-administered IV for OD treatment of HAE attacks: In HAE, studies have demonstrated that home-based infusion is a feasible and often preferred option for patients compared to hospital-based treatment, which led to improved outcomes and HRQoL as a result.(35-37) These studies support the findings from the commissioned DCE study where HCP-administered IV infusion had a greater utility decrement than a self-administered alternative. Further, patient-reported barriers associated with infused treatments more broadly support the finding that an oral alternative would lead to additional HRQoL gains.(38, 39)

B30. As shown in Table 31 of the CS, the analysis accounts for utility decrements of the side effects of SC/IV OD treatments that are estimated from

the DCE study. As the side effects for the OD treatments of patients with HAE are similar to the side effects reported for other SC/IV treatments (i.e. skin reaction to injection, painful burning or stinging sensation when medication is administered, headaches, diarrhoea, nausea and/or indigestion), please comment on how values estimated from the company commissioned DCE study compare to the values from other sources that have been used for other SC/IV treatments (in other disease areas).

Company response: Please see Table 11 below which summarises some utility decrements from some broadly comparable conditions based on frequency and duration of expected side effects. Utility values from the commissioned DCE study are consistent with published values in finding a significant disutility associated with side effects which is distinct from the mode of administration itself. The magnitude of estimates is also broadly comparable to those published in other disease areas.

Summary of findings:

- Injection site reactions: Table 11 shows published utility values ranging from 0.011 (daily injections, Type 2 diabetes) – 0.02 (monthly injections, migraines). These values are comparable to the commissioned DCE study, with overlapping confidence intervals (Utility decrement from commissioned DCE: 0.021, 95% CI: 0.03 – 0.011).

- Headaches, diarrhoea, nausea and/or indigestion: There is a substantial body of literature estimating utility decrements associated with headaches and GI symptoms caused by chemotherapy and other cancer treatments.(40) We have not listed these due to differences in the duration and frequency of side effects compared to HAE on-demand treatments. Utility decrements from non-cancer studies such as Type 2 diabetes (0.03-0.04) are slightly lower than the estimate from the commissioned DCE (average: 0.062, 95% CI: 0.049-0.076), however, published studies typically focus on a single side effect (e.g. GI impacts) whereas the value in this study combines multiple side effects (i.e. multiple GI symptoms and headaches) which may contribute to the larger utility estimate observed in the commissioned DCE.

- We are unaware of any published studies estimating the utility decrement associated with burning and stinging of medication. However, this is a frequently reported, distinct and undesirable feature of icatibant.(41) Additionally the qualitative stage of the commissioned DCE study indicated many patients find this sensation to be more detrimental to their HRQoL than injection-site reactions, indicating that the larger utility decrement estimated in this study has face validity.(23, 24)

Table 11: Summary of adverse event utility decrements from published studies

Reference	Disease area	Overall study description	Side effect utility decrement
Boye et al. (2011) (27)	Type 2 Diabetes	Sample: 151 Patients with type 2 diabetes Country: Scotland Method: Standard gamble (SG) interviews to assess the utility of hypothetical health states and their own current health state. Utility decrements were estimated by calculating the difference between health state with and without injection site reactions.	Injection site reactions: 0.011
Okkels et al. (2024) (42)	Haemophilia	Sample: 812 members of general public Method: time-trade off (TTO) describing haemophilia treatment administration. Adverse events could either be described as: *"The treatment causes injection site reactions which do not require medical intervention", "The treatment causes no injection site reactions"* Frequency of administration: monthly	Injection site reactions: 0.013 (95% CI: 0.005; 0.021)
Matza et al. (2019) (43)	Migraine	Sample: 200 general population, 200 patients with migraine County: UK Method: TTO with vignettes describing different potential treatments	Injection site reactions ("injection site pain"): 0.01 (general population sample), 0.02 (patient sample)

		Frequency of administration: monthly	
Matza, et al. 2007 (44)	Type 2 diabetes	Sample: 129 patients with type 2 diabetes County: England and Scotland SG to assess utility of hypothetical health states and their own current health state	GI symptoms: 0.04 ($p < 0.001$)
Rajan et al, 2016. (45)	Type 2 diabetes	Sample: 59 general population Countries: South Korea and Taiwan Method: SG with vignettes with different combinations of frequency of administration (weekly, daily), weight gain (none, 3%, 5%), nausea/vomiting ("*You sometimes experience nausea/vomiting", "You do not experience nausea/vomiting"*)	GI symptoms (nausea/vomiting): 0.034 (average increment across all health states with, vs. without, nausea/vomiting)

B31. Please explain why Lo *et al. (*2022) considered an attack-free health state with lower value than the general population utility and for this submission the UK general population health state utilities were applied to all patients. Please conduct a scenario analysis where the Lo et al. utilities are used.

Company response: As an interim sense check, we have applied this change to the sebetralstat and icatibant traces. As expected, since it is a relative change across both cohorts, the ICER remains constant. This is because no OD treatment reduces attack frequency. Hence, any change to the overall HRQoL prior to adjustment for disutilities results in a constant, relative difference in the net utility per cycle. We hope this assessment provides some clarity on this aspect, however, KalVista can provide the results of this scenario if it is still required.

B32. On page 126 of the CS, it is mentioned that the preference utility between subcutaneous and oral treatment is not applied in the model base case. This is because the result was not statistically significant, and the 95% confidence interval included a null difference. This decision was based on expert recommendation. Significance, however, was not a deciding factor in the Cox regression model above for TTAR. Please explain why here it is considered. Also, please provide details of expert recommendation.

Company response: Further details about the DCE study is provided in our responses to clarification questions B28-B30 including overview details of expert validation sought.

Importantly the significance you highlight was not a driver for variable selection in the Cox model because the aim of the model is to ensure clinical significance and controlling for different variable effects.

The utility model, however, is applied within a different context, and its validity was assessed based on different criteria. Please see the “4. KalVista [Data on file] HAE Utilities. 2025” source, submitted as data on file in the CS for further details on the DCE study.

Resource use and costs

B33. Page 109 of the CS mentions that events related to side effects are assumed to resolve without additional costs to the NHS. Please comment on the validity of this assumption.

Company response: Please see our response to B22.

B34. On page 128 of the CS, it is mentioned that “to account for drug wastage, the model applies a ceiling function to the weight-based dose, which rounds the dose to the nearest multiple of 0.2”. Please explain in detail how this is implemented (perhaps also by providing an example) and the reasoning behind this approach.

Company response: As stated in the CS, to account for drug wastage, the model applies a ceiling function to the weight-based dose. To illustrate, Ruconest requires a dosage of 50 IU/kg, up to a maximum dosage of 4200 IU. The standard pack size of Ruconest is 2100 IU. Assuming a patient weight of 77.86 kg, the expected dose is calculated as $(77.86 \times 50)/2100 \approx 1390$ units. The ceiling function rounds the dose to the nearest multiple of 0.2. Using the same Ruconest example, the expected dose for Ruconest is hence rounded to 1500 IU.

It is important to clarify that the ceiling function rounds the amount of packs used per dose, not the cost, to the nearest multiple of 0.2. For example, from the Ruconest example, patients at a given age may use 1.6 packs per attack. When the ceiling function is applied, patients use 1.8 packs. This is more precise than using a rounding function, which is typically applied in a way that would estimate, for this example, 2 packs per attack.

B35. Priority question. The cost of rescue therapy has been set at £1,403. Please explain in detail how this cost has been estimated and where can this input be found in the electronic model. Please run alternative scenario analysis to indicate the impact of this parameter on model outcomes.

Company response: The cost of rescue therapy has not been set at £1,403. The cost of rescue therapy varies over time if weight-based dosing treatments are included in the basket of rescue therapy. Please see 'Life 'Life Table and Age HRQoL'!S:U in the model for reference. Please see section 3.5 in the CS for further details. The cost of rescue therapy is a weighted average cost. KalVista believe sufficient evidence on the impact of rescue therapy use on model outcomes has been demonstrated in the DSA.

B36. Priority question. The CS mentions that a full hour cost of HCP time is applied for both subcutaneous and intravenous treatments (page 129). However, SC treatments can be self-administered. Please explain if the full hour cost is only applied to a proportion of the SC treatments provided by

HCP. In addition, please justify the assumption that for patients who require HCP assisted administration, a full hour cost of HCP time is applied for both subcutaneous and intravenous treatments. It would be expected this to be much less for SC compared to IV. For example, in the committee papers of NICE's appraisal of lanadelumab it states that "This product is a subcutaneous injection, which even used every fortnight is very quick and easy to administer. This has the double effect of making the product available to patients who are unable to administer C1-INH because of physical or practical issues such as poor venous access, and also means this is an much easier product for patients leading a less structured lifestyle, for example students or travellers. Use of intravenous C1-INH, whilst effective and many patients are able to successfully self-treat, requires a suitable environment for administration, and considerable time is taken to reconstitute the product, carry out the venepuncture and infuse the product. It is then recommended that the patient rests for at least 30 minutes after infusing. This all results in a considerable amount of time being devoted to this twice a week instead of a short time once a fortnight, or even monthly once patient established on treatment". (https://www.nice.org.uk/guidance/ta606/documents/committee-papers-2). Please explain if the company's assumption has been validated with published evidence or by clinical experts?

Company response: The assumption was applied in the absence of evidence. However, the assumption has a negligible effect on the ICER. For example, when the cost of HCP-assisted administration is set to £0 for SC treatments, the ICER between oral and SC treatments (i.e., sebetralstat versus icatibant) changes by [redacted]%.

B37. Priority question: Please answer the following questions regarding Tables 32 and 33:

a) Please provide measures of uncertainty for the input parameters.

Company response: Please see our response to Question C2.

b) Please clarify whether the Hospital Pharmacy Audit for OD HAE treatments study was commissioned by the company or not.

Company response: The study was commissioned by KalVista.

c) Please justify the assumptions about the percentage of treatments used as rescue therapy. Please clarify that sebetralstat is not used as rescue therapy but patients in the sebetralstat arm do receive rescue therapy.

Company response: In the absence of evidence, it was assumed that rescue therapy use follows the same distribution as the current market share of treatments. Sebetralstat is not used as rescue therapy however, patients in the sebetralstat arm do receive rescue therapy. All treatments receive the same basket of rescue therapy.

d) Please explain why sebetralstat pack size was assumed to be 1800mg and whether there are other pack sizes available.

Company response: Only the 300 mg x 6 pack size is available. There are no other pack sizes available

e) Please clarify the reasons why the treatment self-administration percentage is not 100% for icatibant. Would these reasons not be applicable to sebetralstat as well?

Company response: This is based on data sourced from Longhurst et al. (2018). HCP-assisted administration is largely driven by patient preference and route of administration.

f) Please justify why the unadjusted time to attack resolution (hours) and market shares are fixed in Table 33.

Company response: The unadjusted time to attack resolution is fixed because, based on the current base case, it is a relative effect and does not change the economic outcomes. The market share distribution was intended to be included in the PSA. However, there was a miscoded value in the Dirichlet flag referencing column, Parameters!S159:S162. As a result, CS Table 33 indicates that these inputs are fixed. We have accordingly amended the model. Please see Table 13 of this document.

g) Please justify why the mean number of additional doses required is fixed except for icatibant in Table 33.

Company response: Based on clinician reports and literature, additional dosing for icatibant is more uncertain that other OD treatments. During model validation, clinicians reported higher rates of additional dosing compared to data reported in literature. Therefore, to assess this uncertainty, we have included this variable in the sensitivity analyses.

Cost-effectiveness results

B38. Priority question: In line with the NICE manual, please present the CE results in a full incremental way, with technologies that are dominated and technologies that are extendedly dominated removed from the analysis.

Company response: KalVista reiterate that a basket comparator is most reflective of current clinical practice for HAE OD treatment within the UK. WAO guidelines and clinicians practice an individualised approach to prescribing OD HAE treatment. See our response to B4 for details. Nevertheless, we have provided a full incremental frontier analysis in Table 12.

Table 12: Incremental Frontier CE Analysis

Technology	Total Costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER

Icatibant	£356,827	18.41	-	-	-
Sebetralstat	[redacted]	18.49	[redacted]	0.08	[redacted]
Cinryze	£555,437	18.34	[redacted]	Dominated	[redacted]
Ruconest	£612,962	18.34	[redacted]	Dominated	[redacted]
Berinert	£753,743	18.34	[redacted]	Dominated	[redacted]

KalVista reiterate that a basket comparator is most reflective of clinical practice of individualised OD treatment in HAE. An incremental analysis of cost-effectiveness is not reflective of the real-world clinical practice and treatment patterns within the UK.

Section C: Textual clarification and additional points

C1. Please check the following sentence on page 18 of the CS: "HAE patients report significantly worse HRQoL outcomes compared to healthy individuals, including increased rates of depression and depression". The sentence seems to end with a typo as depression is mentioned twice.

Company response: Thank you for spotting this typographical error, this should read "anxiety and depression".

C2. Please include uncertainty measures (e.g., confidence intervals, standard errors, etc.) to the point estimates in Table 25, 27, 29, 30. In addition, in Table 27 please justify why duration of HAE Attack (hours) was sourced from SMC and not from KONFIDENT and Sebetralstat TTA was estimated in a post hoc analysis and not from KONFIDENT. In Table 30, please clarify whether risk of hospitalisation associated to self-administration also applies to sebetralstat.

Company response: Please see Table 13 in the Appendix (Section D of this clarification response document), which summaries uncertainty measures for the input variables used in the analysis. Please note that Table 13 does not include all

variables which are adjustable in the economic model. However, the table does present all inputs applicable to the CS base case.

The risk of hospitalisation is applied to all treatments, conditional on the proportion of patients who self-administer and the proportion of patients who require HCP-assisted administration.

C3. Please explain what is meant with "Where applicable, utilities and costs are adjusted to the cycle and appropriate event period" on page 109.

Company response: Annual costs are adjusted to a cycle period, and, for example, attack-related utilities are adjusted to the length of an attack. This is a standard adjustment to input costs and utilities in decision modelling.

C4. On page 113 it is mentioned that "the cohort attack rate is time homogenous and does not change from the baseline attack rate, shown in Table 25". However, Table 25 does include a baseline parameter for the cohort attack rate.

Company response: This is an unintended omission. Please see Table 33 in the CS for the baseline attack rate. Alternatively, please see Table 13 in the Appendix of this document.

C5. Page 117 of the CS reports the coefficient value in the Cox model for the relationship between TTA and TTAR is $\beta_{10} \approx$ [redacted]. However, Table 28 reports a different value.

Company response: This is a typographical error. The correct value is [redacted], as found in Table 28 of the CS.

C6. Please amend the References section of the CS since they now jump from 140 to 146.

Company response: Apologies, we do not know why references 141–145 have disappeared from the bibliography. The CS references from 140–146 are as follows:

140.Unit Costs of Health and Social Care. Table 9.2.1 Nurse, Band 6, Cost per working hour [Internet]. 2022/2023. Available from: https://kar.kent.ac.uk/109563/1/The%20unit%20costs%20of%20health%20and%20social%20care%202024%20%28for%20publication%29_Final.pdf.
141.IQVIA. [Data on file] HAE UK monthly IQVIA; 2025.
142.BNF. Icatibant 30mg/3ml solution for injection pre-filled syringes [Internet]. 2024 [cited 5 November 2024]. Available from: https://bnf.nice.org.uk/drugs/icatibant/medicinal-forms/.
143.BNF. Ruconest 2,100unit powder and solvent for solution for injection vials [Internet]. 2024 [cited 5 November 2024]. Available from: https://bnf.nice.org.uk/drugs/conestat-alfa/medicinal-forms/#powder-and-solvent-for-solution-for-injection.
144.BNF. Berinert 500unit powder and solvent for solution for injection vials [Internet]. 2024 [cited 5 November 2024]. Available from: https://bnf.nice.org.uk/drugs/c1-esterase-inhibitor/medicinal-forms/.
145.BNF. Cinryze 500unit powder and solvent for solution for injection vials [Internet]. 2024 [cited 5 November 2024]. Available from: https://bnf.nice.org.uk/drugs/c1-esterase-inhibitor/medicinal-forms/#powder-and-solvent-for-solution-for-injection.
146.Otani IM, Lumry WR, Hurwitz S, Li HH, Craig TJ, Holtzman NS, et al. Subcutaneous Icatibant for the Treatment of Hereditary Angioedema Attacks: Comparison of Home Self-Administration with Administration at a Medical Facility. J Allergy Clin Immunol Pract. 2017;5(2):442-7.e1.

We will also supply an updated CS (plus updated redacted CS) with the amended reference list intact.

Section D: Appendix

As shown in Table 13, when reported SE values are not available, the model calculates a default standard error of 15% around the mean value.

Table 13: Summary of base case inputs

Variable	Value (SE)	Default SE or Reported SE?	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in CS
Discount costs (%)	3.5	Fixed	Fixed	Section 3.2
Discount QALYs (%)	3.5	Fixed	Fixed	
Time horizon (years)	62.30	Fixed	Fixed	
Cycle length (days)	21	Fixed	Fixed	
Baseline Patient Characteristics				
Mean number of attacks per year	14.71 (2.21)	Default	[10.71; 19.34] (Gamma)	Section 3.2
Female (%)	60 (0.09)	Default	[41.8; 76.8] (Beta)	

Age at baseline	37.7 (1.43)	Reported values	[34.96; 40.55] (Gamma)	
Clinical Inputs				
Untreated attack duration (hours)	72 (10.80)	Default	[52.41; 94.66] (Gamma)	Section 3.3
Time to administration (minutes)				
Sebetralstat	55.6 (2.37)	Reported Values	[51.06; 60.34] (Gamma)	Section 3.3
Icatibant	174 (33.71)	Reported values	[114.32; 246.02] (Gamma)	
Ruconest	228 (38.99)	Reported values	[158.08; 310.52] (Gamma)	
Berinert	228 (38.99)	Reported values	[158.08; 310.52] (Gamma)	
Cinryze	228 (38.99)	Reported values	[158.08; 310.52] (Gamma)	
Unadjusted Time to attack resolution (hours)	[redacted]	Fixed	Fixed	
TTA ~ TTAR Hazard Ratio	[redacted]	Reported values	[redacted] (Log-Normal)	
% patients additional doses (per attack)				
Sebetralstat	22.25 (0.03)	Default	[16.1; 29.1] (Beta)	Section 3.3

Icatibant	8.91	Default	[6.5; 11.7] (Beta)	
Ruconest	18.2	Default	[13.2; 23.8] (Beta)	
Berinert	1.11	Default	[0.8; 1.5] (Beta)	
Cinryze	18.2	Default	[13.2; 23.8] (Beta)	
% patients using rescue therapy (per attack)				
Sebetralstat	5.24	Default	[3.8; 6.9] (Beta)	Section 3.3
Icatibant	12.7	Default	[9.2; 16.7] (Beta)	
Ruconest	7.3	Default	[5.3; 9.6] (Beta)	
Berinert	7.3	Default	[5.3; 9.6] (Beta)	
Cinryze	7.3	Default	[5.3; 9.6] (Beta)	
Distribution of attack locations (% per attack)				
Neck and Above	[redacted]	Default	[redacted] (Multivariate)	Section 3.3
Abdominal	[redacted]	Default	[redacted] (Multivariate)	
Other	[redacted]	Default	[redacted] (Multivariate)	

Distribution of attack severity (% per attack - scenario)				
Severe	[redacted]	Default	[redacted] (Multivariate)	Section 3.3
Moderate	[redacted]	Default	[redacted] (Multivariate)	
Mild	[redacted]	Default	[redacted] (Multivariate)	
Risk of hospitalization (% per year)				
Self-Administration	5.8 (0.01)	Default	[4.2; 7.6] (Beta)	Section 3.3
HCP Administration	12.5 (2.55)	Default	[9.1; 16.4] (Beta)	
Side effects (% per administration)				
Icatibant				
Injection skin reaction	97.2 (0.015)	Default	[43.1; 100] (Beta)	Section 3.3
Injection painful burning, stinging	50.9 (0.08)	Default	[36.0; 65.7] (Beta)	
Ruconest				
Injection skin reaction	10.0 (0.02)	Default	[7.3; 13.1] (Beta)	Section 3.3

Injection painful burning, stinging	20.0 (0.03)	Default	[14.5; 26.2] (Beta)	
Berinert				
Injection skin reaction	24.8 (0.04)	Default	[17.9; 32.4] (Beta)	Section 3.3
Injection painful burning, stinging	12.5 (0.02)	Default	[9.1; 16.4] (Beta)	
Cinryze				
Injection skin reaction	24.8 (0.04)	Default	[17.9; 32.4] (Beta)	Section 3.3
Injection painful burning, stinging	12.5 (0.02)	Default	[9.1; 16.4] (Beta)	
HRQoL Inputs				
Acute attack disutility by location				
Neck and Above	-0.48 (0.05)	Reported values	[-0.38; -0.57] (Beta)	Section 3.4
Abdominal	-0.44 (0.05)	Reported values	[-0.35; -0.53] (Beta)	
Other	-0.20 (0.04)	Reported values	[-0.13; -0.28] (Beta)	
Health state utility values (by treatment type)				
Oral	[redacted]	Fixed	Fixed	Section 3.4

Subcutaneous	[redacted]	Fixed	Fixed	
Intravenous (self-administered)	[redacted]	Reported values	[redacted] (Beta)	
Intravenous (HCP administered)	[redacted]	Reported values	[redacted] (Beta)	
Side effects (unadjusted disutilities)				
Injection site reaction	[redacted]	Reported values	[redacted] (Beta)	Section 3.4
Injection painful burning, stinging	[redacted]	Reported values	[redacted] (Beta)	
Headaches, diarrhea, nausea	[redacted]	Reported values	[redacted] (Beta)	
Costs and HRU Inputs				
% market share of comparator treatment (%)t				
Icatibant	[redacted]	Default	[redacted] (Multivariate)	Section 3.2 and 3.5
Ruconest	[redacted]	Default	[redacted] (Multivariate)	
Berinert	[redacted]	Default	[redacted] (Multivariate)	
Cinryze	[redacted]	Default	[redacted] (Multivariate)	

Mean number of additional doses required				
Sebetralstat	1.00	Fixed	Fixed	Section 3.5
Icatibant	1.00 (0.15)	Default	[0.73.; 1.32] (Gamma)	
Ruconest	1.00	Fixed	Fixed	
Berinert	1.00	Fixed	Fixed	
Cinryze	1.00	Fixed	Fixed	
% treatment used for rescue Therapy (fixed %)				
Sebetralstat	0.00	Fixed	Fixed	Section 3.5
Icatibant	[redacted]	Fixed	Fixed	
Ruconest	[redacted]	Fixed	Fixed	
Berinert	[redacted]	Fixed	Fixed	
Cinryze	[redacted]	Fixed	Fixed	
Treatment cost per pack				
Sebetralstat	£[redacted]	Fixed	Fixed	Section 3.5

Icatibant	£837	Fixed	Fixed	
Ruconest	£750	Fixed	Fixed	
Berinert	£670	Fixed	Fixed	
Cinryze	£668	Fixed	Fixed	
Treatment pack size				
Sebetralstat	1800mg	Fixed	Fixed	Section 3.5
Icatibant	30mg	Fixed	Fixed	
Ruconest	2100 IU	Fixed	Fixed	
Berinert	500 IU	Fixed	Fixed	
Cinryze	500 IU	Fixed	Fixed	
Treatment dose per administration				
Sebetralstat	300mg	Fixed	Fixed	Section 3.5
Icatibant	30mg	Fixed	Fixed	

Ruconest	50 IU/kg	Fixed	Fixed	
Berinert	20 IU/kg	Fixed	Fixed	
Cinryze	1000 IU	Fixed	Fixed	
% patients self-administering treatment (%)				
Sebetralstat	100	Fixed	Fixed	Section 3.3
Icatibant	95.8 (0.14)	Default	[41.8.; 100] (Beta)	
Ruconest	61.0 (0.09)	Default	[42.5.; 78.0] (Beta)	
Berinert	61.0 (0.09)	Default	[42.5.; 78.0] (Beta)	
Cinryze	61.0 (0.09)	Default	[42.5.; 78.0] (Beta)	
Cost of administration by admin route				
Oral	0.0	Fixed	Fixed	Section 3.5
Subcutaneous	57.0 (8.55)	Default	[41.5.; 75.9] (Gamma)	
Intravenous	57.0 (8.55)	Default	[41.5.; 75.9] (Gamma)	
Cost of hospitalisation	582.3 (87.34)	Default	[423.8; 765.5] (Gamma)	

References

1. Yong PFK, Coulter T, El-Shanawany T, Garcez T, Hackett S, Jain R, et al. A National Survey of Hereditary Angioedema and Acquired C1 Inhibitor Deficiency in the United Kingdom. The Journal of Allergy and Clinical Immunology: In Practice. 2023;11(8):2476-83.

2. Lumry WR, Aygören-Pürsün E, Zanichelli A, Cohn DM, Farkas H, Bernstein JA, et al. [EAC 2022 poster] KONFIDENT Phase 3 Trial Design for Sebetralstat (KVD900), a Novel Investigational Oral Plasma Kallikrein Inhibitor for the On-Demand Treatment of Hereditary Angioedema Attacks. Eastern Allergy Conference 2022; June 2022; Palm Beach, USA2022.

3. Riedl MA, Farkas H, Aygören-Pürsün E, Psarros F, Soteres DF, Staevska M, et al. [NEJM manuscript] Oral Sebetralstat for On-Demand Treatment of Hereditary Angioedema Attacks. N Engl J Med. 2024;391(1):32-43.

4. KalVista. [Data on File] HCP validation and Clinician survey. [Summary report]. In press 2024.

5. Watt M, Malmenas M, Haeussler K. Letter in reply: network meta-analysis for indirect comparison of lanadelumab and for the treatment of hereditary angioedema. J Comp Eff Res. 2024;13(5):e240041.

6. Riedl MA, Bernstein JA, Li H, Reshef A, Lumry W, Moldovan D, et al. Recombinant human C1-esterase inhibitor relieves symptoms of hereditary angioedema attacks: phase 3, randomized, placebo-controlled trial. Ann Allergy Asthma Immunol. 2014;112(2):163-9.e1.

7. Riedl MA, Farkas H, Aygören-Pürsün E, Psarros F, Soteres DF, Staevska M, et al. [NEJM Supplementary Appendix] Oral Sebetralstat for On-Demand Treatment of Hereditary Angioedema Attacks. N Engl J Med. 2024;391(1):32-43.

8. Maurer M, Aberer W, Bouillet L, Caballero T, Fabien V, Kanny G, et al. Hereditary angioedema attacks resolve faster and are shorter after early icatibant treatment. PLoS One. 2013;8(2):e53773.

9. Craig T, Rojavin MA, Machnig T, Keinecke HO, Bernstein JA. Effect of time to treatment on response to C1 esterase inhibitor concentrate for hereditary angioedema attacks. Annals of Allergy, Asthma, and Immunology. 2013;111(3).

10. Farkas H, Jakab L, Temesszentandra G, Visy B, Harmat G, Fust G, et al. Hereditary angioedema: A decade of human C1-inhibitor concentrate therapy. Journal of Asthma and Immunology. 2007.

11. Bork K, Aygören-Pürsün E, Bas M, Biederman T, Greve J, Hartman K, et al. Guideline: Hereditary angioedema due to C1 inhibitor deficiency. Allergo Journal International. 2019;28:16-29.

12. Christiansen S, O'Connor M, Craig T, Radojicic C, Wedner HJ, Danese S, et al. On-demand treatment of hereditary angioedema attacks: Patient-reported utilization, barriers, and outcomes. Annals of Allergy, Asthma, and Immunology. 2024.

13. Betschel S, Caballero T, Jones DH, Longhurst HJ, Manning M, van Kooten S, et al. The complexities of decision-making associated with on-demand treatment of hereditary angioedema (HAE) attacks. Allergy, Asthma & Clinical Immunology. 2024;1.

14. Andrasi N, Veszeli N, Holdonner A, Temesszentandra G, Kohlami KV, Varga L, et al. Evaluation of the efficacy and safety of home treatment with the recombinant human C1-inhibitor in hereditary angioedema resulting from C1-inhibitor deficiency. International Immunopharmacology. 2020;80.

15.Caballero T, Aberer W, Longhurst HJ, Maurer M, Zanichelli A, Perrin A, et al. The Icatibant Outcome Survey: experience of hereditary angioedema management from six European countries. J Eur Acad Dermatol Venereol. 2017;31(7):1214-22.

16.Riedl M, Bernstein J, Li H, Manning M, Raasch J, Hao J, et al. Safety and Effectiveness of Sebetralstat in Patients with Hereditary Angioedema Receiving Long-term Prophylaxis: Interim Analysis from the KONFIDENT-S Open-label Study (WSAAI 2025 poster). Western Society of Allergy, Asthma & Immunology Annual Meeting (WSAAI 2025); February 9-13, 2025; Waimea, Hawaii2025.

17.KalVista. [Data on file: Updated 10 July 2025]. Post-hoc statistical analysis: Association between Time to Administration and Time to Attack Resolution. 2025.

18.Cicardi M, Banerji A, Bracho F, Malbrán A, Rosenkranz B, Riedl M, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med. 2010;363(6):532-41.

19.Cohn DM. [Phase 3 EAACI 2024 oral presentation] Oral sebetralstat for on-demand treatment of hereditary angioedema: phase 3 KONFIDENT trial results. EAACI (European Academy of Allergy & Clinical Immunology) 2024; 31 May 2024; Valencia, Spain2024.

20.Craig TJ, Levy RJ, Wasserman RL, Bewtra AK, Hurewitz D, Obtułowicz K, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. J Allergy Clin Immunol. 2009;124(4):801-8.

21.Levy RJ, Lumry WR, McNeil DL, Li HH, Campion M, Horn PT, et al. EDEMA4: a phase 3, double-blind study of subcutaneous ecallantide treatment for acute attacks of hereditary angioedema. Ann Allergy Asthma Immunol. 2010;104(6):523-9.

22.Riedl MA, Li HH, Cicardi M, Harper JR, Relan A. Recombinant human C1 esterase inhibitor for acute hereditary angioedema attacks with upper airway involvement. Allergy Asthma Proc. 2017;38(6):462-6.

23.Zuraw B, Cicardi M, Levy RJ, Nuijens JH, Relan A, Visscher S, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. J Allergy Clin Immunol. 2010;126(4):821-7.e14.

24.Lumry WR, Li HH, Levy RJ, Potter PC, Farkas H, Moldovan D, et al. Randomized placebo-controlled trial of the bradykinin B_2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. Ann Allergy Asthma Immunol. 2011;107(6):529-37.

25.Cohn DM, Soteres DF, Craig TJ, Lumry WR, Magerl M, Riedl MA, et al. Interplay between on-demand treatment trials for hereditary angioedema and treatment guidelines. J Allergy Clin Immunol. 2024.

26.ClinicalTrials.gov. Study of Oral Deucrictibant Soft Capsule for On-Demand Treatment of Angioedema Attacks in Adolescents and Adults With Hereditary Angioedema (RAPIDe-3) ClinicalTrials.gov website: National Library of Medicine; 2025 [Available from: https://clinicaltrials.gov/study/NCT06343779.

27.Bork K, Bernstein JA, Machnig T, Craig TJ. Efficacy of Different Medical Therapies for the Treatment of Acute Laryngeal Attacks of Hereditary Angioedema due to C1-esterase Inhibitor Deficiency. J Emerg Med. 2016;50(4):567-80.e1.

28.Helbert M, Pang F, Alvarez-Reyes M, Roskell NS, Diwakar L. (PSY10) An Indirect Comparison of Icatibant and Four Other Therapies for the Symptomatic Treatment of Acute Attacks of Hereditary Angioedema Types I and II. Value in Health. 2012;15(7):PA509-A10.

29.Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygoren-Pursun E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. Allergy. 2022;77(7):1961-90.

30.Cohn DM, Aygören-Pürsün E, Bernstein JA, Farkas H, Lumry WR, Maurer M, et al. Evaluation of patient-reported outcome measures for on-demand treatment of hereditary angioedema attacks and design of KONFIDENT, a phase 3 trial of sebetralstat. Clin Transl Allergy. 2023;13(9):e12288.

31.Aberer W, Maurer M, Bouillet L, Zanichelli A, Caballero T, Longhurst HJ, et al. Breakthrough attacks in patients with hereditary angioedema receiving long-term prophylaxis are responsive to icatibant: findings from the Icatibant Outcome Survey. Allergy Asthma Clin Immunol. 2017;13:31.

32.KalVista. [KONFIDENT CSR report] A Randomized, Double-Blind, Placebo-Controlled, Phase 3, Three-way Crossover Trial to Evaluate the Efficacy and Safety of Two Dose Levels of KVD900, an Oral Plasma Kallikrein Inhibitor, for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients with Hereditary Angioedema Type I or II (KONFIDENT). 2024 03 May 2024.

33.KalVista. [KONFIDENT-S OLE interim CSR report - 14 Sept 2024 data cut off date] Interim Clinical Trial Report: An Open-Label Extension Trial to Evaluate the Long-term Safety of KVD900, an Oral Plasma Kallikrein Inhibitor, for On-demand Treatment of Angioedema Attacks in Adolescent and Adult Patients with Hereditary Angioedema Type I or II (KONFIDENT-S). 2024 19 November 2024.

34.Cancian M, Bocquet A, Busse P, Craig T, El-Shanawany T, Garcez T, et al., editors. Survey results from Italy, the US, UK, and France: Anxiety in patients using injectable on-demand treatments for hereditary angioedema attacks. To be presented at the 2025 C1-INH workshop]. 14th C1-Inhibitor Deficiency and Angioedema Workshop; 2025 Conference date: 29 May - 1 June 2025; Budapest.

35.Craig T, Bernstein JA, Longhurst H, Hao J, Smith MD, Audhya PK, et al. [ACAAI 2024 Time to Treatment Phase 3 poster] Correlation of Time to Treatment with Attack Duration in the Sebetralstat KONFIDENT Phase 3 Trial. ACAAI (American College of Allergy, Asthma & Immunology) 2024; October 2024; Boston, USA2024.

36.Kiani-Alikhan S, Banerji A, Busse P, Craig T, Yong PFK, Hall R, et al. Psychological Burden Associated with Injectable HAE On-Demand Treatments: A Patient and Caregiver Interview Study [Presented at the European Academy of Allergy and Clinical Immunology (EAACI)]. EAACI; June 13-16, 2025; Glasgow, Scotland2025.

37.Yong P, Banerji A, Busse P, Craig T, Kiani-Alikhan S, Hall R, et al. Impact of injectable HAE on-demand treatments on health-related quality of life: a patient and caregiver interview study. [Presented at 14th C1-Inhibitor Deficiency & Angioedema (C1-INH) Workshop]. 14th C1-Inhibitor Deficiency and Angioedema Workshop; Conference date: 29 May - 1 June 2025; Budapest, Hungary2025.

38.Hubig LT, Smith T, Chua GN, Lloyd AJ, Powell L, Johnston K, et al. A stated preference survey to explore patient preferences for novel preventive migraine treatments. Headache. 2022;62(9):1187-97.

39.Holko P, Kawalec P, Mossakowska M. Quality of life related to oral, subcutaneous, and intravenous biologic treatment of inflammatory bowel disease: a time trade-off study. Eur J Gastroenterol Hepatol. 2018;30(2):174-80.

40.Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. Eur J Health Econ. 2011;12(3):219-30.

41.Collins SP, Hong A, Hauber B, Flanders SC, Will O, Maculaitis MC, et al. Patients' Preferences for Attributes of Oral vs Injectable Androgen Deprivation Therapy in Prostate Cancer: A Discrete Choice Experiment. Patient Prefer Adherence. 2025;19:1397-409.

42.Coley CM, Li YH, Medsger AR, Marrie TJ, Fine MJ, Kapoor WN, et al. Preferences for home vs hospital care among low-risk patients with community-acquired pneumonia. Arch Intern Med. 1996;156(14):1565-71.

43.Fried TR, van Doorn C, O'Leary JR, Tinetti ME, Drickamer MA. Older person's preferences for home vs hospital care in the treatment of acute illness. Arch Intern Med. 2000;160(10):1501-6.

44.Ebhabha V, Morrissey H, Ball P. Comparing Patient Preference Between At-home and In-hospital Settings: Systematic Review and Meta-Analysis on Injectable Medications. Arch Pharm Pract. 2023;14(3):98-111.

45.Jørgensen T, Franchi A, Lelli F, Lee X, Bøgelund M, Alulis S. PGI35: Preferences for Route of Administration, Frequency and Location – A Time-Trade-Off Study in the United Kingdom General Population. Value in Health. 2017;20:A637.

46.Wang A, Fouche A, Craig TJ. Patients perception of self-administrated medication in the treatment of hereditary angioedema. Ann Allergy Asthma Immunol. 2015;115(2):120-5.

47.Johnston K, Stoffman JM, Mickle AT, Klaassen RJ, Diles D, Olatunde S, et al. Preferences and Health-Related Quality-of-Life Related to Disease and Treatment Features for Patients with Hemophilia A in a Canadian General Population Sample. Patient Prefer Adherence. 2021;15:1407-17.

48.Kreuz W, Rusicke E, Martinez-Saguer I, Aygören-Pürsün E, Heller C, Klingebiel T. Home therapy with intravenous human C1-inhibitor in children and adolescents with hereditary angioedema. Transfusion. 2012;52(1):100-7.

49.Longhurst HJ, Carr S, Khair K. C1-inhibitor concentrate home therapy for hereditary angioedema: a viable, effective treatment option. Clin Exp Immunol. 2007;147(1):11-7.

50.Petraroli A, Squeglia V, Di Paola N, Barbarino A, Bova M, Spanò R, et al. Home Therapy with Plasma-Derived C1 Inhibitor: A Strategy to Improve Clinical Outcomes and Costs in Hereditary Angioedema. Int Arch Allergy Immunol. 2015;166(4):259-66.

51.Betschel SD, Caballero T, Jones DH, Longhurst HJ, Manning M, van Kooten S, et al. The complexities of decision-making associated with on-demand treatment of hereditary angioedema (HAE) attacks. Allergy Asthma Clin Immunol. 2024;20(1):43.

52.Riedl MA, Banerji A, Busse PJ, Johnston DT, Davis-Lorton MA, Patel S, et al. Patient satisfaction and experience with intravenously administered C1-inhibitor concentrates in the United States. Ann Allergy Asthma Immunol. 2017;119(1):59-64.

53.Lu Y, Dai Z, Chang F, Wang L, He J, Shi P, et al. Whether and How Disutilities of Adverse Events were Used in the Economic Evaluation of Drug Therapy for Cancer Treatment. Pharmacoeconomics. 2023;41(3):295-306.

54.Christiansen S, O'Connor M, Craig T, Radojicic C, Wedner HJ, Danese S, et al. On-demand treatment of hereditary angioedema attacks: Patient-reported utilization, barriers, and outcomes. Ann Allergy Asthma Immunol. 2025;134(5):570-9.e4.

55.Okkels A, Yssing C, Wolden ML, Wahid MN. A time trade-off study in the UK, Canada and the US to estimate utilities associated with the treatment of haemophilia. Health Qual Life Outcomes. 2024;22(1):97.

56.Matza LS, Deger KA, Vo P, Maniyar F, Goadsby PJ. Health state utilities associated with attributes of migraine preventive treatments based on patient and general population preferences. Qual Life Res. 2019;28(9):2359-72.

57.Matza LS, Boye KS, Yurgin N, Brewster-Jordan J, Mannix S, Shorr JM, et al. Utilities and disutilities for type 2 diabetes treatment-related attributes. Qual Life Res. 2007;16(7):1251-65.

58.Rajan N, Boye KS, Gibbs M, Lee YJ, Davey P, Ball M, et al. Utilities for Type 2 Diabetes Treatment-Related Attributes in a South Korean and Taiwanese Population. Value Health Reg Issues. 2016;9:67-71.

NICE National Institute for Health and Care Excellence

QASingle Technology Appraisal

Sebetralstat for treating acute attacks of hereditary angioedema in people 12 years and over [ID6284]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	**Angela Metcalfe**
2. Name of organisation	Hereditary Angioedema UK (HAE UK)
3. Job title or position	CEO
4a. Brief description of the organisation (including who funds it). How many members does it have?	HAE UK is a patient advocacy and support group. There is the CEO and a part time executive officer and a board of 7 Trustees. We represent approximately 700 patients and carers with a diagnosis of HAE of all types
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	**Unrestricted grants in the financial year ended September 2023 (last audited accounts)** **CSL Behring £35,000** **Takeda UK £3,000** **BioCryst Pharmaceuticals £16,500**
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	As the patient advocacy and support group. As the CEO of this charity I engage daily with patients, carers and clinicians and have a full understanding of the impact this life-threatening condition has on patients.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Hereditary Angioedema produces intense and excrutiatingly painful swellings in the abdomen, peripherals (hands and feet), in the face causing temporary blindness when eyelids swell, and can cause death by asphyxiation if swelling occurs in the laryngeal area. Attacks are brought on by a number of factors including anxiety (good and bad), trauma – anything from cutting a finger to being in an accident – and also other illness such as the common cold. Attacks are highly unpredictable and last from anything between 24 and 72 hours, with a post recovery time of 48 to 72 hours. Carers also live with the anxiety of the unpredictability of attacks and in many cases are trained to administer medications which the patient would not be able to do. HOWEVER no two patients are the same with each individual experiencing differency frequency and severity of attacks.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The current range of treatments available to patients are not suitable for all and are highly restricted in prescribing by commissioning guidance that is outdated and does not meet the needs of patients. Currently all medications are only able to be prescribed based on frequency of attack and not on severity.
8. Is there an unmet need for patients with this condition?	Yes. There is a need for a treatment that is oral as an on demand medication for patients who may possibly have a relatively small number of attacks, but also to be able to treat a break through attack. Many patients are needle-phobic and current medications for on demand treatment require continual refrigeration. This severely limits travel, taking medications to school, work etc and has an impact on daily life with medication always having to be carried with the patient.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The overriding advantage of this technology is that it is oral. Patients can travel freely whether for business, pleasure or education in the knowledge that they have a pill with them that can be kept in the wallet, handbag etc that is instantly accessibly and has an extremely efficient and fast effect on stopping an attack. Many patients know their bodies well enough to know that an attack is coming and on demand treatment is currently only available via needle for a refrigerated medication. Some needle based technology for on demand treatment can even require a second dose to be effective, and some times not even that works with patients requiring IV infusion of C1. This technology will allow patients not just freedom to go about their daily lives but will significantly reduce the anxiety of knowing that an pill is instantly on hand to stop a potential attack within a very short period of time.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	HAE UK is not aware of any disadvantage of this technology

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Yes, those with needle phobia ALL patients would benefit from an on demand treatment that did not require refrigeration but was oral, easily administered and highly effective both in treatment and in the speed of action

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Sebetralstat is an oral medication that will relieve treatment for needle phobic patients • Sebetralstat will reduce anxiety for patients as the medication can be easily carried about the patient at all times • Sebetralstat does not require help to be administered by a carer • Sebetralstat would support and work for any type of patient with any form of HAE – ALL HAE PATIENTS ARE DIFFERENT • Sebetralstat supports the unmet need of a fast, easy and effective treatment for the onset of an attack

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sebetralstat for treating acute attacks of hereditary angioedema in people 12 years and over [ID6284]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Society for Allergy and Clinical Immunology
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Society for Allergy & Clinical Immunology (BSACI) is the national, professional, and academic society which represents the specialty of allergy at all levels. Its aim is to improve the management of allergies and related diseases of the immune system in the United Kingdom, through education, training, and research.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To treat acute swelling (angioedema) attacks associated with hereditary angioedema.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An acute treatment would be expected to reduce the time to onset of symptoms relief, improvement in symptoms and resolution of symptoms. However, there is inherent variability between attacks even in the same individual, and limited published clinical data/consensus as to what constitutes a clinically significant treatment response for acute HAE treatment.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is an unmet need in this condition. All licensed current treatments available for acute attacks are injectable medications, that are more difficult to transport around and to administer. This can result in delays to treatment, resulting in poorer outcomes from the acute treatment. The injectable treatments available are icatibant, which is given subcutaneously and C1 inhibitor, which is given intravenously. The icatibant does cause significant pain on injection although it is easy to learn to self-administer. It has a short half-life and a second dose is required about 10-20% of the time. C1 inhibitor is given intravenously and usually requires attendance at an emergency department or administration by a healthcare professional if a patient requires this – which does further delay the administration for acute attacks.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	The condition is treated with acute on-demand treatments (for when an angioedema attack occurs) and with prophylaxis (to prevent angioedema attacks from occurring). All patients are recommended to have an available supply of acute on-demand treatment as not all patients are on prophylaxis and breakthrough attacks can also occur in patients who are on prophylaxis.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Access to licensed therapies for acute treatment are determined by the NHSE clinical commissioning policies on treatment of acute attacks in hereditary angioedema (April 2013). Access to long-term prophylaxis are guided by the NHSE commissioning policy on plasma-derived inhibitor for prophylactic treatment (2016), and NICE TAs on lanadelumab and berotralstat. NHSE has published an algorithm in 2025 summarising these documents. International guidelines for this condition include the 2021 international WAO/EAACI guideline for the management of hereditary angioedema, although the treatment recommendations in there cannot be applied to all patients due to the access criteria within the NHSE commission policies and NICE TAs.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is relatively well defined, as access criteria to treatment are determined by the NHSE commissioning policies and NICE TAs.
9c. What impact would the technology have on the current pathway of care?	This technology would simplify patients treating acute HAE attacks by providing an oral alternative where currently the only available treatment options are all injectable medications. This would enable quicker administration of acute treatment, reduce anxiety associated with treatment and allow better outcomes as early treatment of acute attacks is associated with this. The medication would also be more portable, making it easier for patients to access the medication when needed. People with needle phobia and children may find the availability of an oral method of administration particularly helpful.
10. Will the technology be used (or is it already used) in the same way as current	The technology would be used for acute treatment of HAE attacks, for the same indication as current available acute treatments.

care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	Current care for acute attacks include SC icatibant and IV C1 inhibitor. SC icatibant is usually self-administered but required appropriate training by a healthcare professional. IV C1 inhibitor is usually administered in a healthcare setting, although a small number of patients have been trained to self-administer this. Administration of IV C1 inhibitor usually requires attendance at an emergency department, along with the healthcare resource use associated with that. The new technology would not require either training to self-administer or emergency department attendance as it is an oral therapy.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology should be prescribed from specialist clinics experienced in managing HAE. The technology would be self-administered by patients for treatment of acute HAE attacks.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific investment would be required to introduce the technology.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, the technology would be expected to provide meaningful benefits compared with current care. An oral treatment for acute attacks would enable acute treatment to be administered earlier. Earlier administration of acute attacks of HAE has been shown to result in better outcomes, with quicker resolution and shorter duration.
11a. Do you expect the technology to increase length of life more than current care?	The technology is unlikely to increase length of life more than current care.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, the technology would be expected to increase HR-QoL more than current care. Current treatments for acute attacks are all injectable treatments, which can cause significant pain on injection as well as being inconvenient, cause anxiety for patients, are difficult to administer and/or require emergency department attendance. The availability of an oral treatment would address all these issues.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would be expected to be equally effective in all patients with HAE.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology will be easier for patients and healthcare professionals compared to current care. The additional elements/issues related to the use of injectable therapies are described above in previous answers, and an oral therapy would address these issues. It is also likely to be a lot more acceptable to patients because the technology is an oral treatment rather than an injectable therapies. Compared to injectable therapies, an oral treatment would be easy and quick to administer, remove pain, anxiety, difficulties, inconvenience and/or emergency department attendance associated with injectable therapies.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	For current acute treatments, all patients are offered/recommended to have acute treatment available to them to use as acute attacks are unpredictable. There are no rules for stopping acute treatment as all patients require this, although patients may express a preference for a particular type of acute treatment for various reasons. The technology would be expected to be used in a similar way to current acute treatments.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	It is unlikely that any substantial health-related benefits are not included in the QALY calculation.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, the technology is innovative in its potential to make a significant and substantial impact. It is the first oral therapy available for acute treatment of HAE attacks, and would offer multiple advantages compared to injectable therapies, as described in previous answers.
16a. Is the technology a 'step-change' in the management of the condition?	Yes, this technology would be considered a 'step-change' for acute treatment of HAE attacks. It is the first oral therapy available for acute treatment of HAE attacks, and would offer multiple advantages compared to injectable therapies, as described in previous answers.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, the technology does address an unmet need of the patient population. In general, current injectable therapies are painful, can cause anxiety and can be difficult/inconvenient to administer – resulting in treatment delays and poorer outcomes when used. Additionally, when patients have to present to the emergency department for acute treatment of HAE, there have been reports of additional difficulties and delays. Children, patients who are needle phobic or patients who are unable to self-administer medication (for any reason, including if an HAE attack temporarily incapacitates the use of their hands)

	will likely particularly benefit from an oral acute treatment as well, although an oral acute treatment would benefit all patients with HAE.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Technology has been well tolerated in clinical trials, with no side effects or adverse effects expected to have a significant effect.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the clinical trials used the technology for acute treatment of HAE attacks, which is where this technology would be used in UK clinical practice.
18a. If not, how could the results be extrapolated to the UK setting?	NA
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes would be reduction in attack severity, time to symptom relief, reduction in attack duration and time to attack resolution. These were measure in the trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
18d. Are there any adverse effects that were not apparent in clinical	None that we are aware of.

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Data on this technology is currently available only from clinical trials.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	None that we are aware of
21b. Consider whether these issues are different from issues with current care and why.	NA

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• The technology is the first available oral therapy for treatment of acute HAE attacks. • Current available technologies are all injectable medications and cause pain, inconvenience/difficulties in administration, are less easy to carry around, have a requirement for training and/or emergency department attendance, and can be associated with anxiety. All these often result in delays in treating acute attacks and poorer outcomes. • An oral acute therapy would obviate all the issues related to injectable therapies and would be a step-change in the management of acute attacks in HAE. • Children, people who are needle-phobic and people who are unable to self-administer injections are likely to find an oral therapy to be particularly advantageous, although this would benefit **all** patients with HAE for treating their acute attacks. •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sebetralstat for treating acute attacks of hereditary angioedema in people 12 years and over [ID6284]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Society for Immunology Clinical Immunology Professional Network (BSI-CIPN)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes – [redacted] (completing sections 1-5) A specialist in the treatment of people with this condition? Yes – Dr Patrick Yong (Completing sections 6 -22)
5a. Brief description of the organisation (including who funds it).	The BSI-CIPN is a professional network hosted within the British Society for Immunology, a learned society. The BSI-CIPN is an integrated and impactful professional network for individuals working within clinical immunology. The network includes over 200 professionals working in the clinical immunology field, including clinical immunologists, allergists, healthcare scientists, pharmacists and specialist nurses. The BSI-CIPN is funded through the British Society for Immunology, which has a range of income streams which can be viewed in our 2024 annual report here. The BSI-CIPN also has some ringfenced funding as a result of a merger with the UK Primary Immunodeficiency Network in 2022.

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]

If so, please state the name of manufacturer, amount, and purpose of funding.

All funding detailed below is between 01/05/2024 and 27/05/2025

Funder	Description	Gross
CSL Behring UK Ltd		
	Gold sponsorship of BSI-CIPN Conference 2024	34,800.00
	Grant for nurses training programme	40,000.00
Total CSL Behring UK Ltd		**74,800.00**
KalVista Pharmaceuticals Ltd		
	Platinum sponsorship of BSI-CIPN Conference 2024	47,994.00
	Sponsorship of BSI-CIPN/KalVista HAE Webinar on May 21st 2025	18,000.00
Total KalVista Pharmaceuticals Ltd		**65,994.00**
Pharming Technologies B.V.		
	Platinum sponsorship of BSI-CIPN Conference 2024	35,500.00
Total Pharming Technologies B.V.		**35,500.00**
Takeda UK Limited		
	Sponsorship of BSI-CIPN conference 2024	59,394.00
	Grant for nurses training programme	40,000.00
Total Takeda UK Limited		**99,394.00**

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?

No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To treat acute swelling (angioedema) attacks associated with hereditary angioedema.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An acute treatment would be expected to reduce the time to onset of symptoms relief, improvement in symptoms and resolution of symptoms. However, there is inherent variability between attacks even in the same individual, and limited published clinical data/consensus as to what constitutes a clinically significant treatment response for acute HAE treatment.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is an unmet need in this condition. All licensed current treatments available for acute attacks are injectable medications, that are more difficult to transport around and to administer. This can result in delays to treatment, resulting in poorer outcomes from the acute treatment. The injectable treatments available are icatibant, which is given subcutaneously and C1 inhibitor, which is given intravenously. The icatibant does cause significant pain on injection although it is easy to learn to self-administer. It has a short half-life and a second dose is required about 10-20% of the time. C1 inhibitor is given intravenously and usually requires attendance at an emergency department or administration by a healthcare professional if a patient requires this – which does further delay the administration for acute attacks.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	The condition is treated with acute on-demand treatments (for when an angioedema attack occurs) and with prophylaxis (to prevent angioedema attacks from occurring). All patients are recommended to have an available supply of acute on-demand treatment as not all patients are on prophylaxis and breakthrough attacks can also occur in patients who are on prophylaxis.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Access to licensed therapies for acute treatment are determined by the NHSE clinical commissioning policies on treatment of acute attacks in hereditary angioedema (April 2013). Access to long-term prophylaxis are guided by the NHSE commissioning policy on plasma-derived inhibitor for prophylactic treatment (2016), and NICE TAs on lanadelumab and berotralstat. NHSE has published an algorithm in 2025 summarising these documents. International guidelines for this condition include the 2021 international WAO/EAACI guideline for the management of hereditary angioedema, although the treatment recommendations in there cannot be applied to all patients due to the access criteria within the NHSE commission policies and NICE TAs.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is relatively well defined, as access criteria to treatment are determined by the NHSE commissioning policies and NICE TAs.
9c. What impact would the technology have on the current pathway of care?	This technology would simplify patients treating acute HAE attacks by providing an oral alternative where currently the only available treatment options are all injectable medications. This would enable quicker administration of acute treatment, reduce anxiety associated with treatment and allow better outcomes as early treatment of acute attacks is associated with this. The medication would also be more portable, making it easier for patients to access the medication when needed. People with needle phobia and children may find the availability of an oral method of administration particularly helpful.
10. Will the technology be used (or is it already used) in the same way as current	The technology would be used for acute treatment of HAE attacks, for the same indication as current available acute treatments.

care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	Current care for acute attacks include SC icatibant and IV C1 inhibitor. SC icatibant is usually self-administered but required appropriate training by a healthcare professional. IV C1 inhibitor is usually administered in a healthcare setting, although a small number of patients have been trained to self-administer this. Administration of IV C1 inhibitor usually requires attendance at an emergency department, along with the healthcare resource use associated with that. The new technology would not require either training to self-administer or emergency department attendance as it is an oral therapy.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology should be prescribed from specialist clinics experienced in managing HAE. The technology would be self-administered by patients for treatment of acute HAE attacks.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific investment would be required to introduce the technology.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, the technology would be expected to provide meaningful benefits compared with current care. An oral treatment for acute attacks would enable acute treatment to be administered earlier. Earlier administration of acute attacks of HAE has been shown to result in better outcomes, with quicker resolution and shorter duration.
11a. Do you expect the technology to increase length of life more than current care?	The technology is unlikely to increase length of life more than current care.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, the technology would be expected to increase HR-QoL more than current care. Current treatments for acute attacks are all injectable treatments, which can cause significant pain on injection as well as being inconvenient, cause anxiety for patients, are difficult to administer and/or require emergency department attendance. The availability of an oral treatment would address all these issues.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would be expected to be equally effective in all patients with HAE.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology will be easier for patients and healthcare professionals compared to current care. The additional elements/issues related to the use of injectable therapies are described above in previous answers, and an oral therapy would address these issues. It is also likely to be a lot more acceptable to patients because the technology is an oral treatment rather than an injectable therapies. Compared to injectable therapies, an oral treatment would be easy and quick to administer, remove pain, anxiety, difficulties, inconvenience and/or emergency department attendance associated with injectable therapies.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	For current acute treatments, all patients are offered/recommended to have acute treatment available to them to use as acute attacks are unpredictable. There are no rules for stopping acute treatment as all patients require this, although patients may express a preference for a particular type of acute treatment for various reasons. The technology would be expected to be used in a similar way to current acute treatments.
15. Do you consider that the use of the technology	It is unlikely that any substantial health-related benefits are not included in the QALY calculation.

will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, the technology is innovative in its potential to make a significant and substantial impact. It is the first oral therapy available for acute treatment of HAE attacks, and would offer multiple advantages compared to injectable therapies, as described in previous answers.
16a. Is the technology a 'step-change' in the management of the condition?	Yes, this technology would be considered a 'step-change' for acute treatment of HAE attacks. It is the first oral therapy available for acute treatment of HAE attacks, and would offer multiple advantages compared to injectable therapies, as described in previous answers.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, the technology does address an unmet need of the patient population. In general, current injectable therapies are painful, can cause anxiety and can be difficult/inconvenient to administer – resulting in treatment delays and poorer outcomes when used. Additionally, when patients have to present to the emergency department for acute treatment of HAE, there have been reports of additional difficulties and delays. Children, patients who are needle phobic or patients who are unable to self-administer medication (for any reason, including if an HAE attack temporarily incapacitates the use of their hands) will likely particularly benefit from an oral acute treatment as well, although an oral acute treatment would benefit all patients with HAE.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Technology has been well tolerated in clinical trials, with no side effects or adverse effects expected to have a significant effect.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the clinical trials used the technology for acute treatment of HAE attacks, which is where this technology would be used in UK clinical practice.
18a. If not, how could the results be extrapolated to the UK setting?	NA
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes would be reduction in attack severity, time to symptom relief, reduction in attack duration and time to attack resolution. These were measure in the trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that we are aware of.
19. Are you aware of any relevant evidence that	No

might not be found by a systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	Data on this technology is currently available only from clinical trials.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	None that we are aware of
21b. Consider whether these issues are different from issues with current care and why.	NA

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• The technology is the first available oral therapy for treatment of acute HAE attacks. • Current available technologies are all injectable medications and cause pain, inconvenience/difficulties in administration, are less easy to carry around, have a requirement for training and/or emergency department attendance, and can be associated with anxiety. All these often result in delays in treating acute attacks and poorer outcomes. • An oral acute therapy would obviate all the issues related to injectable therapies and would be a step-change in the management of acute attacks in HAE. • Children, people who are needle-phobic and people who are unable to self-administer injections are likely to find an oral therapy to be particularly advantageous, although this would benefit **all** patients with HAE for treating their acute attacks. •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sebetralstat for treating acute attacks of hereditary angioedema in people 12 years and over [ID6284]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

About you

1. Your name	Dr Patrick Yong
2. Name of organisation	The Royal College of Pathologists
3. Job title or position	Consultant Immunologist
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To treat acute swelling (angioedema) attacks associated with hereditary angioedema.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An acute treatment would be expected to reduce the time to onset of symptoms relief, improvement in symptoms and resolution of symptoms. However, there is inherent variability between attacks even in the same individual, and limited published clinical data/consensus as to what constitutes a clinically significant treatment response for acute HAE treatment.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is an unmet need in this condition. All licensed current treatments available for acute attacks are injectable medications, that are more difficult to transport around and to administer. This can result in delays to treatment, resulting in poorer outcomes from the acute treatment. The injectable treatments available are icatibant, which is given subcutaneously and C1 inhibitor, which is given intravenously. The icatibant does cause significant pain on injection although it is easy to learn to self-administer. It has a short half-life and a second dose is required about 10-20% of the time. C1 inhibitor is given intravenously and usually requires attendance at an emergency department or administration by a healthcare professional if a patient requires this – which does further delay the administration for acute attacks.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	The condition is treated with acute on-demand treatments (for when an angioedema attack occurs) and with prophylaxis (to prevent angioedema attacks from occurring). All patients are recommended to have an available

	supply of acute on-demand treatment as not all patients are on prophylaxis and breakthrough attacks can also occur in patients who are on prophylaxis.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Access to licensed therapies for acute treatment are determined by the NHSE clinical commissioning policies on treatment of acute attacks in hereditary angioedema (April 2013). Access to long-term prophylaxis are guided by the NHSE commissioning policy on plasma-derived inhibitor for prophylactic treatment (2016), and NICE TAs on lanadelumab and berotralstat. NHSE has published an algorithm in 2025 summarising these documents. International guidelines for this condition include the 2021 international WAO/EAACI guideline for the management of hereditary angioedema, although the treatment recommendations in there cannot be applied to all patients due to the access criteria within the NHSE commission policies and NICE TAs.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is relatively well defined, as access criteria to treatment are determined by the NHSE commissioning policies and NICE TAs.
9c. What impact would the technology have on the current pathway of care?	This technology would simplify patients treating acute HAE attacks by providing an oral alternative where currently the only available treatment options are all injectable medications. This would enable quicker administration of acute treatment, reduce anxiety associated with treatment and allow better outcomes as early treatment of acute attacks is associated with this. The medication would also be more portable, making it easier for patients to access the medication when needed. People with needle phobia and children may find the availability of an oral method of administration particularly helpful.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology would be used for acute treatment of HAE attacks, for the same indication as current available acute treatments.
10a. How does healthcare resource use differ	Current care for acute attacks include SC icatibant and IV C1 inhibitor. SC icatibant is usually self-administered but required appropriate training by a healthcare professional. IV C1 inhibitor is usually administered in a healthcare setting, although a small number of patients have been trained to self-administer this. Administration

between the technology and current care?	of IV C1 inhibitor usually requires attendance at an emergency department, along with the healthcare resource use associated with that. The new technology would not require either training to self-administer or emergency department attendance as it is an oral therapy.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology should be prescribed from specialist clinics experienced in managing HAE. The technology would be self-administered by patients for treatment of acute HAE attacks.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific investment would be required to introduce the technology.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, the technology would be expected to provide meaningful benefits compared with current care. An oral treatment for acute attacks would enable acute treatment to be administered earlier. Earlier administration of acute attacks of HAE has been shown to result in better outcomes, with quicker resolution and shorter duration.
11a. Do you expect the technology to increase length of life more than current care?	The technology is unlikely to increase length of life more than current care.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, the technology would be expected to increase HR-QoL more than current care. Current treatments for acute attacks are all injectable treatments, which can cause significant pain on injection as well as being inconvenient, cause anxiety for patients, are difficult to administer and/or require emergency department attendance. The availability of an oral treatment would address all these issues.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would be expected to be equally effective in all patients with HAE.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology will be easier for patients and healthcare professionals compared to current care. The additional elements/issues related to the use of injectable therapies are described above in previous answers, and an oral therapy would address these issues. It is also likely to be a lot more acceptable to patients because the technology is an oral treatment rather than an injectable therapies. Compared to injectable therapies, an oral treatment would be easy and quick to administer, remove pain, anxiety, difficulties, inconvenience and/or emergency department attendance associated with injectable therapies.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	For current acute treatments, all patients are offered/recommended to have acute treatment available to them to use as acute attacks are unpredictable. There are no rules for stopping acute treatment as all patients require this, although patients may express a preference for a particular type of acute treatment for various reasons. The technology would be expected to be used in a similar way to current acute treatments.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-	It is unlikely that any substantial health-related benefits are not included in the QALY calculation.

adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, the technology is innovative in its potential to make a significant and substantial impact. It is the first oral therapy available for acute treatment of HAE attacks, and would offer multiple advantages compared to injectable therapies, as described in previous answers.
16a. Is the technology a 'step-change' in the management of the condition?	Yes, this technology would be considered a 'step-change' for acute treatment of HAE attacks. It is the first oral therapy available for acute treatment of HAE attacks, and would offer multiple advantages compared to injectable therapies, as described in previous answers.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, the technology does address an unmet need of the patient population. In general, current injectable therapies are painful, can cause anxiety and can be difficult/inconvenient to administer – resulting in treatment delays and poorer outcomes when used. Additionally, when patients have to present to the emergency department for acute treatment of HAE, there have been reports of additional difficulties and delays. Children, patients who are needle phobic or patients who are unable to self-administer medication (for any reason, including if an HAE attack temporarily incapacitates the use of their hands) will likely particularly benefit from an oral acute treatment as well, although an oral acute treatment would benefit all patients with HAE.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Technology has been well tolerated in clinical trials, with no side effects or adverse effects expected to have a significant effect.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the clinical trials used the technology for acute treatment of HAE attacks, which is where this technology would be used in UK clinical practice.
18a. If not, how could the results be extrapolated to the UK setting?	NA
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes would be reduction in attack severity, time to symptom relief, reduction in attack duration and time to attack resolution. These were measure in the trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that we are aware of.

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Data on this technology is currently available only from clinical trials.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	None that we are aware of
21b. Consider whether these issues are different from issues with current care and why.	NA

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• The technology is the first available oral therapy for treatment of acute HAE attacks. • Current available technologies are all injectable medications and cause pain, inconvenience/difficulties in administration, are less easy to carry around, have a requirement for training and/or emergency department attendance, and can be associated with anxiety. All these often result in delays in treating acute attacks and poorer outcomes. • An oral acute therapy would obviate all the issues related to injectable therapies and would be a step-change in the management of acute attacks in HAE. • Children, people who are needle-phobic and people who are unable to self-administer injections are likely to find an oral therapy to be particularly advantageous, although this would benefit **all** patients with HAE for treating their acute attacks. •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sebetralstat for treating acute attacks of hereditary angioedema in people 12 years and over [ID6284]

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Immunology and Allergy Clinical Reference Group (CRG), NHS England
3. Job title or position	[redacted]

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? No Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? Yes An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? Yes Other (please specify): [redacted]
5a. Brief description of the organisation (including who funds it).	The Clinical Reference Group is an advisory body to NHS England and provides expert opinion on service commissioning, specification and governance. It is a part of NHSE and its resources funded by NHSE.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are World Allergy Organization and European Academy of Allergy and Clinical Immunology guidelines used for the treatment of hereditary angioedema (https://onlinelibrary.wiley.com/doi/10.1111/all.15214), these are supplemented by national commissioning guidance and a Clinical Commissioning Algorithm for hereditary and acquired angioedema secondary to C1 esterase inhibitor deficiency (hereditary-amd-acquired-angioedema-algorithms.pdf). There are also UK consensus guidelines.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is clearly defined and there is little or no difference of opinion regarding acute attack therapy
8. What impact would the technology have on the current pathway of care?	This would be the first oral therapy for acute attacks. Currently commissioned therapies are administered either via the subcutaneous (SC) or intravenous (IV) route, requiring administration training or emergency department (ED) attendance (e.g. for intravenous treatment), so availability of an oral treatment option would be a significant advance for patients/their carers.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	Not currently used – only IV or SC therapies available as licensed medicines
10. Will the technology be used (or is it already used) in the same way	The technology would replace the existing IV or SC therapies for responder patients >12 yrs and improve early self-treatment.

as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	The need for ED attendance would reduce for acute therapy to be administered, and the burden of training for self- administration on outpatient care would reduce.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This is specialist clinic only in tertiary care.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This would be within existing clinic framework and less intensive than that required for currently commissioned therapies.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	No additional testing required.
11. What is the outcome of any evaluations or audits of the use of the technology?	Phase 3 trials with demonstration of reduction to time of symptom relief and reduced severity and earlier resolution of the attack. No adverse safety signal. Equivalent as far as can be assessed to IV or S C therapies currently available.

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No equality issues other than age (lower) since PIP not yet complete so only for >12 yrs.
12b. Consider whether these issues are different from issues with current care and why.	Both icatibant and C1 esterase are available for all ages, so in due course this medicine should be made available if approved in the current age group to all ages once appropriate studies have been undertaken. The acceptability of a tablet for all ages vs injectable therapy is very important in accessing emergency treatment. Attacks are likely to be treated sooner and in all other studies earlier treatment is associated with better outcomes. When therapy has to be given IV or SC the time to treatment is slower still and associated with poorer outcomes, so again an oral therapy would have significant impact on all patients of all ages in equitably accessing care.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sebetralstat for treating acute attacks of hereditary angioedema in people 12 years and over [ID6284]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Tuesday 23 September 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating hereditary angioedema and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Patrick Yong
2. Name of organisation	Frimley Health NHS Foundation Trust
3. Job title or position	Consultant Immunologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with hereditary angioedema? ☐ A specialist in the clinical evidence base for hereditary angioedema or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
8. What is the main aim of treatment for hereditary angioedema? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	
10. In your view, is there an unmet need for patients and healthcare professionals in hereditary angioedema?	
11. How is hereditary angioedema currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	

• Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. How do data on real-world experience compare with the trial data?	
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this	

treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sebetralstat for treating acute attacks of hereditary angioedema in people 12 years and over [ID6284]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Tuesday 23 September 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating hereditary angioedema and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Sinisa Savic
2. Name of organisation	University of Leeds and Leeds Teaching Hospitals NHS Trust
3. Job title or position	Professor of Clinical immunology and honorary consultant immunologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with hereditary angioedema? ☐ A specialist in the clinical evidence base for hereditary angioedema or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for hereditary angioedema? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Hereditary Angioedema (HAE) is characterised by sudden, recurrent episodes of swelling that can last up to five days and occur without warning in body parts such as the hands, feet, genitals, face, tongue, neck, abdomen, and airway, with or without early warning signs. Attacks can be functionally impairing, debilitating, or,

	in the case of airway involvement, potentially life-threatening. Traditionally, treatment focused on managing and preventing angioedema attacks. However, the wider impact of HAE on patients' quality of life has increasingly been recognised, and with modern therapies the goals of treatment continue to evolve. Therefore, as recommended by international expert guidelines and adopted by clinicians in England, the main aim of treatment for HAE is to achieve complete control of the disease and the normalisation of patients' lives. This means preventing or minimising attacks so that patients can live safely, fully, and without restrictions, while also addressing the broader physical, psychological, and social burden of the disease. Treatment has two key components: rapid on-demand therapy to manage acute, potentially life-threatening episodes—especially those affecting the airway—and long-term prophylaxis to prevent attacks and maintain sustained control.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	For HAE a clinically significant treatment response can be defined in several complementary ways, reflecting both attack outcomes and overall disease control: 1. On-demand therapy: A clinically significant response is rapid relief of symptoms when treatment is given at the onset of an attack, leading to meaningful reduction in attack duration, severity, and functional impairment. Early and effective treatment should prevent progression to airway compromise, reduce the need for hospital or A&E attendance, and allow patients to resume normal daily activities more quickly. 2. Long-term prophylaxis: A clinically significant response is a sustained reduction in attack frequency, ideally achieving complete prevention of attacks (total disease control). Even partial reductions in frequency and severity may be clinically meaningful if they reduce morbidity, hospitalisations, and anxiety about future attacks. 3. Quality of life: Beyond objective attack outcomes, a clinically significant response should include improvements in patient-reported outcomes such as reduced anticipatory anxiety, greater independence, and improved participation in work, school, and social activities. International WAO/EAACI guidelines emphasise that the ultimate goal is normalisation of patients' lives—so a clinically significant response should be one

	that not only reduces attacks but also restores safety, confidence, and daily functioning.
10. In your view, is there an unmet need for patients and healthcare professionals in hereditary angioedema?	Yes, there remains a clear unmet need for both patients and healthcare professionals in HAE. While modern therapies have transformed management and made it possible for many patients to remain attack-free, not all patients respond well to current treatment options for acute attacks. In addition, the treatments available are not always convenient—particularly injectable therapies, which can be difficult for some patients to use, especially during a severe episode or for those with needle phobia. Beyond the acute setting, restrictive access criteria and variation in availability of long-term prophylaxis mean that many patients still experience a significant disease burden. The unpredictable nature of HAE, coupled with the physical, psychological, and social impact of the condition, highlights the need for more accessible, effective, and patient-friendly treatment options. Addressing these unmet needs is crucial not only to improve safety and clinical outcomes but also to ensure that patients can live fully normalised lives.
11. How is hereditary angioedema currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	In the NHS, all patients with HAE are managed and followed up in specialist immunology centres. Care is broadly aligned with international WAO/EAACI guidelines, which recommend universal access to on-demand therapy and the use of long-term prophylaxis based on disease activity, burden, and patient preference. However, the treatment landscape in the UK is more restricted due to commissioning policies. On-demand treatment remains injectable only, which is effective but not always convenient or acceptable to patients. These restrictions mean that, while specialist care is well-established, access to the full range of recommended treatments is constrained compared with international practice.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	Sebetralstat is currently available via early access to medicine scheme in selected immunology specialist centres. If adopted for use the prescribing will be via specialist immunology centres. No additional investment or training will be required for its adoption across the NHS

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, Sebetralstat, as the first oral on-demand therapy for HAE, has the potential to make treatment more accessible, improve adherence, and encourage earlier use at the onset of symptoms. This is highly relevant given international guideline recommendations that all patients should carry on-demand therapy for at least two attacks and treat early. An oral option could therefore reduce disease burden, minimise morbidity, and lower reliance on A&E attendance or hospital admissions.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	For many patients, especially those with needle phobia, difficulties with self-injection, or limited access to healthcare facilities, Sebetralstat may be more appropriate because of its oral route of administration, which improves convenience and could encourage earlier treatment of attacks. This is particularly relevant given that delays in treatment are associated with more severe and prolonged episodes. Adolescents and adults who wish to avoid the burden of carrying injectable therapies, or those who struggle with self-administration during acute episodes, may also find Sebetralstat more suitable. On the other hand, certain patient groups may require careful consideration. For example, patients unable to swallow oral medication may find oral therapy less appropriate. In these situations, access to alternative on-demand injectable therapies remains essential.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	Yes, oral on-demand treatment, Sebetralstat, will be significantly easier to use for the majority of patients compared to currently available therapies.

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The same rules that are currently used to provide on-demand treatment for HAE will be applied to Sebetralstat. According to international WAO/EAACI guidelines, all patients with a confirmed diagnosis of HAE should have immediate access to on-demand therapy, regardless of attack frequency or severity, since early treatment is essential to minimise the duration and impact of swelling episodes. Current recommendations state that every patient should carry on-demand treatment sufficient for at least two attacks at all times, as delays in treatment are associated with more severe and prolonged episodes. No additional diagnostic testing is required before initiating Sebetralstat beyond the initial confirmation of HAE, as the principle of care is that all patients deserve timely access to effective acute therapy.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes. In addition to improvements that will be reflected in QALYs (faster/earlier treatment → shorter, less severe attacks), Sebetralstat's oral, on-demand route is likely to deliver several process and life-impact benefits that standard utility instruments under-capture: 1. Removal of injection barriers (needle phobia; difficulty self-injecting during an attack) → less treatment delay and "rationing" of doses. Needle fear affects significant proportion of adults and contributes to delayed or avoided treatment, which worsens attacks; an oral option directly addresses this barrier. 2. Greater autonomy and usability in real-world settings (home, work, school, travel), aligning with guidance that every patient should carry enough on-demand therapy for two attacks and treat early—both harder to achieve with injectables. 3. Reduced A&E reliance due to easier, earlier self-treatment at home 4. Lower anxiety/anticipatory stress and improved dignity/privacy from being able to treat discreetly without needles—important given the documented psychological burden and treatment avoidance related to injections.

	5. Caregiver benefits (less need for another person to administer injections during severe attacks), which typical patient-only utility measures do not capture well. 6. Better alignment with shared-decision making and patient preference, a stated unmet need in the UK HAE pathway, potentially improving adherence and control beyond what is captured by EQ-5D-style instruments.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, Sebetralstat can be considered innovative in its potential to deliver significant health-related benefits for patients with HAE. Current on-demand treatments are effective but rely exclusively on injectable administration, which is not always convenient or acceptable for patients. Many individuals report difficulties with injections due to needle phobia, challenges in self-administration during severe attacks, or delays in accessing emergency care. These barriers often result in postponed treatment, which is known to increase the severity and duration of HAE attacks, negatively impacting quality of life. Sebetralstat, as the first oral on-demand therapy for HAE, directly addresses these unmet needs. Its oral route of administration represents a substantial innovation by making treatment more convenient, accessible, and acceptable to a broader group of patients. This could lead to earlier treatment of attacks, improved symptom control, reduced need for emergency care, and greater independence for patients. Importantly, the ability to take an oral medication discreetly and without the logistical challenges of injections may reduce anxiety associated with attacks, further improving health-related quality of life. By expanding the treatment landscape beyond injectables, Sebetralstat has the potential to improve the way current needs are met, offering a patient-centred, less invasive, and more practical option that aligns with modern treatment goals of achieving complete disease control and normalisation of life for people living with HAE.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The treatment is very well tolerated. Only minor side-effects have been reported in the trials and subsequent open labelled studies

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes, several UK centres also took part in the trials
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	The open label extension study confirmed the safety and efficacy of Sebetralstat shown in the original trials. Furthermore, far fewer patients needed or used the second dose of the treatment, and still achieved excellent attack control/resolution
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.	No

Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The treatment goal in HAE is complete disease control and normalisation of life through rapid on-demand therapy and, where appropriate, long-term prophylaxis.
Current injectable on-demand options are effective but inconvenient, and not all patients respond well, leaving a clear unmet need.
Sebetralstat is the first oral on-demand therapy, offering a step-change in accessibility, acceptability, and earlier treatment.
It will be used under the same rules as current on-demand therapy, requiring no additional diagnostic testing.
Trial and real-world evidence confirm it is safe, well tolerated, and effective, representing a meaningful advance in HAE care.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sebetralstat for treating acute attacks of hereditary angioedema in people 12 years and over [ID6284]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with hereditary angioedema or caring for a patient with hereditary angioedema. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Thursday 25 September 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for a patient with hereditary angioedema

Table 1 About you, hereditary angioedema, current treatments and equality

1. Your name	Angela Metcalfe
2. Are you (please tick all that apply)	☐ A patient with hereditary angioedema? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with hereditary angioedema? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Hereditary Angioedema UK (HAE UK)
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with hereditary angioedema? **If you are a carer (for someone with hereditary angioedema) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for hereditary angioedema on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for hereditary angioedema (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of sebetralstat over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does sebetralstat help to overcome or address any of the listed disadvantages of current treatment**	

that you have described in question 8? If so, please describe these	
10. If there are disadvantages of sebetralstat over current treatments on the NHS please describe these. For example, are there any risks with sebetralstat? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from sebetralstat or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering hereditary angioedema and sebetralstat? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sebetralstat for treating acute attacks of hereditary angioedema in people 12 years and over [ID6284]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with hereditary angioedema or caring for a patient with hereditary angioedema. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Thursday 25 September 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with hereditary angioedema

Table 1 About you, hereditary angioedema, current treatments and equality

1. Your name	Tim Crouch
2. Are you (please tick all that apply)	☒ A patient with hereditary angioedema? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with hereditary angioedema? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Hereditary Angioedema UK (HAE UK)
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: **As a trustee of HAEUK I have met many patients from across the UK at patient meetings and shared their experiences of this disease.**

Patient expert statement

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with hereditary angioedema? **If you are a carer (for someone with hereditary angioedema) please share your experience of caring for them**	I inherited Type 1 HAE from my mother and was therefore familiar with the condition. First presentation for me was aged 14 (1963) with abdominal pain due to intestinal swelling. In those days there were no specific treatments. For those unfortunate enough to suffer with laryngeal swelling in those times the outcome was often fatal. Since those early days I have had somewhere between four to eight episodes of swelling per annum. Stanozolol was introduced as prophylaxis, this had little effect and the drug was discontinued. After a frightening episode of upper airways obstruction due to laryngeal oedema in which I ended up in Intensive Care I was commenced on Danazol as prophylaxis, the effectiveness of which has been uncertain, and I was also commenced on the anti-bradykinin agent Icatabant which has largely been effective in aborting an attack. In the event of Icatabant failure I have C1 esterase inhibitor which I self-administer by iv injection. This is always effective. I consider myself lucky in that the episodes are relatively infrequent compared to many with the condition. Before the days of effective treatment, I learned to just to put up with attacks in the knowledge that things would settle after about forty eight hours Stress is a well-recognised trigger and attacks often occurred when travelling abroad and as a student at exam times. Things have improved enormously since the introduction of drugs to abort the attacks. Despite this the future for the treatment of HAE across the board lies in the development and wider use of effective prophylaxis particularly those with frequent

	attacks and the introduction of the oral anti kallikrein agent sebetralstat would represent an enormous benefit to HAE patients
7a. What do you think of the current treatments and care available for hereditary angioedema on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a - Treatment has progressed in recent years, particularly in terms of drugs to abort attacks, namely the anti-bradykinin agent Icatabant and the use of C1 Inhibitor. The standard prophylaxis treatments, androgens and antifibrinolytics, are of doubtful effectiveness. However, there is progress in this area with kallikrein inhibitors and the latest development of the factor X11 inhibitor and these agents are without doubt more effective than their predecessors. These drugs need to reach a certain threshold of attack frequency before they are prescribed. I hope that with time this will not apply. Most of these drugs are administered by subcutaneous injection or iv injection. Some patients struggle to self-administer and this can be a problem occasionally requiring an expensive trip to A&E. Some patients live a considerable distance from a hospital that offers care for HAE patients. The introduction of an oral kallikrein inhibitor for an acute attack will improve the lives of HAE patients enormously. They will be able to avoid the inconvenience of administering a sub cutaneous injection, perhaps in public, speed of administration being crucial and taking an oral preparation will get around this. 7b - Despite advances in treatment, the burden of HAE remains heavy for patients. Attacks can be very disabling; the frequency can be very variable from patient to patient. The disease is rare (1:50000) and therefore is not understood by employers, teachers' friends and family. Because HAE is so rare some GPs and A&E staff are unfamiliar with this disease leading to delays in treatment or diagnosis. All these things have a significant effect on quality of life which is ongoing.
8. If there are disadvantages for patients of current NHS treatments for hereditary angioedema (for	Current commonly used prophylaxis is of doubtful help. Androgens may have significant side effects. C1 inhibitor is extracted from human plasma and although

example, how they are given or taken, side effects of treatment, and any others) please describe these	the risk of transmission of viral disease should be extremely low there is a very slight possibility. Thrombosis is also a rare side effect. In some extreme case C1 is used as prophylaxis. As described in 7a, most treatments are by either subcutaneous or iv injection. Not all patients are able to self-administer.
9a. If there are advantages of sebetralstat over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does sebetralstat help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	9a - The development of newer prophylaxis for HAE patients is encouraging. The introduction of oral sebetralstat will be an absolute game changer for the reasons stated in 7a. The ability of patients to abort an acute attack will be substantially improved and as a spin off the need for A&E attendance for iv C1 administration will be reduced. 9b – Oral administration. 9c – As 7a, 9a and 9b above.
10. If there are disadvantages of sebetralstat over current treatments on the NHS please describe these. For example, are there any risks with sebetralstat? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Headaches appears to be the most common side effect.
11. Are there any groups of patients who might benefit more from sebetralstat or any who may benefit less? If so, please describe them and explain why	None

Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering hereditary angioedema and sebetralstat? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	None
13. Are there any other issues that you would like the committee to consider?	Can I ask you to be aware that after a lifetime with HAE and with a medical background I am well adjusted to it all. The views that I have expressed are primarily based on my experience as a trustee for HAEUK and with ten years in this role I have attended many patient meetings which has enabled me to understand the many facets of HAE and how it affects lives of those who suffer from this rare disease. Thank you for considering the points that I have made.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- As a someone with a lifetime of HAE and the sharing experiences with other HAE patients through my work with HAEUK I find it hard to emphasise enough the difference to life that an oral preparation to abort an acute attack would make.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over [ID6284]

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

Authors
Huiqin Yang, Reviews Manager, KSR Ltd, United Kingdom (UK)
Isaac Corro Ramos, Health Economics Researcher, Institute for Medical Technology Assessment (iMTA), EUR, the Netherlands (NL)
Marten Poley, Health Economist, Erasmus School of Health Policy & Management (ESHPM), EUR, the NL
Venetia Qendri, Health Economics Researcher, ESHPM, EUR, the NL
Kevin McDermott, Systematic Reviewer, KSR Ltd, UK
Xiaoyu Tian, Systematic Reviewer and Health Economist, KSR Ltd, UK
Lisa Stirk, Senior Information Specialist, KSR Ltd, UK
Nigel Armstrong, Health Economics Manager, KSR Ltd, UK

Correspondence to
Dr Huiqin Yang
Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, YO19 6FD
United Kingdom

Date completed 30 July 2025

Source of funding: This report was commissioned by the National Institute for Health Research (NIHR) Evidence Synthesis Programme as project number 175970.

Declared competing interests of the authors None.

Acknowledgements: We gratefully acknowledge the expert clinical advice input from Alexandros Grammatikos, North Bristol NHS Trust; Anthony Dorr, Barts Health NHS Trust; and Tariq El-Shanawany, University Hospital of Wales.

Tarig El-Shanawany made the following statement: "*I have participated in Advisory Boards for the company (Kalvista) but I have not worked on the submission for the sebetralstat appraisal. I also participated on the NICE HTA Access Forum on 17th December, but again have not been involved in writing or editing the submission. I have received payment from Takeda for an advisory board. They manufacture Firazyr which is used in the treatment of HAE attacks. However, this product is now off patent and generics are available and our department no longer uses Firazyr. Firazyr works via a different mechanism of action to sebetralstat, so I don't think it is an example of a "same health technologies being compared for this indication"*."

Confidential (CON) data are highlighted in blue throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Yang H, Corro Ramos I, Poley M, Qendri V, McDermott K, Tian X, Stirk L, Armstrong N. Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over [ID6284]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2025.

Contributions of authors:

Huiqin Yang acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Nigel Armstrong also acted as project lead as well as health economist on this assessment and contributed to the writing of the report. Isaac Corro Ramos acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Marten Poley and Venetia Qendri acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Xiaoyu Tian acted as systematic reviewer as well as health economists on this assessment. Huiqin Yang and Nigel Armstrong critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AC	Appraisal Committee
ACE	Angiotensin-converting enzyme
AdViSHE	Assessment of the Validation Status of Health-Economic decision models tool
AE	Adverse event
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BNF	British National Formulary
BR2	Bradykinin receptor 2
BSC	Best supportive care
C1-INH	C1 inhibitor
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CiC	Commercial in Confidence
CON	Confidential
COVID-19	Coronavirus disease 2019
CrI	Credible interval
CS	Company submission
CSR	Clinical Study Report
DCE	Discrete Choice Experiment
DP	Decision problem
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
ECM	Established clinical management
EDC	Electronic data capture
EED	Economic Evaluation Database
eMIT	electronic Market Information Tool
EQ-5D	European Quality of Life-5 Dimensions
ESHPM	Erasmus School of Health Policy & Management
EUR	Erasmus University Rotterdam
FAS	Full Analysis Set
FE	Fixed effects
FE	Fixing errors
FV	Fixing violations
GA-NRS	General Anxiety - Numeric Rating Scale
GnRH	Gonadotropin-releasing hormone
H	Hour
HAE	Hereditary angioedema
HCP	Health care practitioner
HCRU	Healthcare resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health Technology Assessment
IC	Indirect comparison

ICER	Incremental cost-effectiveness ratio
IMP	Investigational medicinal product
iMTA	Institute for Medical Technology Assessment
Incr.	Incremental
INMB	Incremental net monetary benefit
INR	International normalised ratio
IPD	Individual patient data
IQR	Interquartile range
ISPOR	Professional Society for Health Economics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IU	International units
IV	Intravenous
kg	kilogram
KSR	Kleijnen Systematic Reviews Ltd
LAR	Legally authorised representative
LOCF	Last observation carried forward
LTP	Long term prophylaxis
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MJ	Matters of judgement
ml	Millilitre
MPSC	Medicines procurement supply chain
N/A	Not applicable
NE	Not estimated
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NL	Netherlands
NMA	Network meta-analysis
NR	Not reported
OD	On demand
OLE	Open-label extension
OS	Overall survival
PAS	Patient Access Scheme
PD	Pharmacodynamic
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity scale
PICO	Population, Intervention, Comparator, Outcome
PK	Pharmacokinetic
PPS	Per Protocol Set
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PROMs	Patient reported outcome measures
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PS	Propensity score
PSW	Propensity score weighting
PT	Preferred term
Q1	25th percentile
Q3	75th percentile
QALY	Quality-adjusted life year

QoL	Quality of life
R	Randomisation
RCT	Randomised controlled trial
RE	Random effects
rhC1-INH	Recombinant human C1 esterase inhibitor
RoB	Risk of bias
SAE	Serious adverse event
SAS	Safety Analysis Set
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMD	Standardised mean difference
SOC	System organ class
SoC	Standard of care
STA	Single Technology Appraisal
STCs	Simulated treatment comparisons
STP	Short-Term Prophylactic
TA	Technology Appraisal
TEAE	Treatment emergent adverse event
TRAE	Treatment-related adverse event
TTA	Time to treatment administration
TTAR	Time to attack resolution
TTO	Time trade-off
UK	United Kingdom
ULN	upper limit of normal
US	United States
USA	United States of America
VAS	Visual analogue scale
VBA	Visual Basic for Applications
WTP	Willingness-to-pay

Table of Contents

Table of Tables

Table of Figures

1. Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem (DP), Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness (CE). A summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (DP), 3 (clinical effectiveness) and 4 (CE) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID6284	Summary of issue	Report Sections
1	Key issue 1: Uncertainty as to whether the HAE-nC1-INH subtype is included	2.1
2	Lack of adjustment for some important prognostic variables in the MAIC analysis	3.3 and 3.4
3	The EAG disagrees with the definition of the comparator technology as a basket of available treatments	4.2.4
4	The model results are extremely sensitive to changes in some key cost input parameters	4.2.5.3 4.2.7.2
5	Lack of comparative data to determine clinical effectiveness	4.2.5
6	The model results are counterintuitive for some scenario analyses	5.2.1
C1-INH = C1 inhibitor; EAG = External Assessment Group; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison		

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the following:

- Icatibant price based on most recent electronic Market Information Tool (eMIT) public price (£172.32).[1]
- Life tables (before coronavirus disease 2019 [COVID-19]) based on 2016-2018 (Section 4.2.6.3).
- Proportion of rescue medication in patients using icatibant set at 9.78% as in Aberer et al 2017.[2]
- HCP-time for subcutaneous assisted administration set at 20 minutes in line with experts consulted by the EAG.[3]
- The EAG prefers using a fully incremental analysis as explained in Section 4.2.4 of this report.

1.2 Overview of key model outcomes

NICE Technology Appraisals (TAs) compare how much a new technology improves length (overall survival [OS]) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, based on the company's base-case results, where the comparator is defined as a basket of available on-demand treatments, the new technology is modelled to affect QALYs by modestly increasing total QALYs by reducing time to treatment administration (TTA) (and thus time to attack resolution [TTAR]). Also, the technology is modelled to affect costs by reducing costs in all categories except those associated with additional dosing.

The company's base-case results are extremely sensitive to changes on key cost parameters such as the proportion of patients needing additional treatment doses or rescue therapy, or market shares. A small change on one of these parameters can result in sebetralstat dominance or an ICER well above the common CE thresholds used by NICE for decision making.

The EAG's view is that the definition of the comparator as a basket of treatments is not appropriate and that a fully incremental analysis should be conducted. When this occurs, the ICER increases greatly given that the more costly comparator treatments are dominated, and at the current estimated ICER, all the uncertainties identified by the EAG are deemed irrelevant for decision making purposes.

1.3 The DP: summary of the EAG's key issues

The DP addressed in the company submission (CS) is broadly in line with the Final Scope issued by NICE.

Table 1.2: Key issue 1: Uncertainty as to whether the HAE-nC1-INH subtype is included

Report Section	2.1
Description of issue and why the EAG has identified it as important	The company mention a third subtype, HAE-nC1-INH, previously classified as HAE Type III. There is a lack of evidence on this subtype.
What alternative approach has the EAG suggested?	The EAG requested clarification as to whether this subtype was part of the DP to which the company responded that it was very rare and that: "The focus within sebetralstat's clinical programme has been on Types I and II…"
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The company appear to have excluded this subtype from the DP, but clarification that this is the case would be helpful, even if the number of patients with this subtype is very small.
C1-INH = C1 inhibitor; CE = cost effectiveness; DP = decision problem; EAG = External Assessment Group; HAE = hereditary angioedema	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified one main concern with the evidence presented on the clinical effectiveness: there was a lack of adjustment for some important prognostic variables in the MAIC analysis due to the lack of availability of these variables (see Table 1.3).

Table 1.3: Key issue 2: Lack of adjustment for some important prognostic variables in the MAIC analysis due to the lack of availability of these variables

Report Section	3.3 and 3.4
Description of issue and why the EAG has identified it as important	It should be noted that a number of important prognostic variables (HAE Type [Type I versus Type II], comorbidity categories and baseline attack frequency) were not adjusted for in the MAIC analyses due to the lack of availability of these variables in the data. Therefore, the lack of adjustment for these important prognostic variables in the MAIC analysis may have compromised the validity of results of MAIC analysis.
What alternative approach has the EAG suggested?	All-important prognostic variables should be adjusted for in the MAIC analysis.
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends that all important prognostic variables should be adjusted for in the MAIC analysis where possible.
CE = cost effectiveness; EAG = External Assessment Group; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison	

1.5 The CE evidence: summary of the EAG's key issues

A full summary of the CE evidence review conclusions can be found in Section 5.5 of this report. The EAG's summary and detailed critique can be found in Section 4, the company's CE results are presented in Section 5.1, and the EAG's amendments to the company's model and results are in Section 5.2. The key issues in the CE evidence are discussed in Tables 1.4 and 1.5 below.

Table 1.4: Key issue 3: The EAG disagrees with the definition of the comparator technology as a basket of available treatments

Report Sections	4.2.4
Description of issue and why the EAG has identified it as important	The EAG considers that the definition of SoC as a basket of current OD treatments is not justified since there is no similar mechanism of action and no clinical equivalence between bradykinin B2 receptor antagonists and C1-INH.
What alternative approach has the EAG suggested?	The EAG has conducted a fully incremental analysis in line with the NICE reference case.
What is the expected effect on the CE estimates?	The ICER increases greatly given that the more costly comparator treatments are dominated.
What additional evidence or analyses might help to resolve this key issue?	Determine whether the definition of SoC as a basket of comparator treatments is appropriate or not.
C1-INH = C1 inhibitors; CE = cost effectiveness; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; OD = on demand; SoC = standard of care	

1.6 Secondary issues identified by the EAG

The EAG secondary key issues are those that have a significant impact on the model results under the assumption that the comparator in defined as a basket of treatments (which the EAG considers inappropriate).

Table 1.5: Key issue 4: The model results are extremely sensitive to changes in some key cost input parameters

Report Sections	**4.2.5.3 and 4.2.7.2**
Description of issue and why the EAG has identified it as important	The model results are extremely sensitive to changes on key cost parameters such as the proportion of patients needing additional treatment doses or rescue therapy, or market shares. A small change on one of these parameters can result in sebetralstat dominance or an ICER well above the common CE thresholds used by NICE for decision making.
What alternative approach has the EAG suggested?	Additional scenario analyses were explored by the EAG.
What is the expected effect on the CE estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Collect additional data on parameters such as the proportion of patients needing additional treatment doses or rescue therapy, or market shares to improve precision and reduce uncertainty.
CE = cost effectiveness; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence	

Table 1.6: Key issue 5: Lack of comparative data to determine clinical effectiveness

Report Sections	**4.2.5**
Description of issue and why the EAG has identified it as important	The company relied on a post-hoc analysis using TTA and attack location as predictors for TTAR. In terms of evidence hierarchy, well-conducted ITCs usually rank higher and should be preferred for estimating relative treatment effects (i.e., differences in TTAR between different treatment options).
What alternative approach has the EAG suggested?	Additional scenario analyses explored by the company.
What is the expected effect on the CE estimates?	Unclear, but likely minor/moderate.
What additional evidence or analyses might help to resolve this key issue?	Conduct or identify additional studies to incorporate clinical effectiveness comparative data in the economic analyses.
CE = cost effectiveness; EAG = External Assessment Group; ITC = indirect treatment comparison; TTA = time to treatment administration; TTAR = time to attack resolution	

Table 1.7: Key issue 6: The model results are counterintuitive for some scenario analyses

Report Sections	**4.2.5**
Description of issue and why the EAG has identified it as important	The model produces some counterintuitive outcomes not aligning with health economic expectations. Increasing disease burden either by increasing the annual attack rate or by decreasing the proportion of patients receiving LTP therapies, worsens the ICER

Report Sections	4.2.5
	for sebetralstat as compared to SoC, which is contrary to what would be expected.
What alternative approach has the EAG suggested?	The EAG conducted additional analyses to explore this outcome by simplifying cost assumptions. These analyses showed that incremental costs increase more rapidly than QALYs as disease burden rises, worsening the ICER. While the EAG attempted to further investigate the issue, the underlying structural or computational cause could not be fully identified within the available time.
What is the expected effect on the CE estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Investigate further this model behaviour to strengthen confidence in the model outcomes.
CE = cost effectiveness; EAG = External Assessment Group; ICER = incremental cost effectiveness ratio; LTP = long term prophylaxis; QALYs = quality-adjusted life year; SoC = standard of care	

1.7 Company's modelling errors identified by the EAG

No errors were found by the EAG in the model provided in response to the clarification letter.

1.8 Summary of the EAG's preferred assumptions and resulting ICER

The EAG made several changes to the company's updated model (received with the response to the clarification letter), which together defined the EAG base-case. The step-by-step changes made by the EAG to derive its base-case with their individual impact can be seen in Table 1.8. The changes with the greatest impact on the results were the use of the public eMIT price for icatibant and the removal of the assumption that the standard of care (SoC) comparator could be represented as a basket of treatments. The last was expected, since the only comparator not dominated is icatibant (subcutaneous [SC]); all the intravenous (IV) options are dominated due to their higher costs. Compared to icatibant, sebetralstat had an ICER of £[redacted] per QALY gained in the EAG base-case.

Table 1.8: Individual impact of EAG's preferred assumptions and EAG base-case deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CS base-case					
Sebetralstat	[redacted]	18.35	-	-	-
SoC	556,122	18.24	[redacted]	0.1109	[redacted]
Company base-case after clarification					
Sebetralstat	[redacted]	18.49	-	-	-
SoC	540,881	18.38	[redacted]	0.1112	[redacted]
EAG Change 1 – icatibant eMIT price (£172.32)					
Sebetralstat	[redacted]	18.49	-	-	-
SoC	406,938	18.38	[redacted]	0.1112	[redacted]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG Change 2 – life tables based on 2016-2018 (before COVID-19)					
Sebetralstat	[redacted]	18.58			
SoC	543,628	18.47	[redacted]	0.1118	[redacted]
EAG Change 3 – Proportion of rescue medication in patients using icatibant set at 9.78%					
Sebetralstat	[redacted]	18.49			
SoC	533,665	18.38	[redacted]	0.1112	[redacted]
EAG Change 4 – HCP-time for subcutaneous assisted administration set at 20 minutes					
Sebetralstat	[redacted]	18.49			
SoC	540,559	18.38	[redacted]	0.1112	[redacted]
EAG Change 5 – comparator not defined as SoC (fully incremental analysis) – EAG's base-case					
Sebetralstat	[redacted]	18.49	-	-	-
Icatibant	356,827	18.41	[redacted]	0.0775	[redacted]
Ruconest	612,962	18.34	[redacted]		
Berinert	753,743	18.34	[redacted]		
Cinryze	555,437	18.34	[redacted]		
EAG base-case					
Sebetralstat	[redacted]	18.58	-	-	-
Icatibant	97,474	18.50	[redacted]	0.0779	[redacted]
Ruconest	607,764	18.43	[redacted]		
Berinert	749,248	18.43	[redacted]		
Cinryze	550,003	18.43	[redacted]		

Source: Based on the model submitted following the clarification[4]
COVID-19 = coronavirus disease 2019; CS = company submission; EAG = External Assessment Group; eMIT = electronic Market Information Tool; HCP = health care practitioner; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care

1.9 Outline of confidential comparator or subsequent treatment prices

A confidential appendix to this EAG report includes analyses using confidential comparator prices. The treatments that have commercial arrangements can be found in Section 5.4 of this report.

2. Critique of company's definition of decision problem

Table 2.1: Statement of the decision problem (DP) (as presented by the company)

	Final Scope issued by NICE	DP addressed in the CS	Rationale if different from the NICE Final Scope	EAG comment
Population	People 12 years and over with HAE having an acute attack	Same as scope	People 12 years and over with HAE having an acute attack	
Intervention	Sebetralstat	Same as scope	Sebetralstat	
Comparator(s)	ECM for the treatment of acute attacks of HAE which may include: • C1-esterase inhibitors (this includes cinryze, berinert and ruconest) • icatibant	Same as scope	ECM for the treatment of acute attacks of HAE which may include: • C1-esterase inhibitors (this includes cinryze, berinert and ruconest) • icatibant	
Outcomes	The outcome measures to be considered include: • severity of angioedema attacks • duration of angioedema attacks • time to beginning of symptom relief • reduction in symptoms of angioedema attacks • mortality • use of rescue medication • frequency and duration of hospitalisation • adverse effects of treatment • HRQoL (for patients and carers).	Same as scope	The outcome measures to be considered include: • severity of angioedema attacks • duration of angioedema attacks • time to beginning of symptom relief • reduction in symptoms of angioedema attacks • mortality • use of rescue medication • frequency and duration of hospitalisation • adverse effects of treatment • HRQoL (for patients and carers).	

	Final Scope issued by NICE	DP addressed in the CS	Rationale if different from the NICE Final Scope	EAG comment
Economic analysis	The reference case stipulates that the CE of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and CE should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	Not completed in the CS	Not completed in the CS	The company used £837 as the price for icatibant based on the British National Formulary (BNF) list prices. The most recent eMIT public price is £172.32, which the EAG used in their base case.
Other considerations	None specified	None identified	N/A – in line with the NICE Final Scope	N/A

CE = cost effectiveness; CS = company submission; DP = decision problem; ECM = established clinical management; HAE = hereditary angioedema; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; N/A = not applicable; PSS = Personal Social Services; QALY = quality-adjusted life year

2.1 Population

The population defined in the National Institute for Health and Care Excellence (NICE) scope is the same as that in the decision problem (DP), i.e.: people 12 years and over with hereditary angioedema (HAE) having an acute attack.[5, 6] Figure 2 of the company submission (CS) shows that those patients eligible for sebetralstat are those with "Breakthrough Acute attack of HAE of sufficient severity to require admission/injected treatment on risk assessment".

EAG comment: It is noted that the population in the DP addressed in the CS is aligned with the NICE Final Scope.[5, 6] However, although all of the evidence in the CS is in the population of Type I or II (see Section 3.2.2), the company also mentions that: "a third much rarer subtype of HAE exists and presents with normal C1-inhibitors (C1-INH) (HAE-nC1-INH; previously classified as HAE Type III)."[6] They were therefore asked to clarify whether HAE Type III (HAE-nC1-INH) has been considered in the CS, and, if it has not been included, to explain the rationale for its exclusion and describe the potential implications of this exclusion on the clinical effectiveness assessment and cost effectiveness (CE) assessment.[7] In response, the company stated: "The third subtype of HAE that presents with normal C1-INH and function (HAE-nC1-INH; previously classified as HAE Type III), exists but is extremely rare with genetic mutations that result in a very small percentage of patients affected within a country – UK prevalence is estimated at around 1:3,000,000."[8] They also stated in their response that: "The focus within sebetralstat's clinical programme has been on Types I and II where much is understood about the biochemical pathway and sebetralstat's action to reduce HAE swellings. The focus on only these two subtypes within the sebetralstat clinical programme helped to ensure a relatively homogeneous study population within the trials to limit any inherent unknowns related to the HAE-nC1-INH subtype." It therefore appears that the company do not intend patients with the third subtype to be eligible for sebetralstat, which would exclude them from the DP. Although this is a very small number of patients in this population, the uncertainty as to whether it is included in the DP, and lack of evidence on this population, implies a key issue.

2.2 Intervention

The intervention in the NICE scope and the DP are the same i.e. sebetralstat.[5, 6] As stated in Table 2 of the CS, the recommended dose of sebetralstat is a 1 x 300 mg tablet to be taken orally by patients at the earliest recognition of a HAE attack, with an additional dose taken if needed.[6]

EAG comment: The EAG notes that the intervention is 300 mg to 600 mg as required, as opposed to 300 mg or 600 mg, as in the key trials (see Section 3). This is incorporated as a dose of 300 mg, with an additional dose as required, in the cost-effectiveness analysis (CEA) (see Section 4).

2.3 Comparators

The comparators in the scope are the same as in the DP i.e.:

Established clinical management (ECM) for the treatment of acute attacks of HAE which may include:

- C1-INHs (this includes cinryze, berinert and ruconest)
- Icatibant

This is also consistent with the place in the care pathway, as shown in Figure 2 of the CS. In the CEA, ECM is implemented as a basket of comparators labelled as standard of care (SoC) with the percentages of each of the four treatments determined by market share.

EAG comment: Ideally, sebetralstat should be compared separately with each comparator in a full incremental analysis in order to establish whether it could be cost effective.

2.4 Outcomes

The outcomes in the DP as the same as those in the NICE scope.[5, 6]

EAG comment: None.

2.5 Other relevant factors

None.

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

The company performed a systematic literature review (SLR) to identify and summarise the available randomised controlled trial (RCT) and other relevant evidence relating to the efficacy and safety of sebetralstat for the treatment of patients with acute attacks of HAE.

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[6] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.[9] The EAG has presented only the major limitations of each search strategy in the report.

Appendix B of the CS details the SLR conducted to identify relevant clinical evidence on the efficacy and safety of sebetralstat for acute attacks of HAE.[10] Searches were conducted in February 2024 and updated in November 2024.

EAG comments:

- Searches were undertaken to identify clinical evidence on the efficacy and safety of sebetralstat for treating acute attacks of HAE. The CS, Appendix B and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[6, 8, 10]
- The following databases were searched on 12 February 2024 from inception: Embase, MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL). Update searches were conducted on 15 November 2024. The CS also states that the Cochrane Database of Systematic Reviews (CDSR) was searched to identify relevant SLRs and meta-analyses.
- Three key conference proceedings were manually searched - the European Academy of Allergy and Clinical Immunology, the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma & Immunology. ClinicalTrials.gov was searched to identify ongoing and recently completed clinical trials, and medRxiv was searched for relevant preprints.
- The Embase and MEDLINE clinical effectiveness strategies searched for a range of terms for HAE. This population facet was then either combined with terms for sebetralstat/comparator treatments or limited to clinical trials using a study design filter. No publication date or language limits were applied. The CENTRAL search strategy searched only for HAE with no additional limits.
- The update searches were conducted by applying a 2024 publication year limit to the original searches. The EAG believed that the use of additional database fields (such as record entry date or update date) would have increased the chance of retrieving records with a pre-2024 publication date which had been added to the database since the date of the original search.
- All clinical effectiveness searches were well structured, transparent and reproducible, and contained a good range of search terms, synonyms and subject headings. Study design filters, where used, were not referenced, so it was unclear whether the filters used were published

objectively-derived filters. The filters contained a combination of subject heading terms and free text terms however, and the EAG considered them to be appropriate.

3.1.2 Inclusion criteria

The CS states that 'positive exclusion methods were used to exclude studies based on direct evidence that the study did not answer the research question. Articles were only rejected if they did not meet one or all of the inclusion criteria. Articles remained in the review until a stage when sufficient information was available to determine eligibility'. Table 3.1 details the eligibility criteria as provided in Appendix B of the CS.[10] It should be noted that the CS emphasises that '*this SLR was conducted at the Global level and therefore included ecallantide as an intervention since it has marketing authorisation in the US. For the purpose of the UK appraisal, ecallantide was not included in the UK PICO and therefore any included studies identified by the Global SLR that included ecallantide have been removed to provide included studies relevant for the UK* ([10]'.

Table 3.1: Eligibility criteria used in the search strategy for RCT and non-RCT evidence

	Inclusion	Exclusion
Population	Patients with HAE (HAE C1-INH Types I & II) in any setting of care.	Patients with normal C1-INH. Patients with non-HAE.
Interventions	Kalikrein inhibitors: • Sebetralstat • Ecallantide (Note: this SLR was conducted at the Global level and therefore included ecallantide as an intervention since it has marketing authorisation in the USA. For the purpose of the UK appraisal, ecallantide was not included in the UK PICO and any included studies identified by the Global SLR that included ecallantide have been removed to provide included studies relevant for the UK C1-INH: • Berinert • Ruconest • Cinryze BR2 receptor antagonists: • Icatibant	No intervention of interest evaluated.
Comparators	• Placebo or BSC • Any treatment that facilitates an indirect comparison (e.g. androgens)	No comparator of interest evaluated.

	Inclusion	Exclusion
Outcomes	• Time to treatment • Time to symptom relief • Time to minimal symptoms/almost complete symptom relief • Time to complete resolution • Redosing rate • Use of rescue medication • Safety, AEs by grade, drug-related AEs, type and severity, discontinuation due to AEs	N/A
Study design	RCTs and OLEs. SLRs and meta-analyses of RCTs (for hand-searching of references only).	Observational studies. Retrospective studies. Case-series/case studies. Editorials, commentary, letters, narrative reviews. PK or PD studies Animal or in vitro studies
Language restrictions	English language only.	Non-English language publications.
Source: Adapted from Table 7 of the CS, Appendix B[10] AEs = adverse events; BR2 = bradykinin receptor 2; BSC = best supportive care; CS = company submission; HAE = hereditary angioedema; IC = indirect comparison; N/A = not applicable; OLE = open-label extension; PD = pharmacodynamic; PICO = Population, Intervention, Comparator, Outcome; PK = pharmacokinetic; RCT = randomised controlled trial; SLR = systematic literature review; UK = United Kingdom; USA = United States of America		

3.1.3 Critique of screening and data extraction

Studies were selected for inclusion through a two-stage screening. All relevant abstracts and titles were screened against the eligibility criteria and all included at that stage were then retrieved as full text articles and screened. Those that were included the progressed to data extraction and quality appraisals.

The CS states that '*Two reviewers worked independently to screen records and extract data, with any disagreements or discrepancies resolved through discussion and agreement between the reviewers. Following initial discussions between the 2 reviewers, a consensus was reached on any remaining discrepancies*.'[10]

We asked the company to describe how disagreements were resolved between the two reviewers when no consensus could be reached. In their response the company clarified that '*There were limited instances where disagreements were unresolvable between the two reviewers. On these occasions, the reviewers would engage with the project lead to seek her input*'[8].

EAG comment: Duplicate screening and data extraction reflects an optimal method to reduce likelihood of errors and biases and the addition of a third reviewer to arbitrate any disagreements that could not be resolved is again good practice.

3.1.4 Quality assessment

The Cochrane Risk of Bias 2.0 tool was used to perform quality appraisals of included studies. The CS did not provide information on how appraisals were conducted so the EAG requested further information. In their response to clarification the company stated that '*Two reviewers conducted the quality appraisals and would consider any disagreements. The project lead was engaged whenever her input was required*.'[8].

The results of the quality appraisals are detailed below with any EAG comments listed.

Table 3.2: KONFIDENT quality appraisal

Appraisal	KONFIDENT [Phase 3 KVD900-301 study; NCT05259917]	EAG comments
Was randomisation carried out appropriately?	Yes. Patients received the following treatments in a 1:1:1:1:1:1 ratio using a permuted-block randomisation method, double-dummy blinded, crossover fashion to treat three separate eligible HAE attacks: • 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 matching placebo tablet) • 600 mg KVD900 (2 × 300 mg KVD900 tablets) • Placebo for KVD900 (2 matching placebo tablets)	N/A
Was the concealment of treatment allocation adequate?	Yes. Matching placebo tablets were administered.	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Disease characteristics were well balanced between treatment groups at baseline.	Generally, well matched but also some imbalances (>5%) in some characteristics such as gender and geographical location
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. The sponsor, investigators, trial-site personnel, and patients were unaware of the trial-group assignments.	N/A
Were there any unexpected imbalances in drop-outs between groups?	No. [redacted] patients in sequence A, [redacted] patients in sequence B, [redacted] in sequence C, [redacted] sequence D, [redacted] sequence E, [redacted] sequence F dropouts occurred in the different groups. In total, [redacted] discontinued (safety set). The primary reason	N/A

Appraisal	KONFIDENT [Phase 3 KVD900-301 study; NCT05259917]	EAG comments
	for trial discontinuation was that the specified number of attacks for trial completion was reached and ongoing patients were terminated. This was recorded as trial termination by sponsor ([redacted] patients) in the EDC. (Source: Table 5-1 of the KONFIDENT CSR report). Even though the numbers of dropouts between the groups were slightly different, the small patient numbers involved do not statistically infer that they are imbalanced or unexpected.	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All the outcomes measured are reported in the CSR.	N/A
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. An ITT analysis with imputation for missing data was performed to assess the sensitivity of the findings to the exclusion of participants who underwent randomisation but did not have any attacks during the trial period. The FAS included all randomised patients who received trial medication from at least one period for the respective qualifying HAE attack. If one or more patient(s) received the incorrect trial medication, data summarised using the FAS were presented according to the randomised treatment. The FAS was the population for efficacy analyses. Efficacy end points were censored at 0 hours if the end point could not be derived owing to missing data (e.g., if data from only 1 time point were available). Analyses were conducted under the assumption	N/A

Appraisal	KONFIDENT [Phase 3 KVD900-301 study; NCT05259917]	EAG comments
	that missing data were missing at random.	
Source: Adapted from Table 13, CS Appendices[10] CS = company submission; CSR = Clinical Study Report; EAG = External Assessment Group; EDC = electronic data capture; FAS = Full Analysis Set; HAE = hereditary angioedema; ITT = intention-to-treat; mg = milligram; N/A = not applicable		

Table 3.3: Critical appraisal: KONFIDENT-S OLE trial

Appraisal	KONFIDENT-S [KVD900-302 OLE trial; NCT05505916]	EAG comments
Was randomisation carried out appropriately?	Yes, The trial included rollover patients (those randomised in the KONFIDENT Phase 3, KVD900-301 trial) and non-rollover patients (those randomised in the KVD900-201 Phase 2 trial or sebetralstat- naïve patients).	N/A
Was the concealment of treatment allocation adequate?	Yes. No concealment of treatment allocation was required as KONFIDENT-S (KVD900-302) is an ongoing open-label, multicentre extension trial.	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	[redacted]	Generally, well matched but noticeable differences >5% between arms with regards to geographical origin and ethnicity.
Were the care providers, participants and outcome assessors blind to treatment allocation?	No. KONFIDENT-S (KVD900-302) is an ongoing open-label, multicentre extension trial.	N/A
Were there any unexpected imbalances in drop-outs between groups?	No. [redacted] patients had discontinued from the trial. The primary reasons for discontinuations from the trial were withdrawal by patient ([redacted] patients) and AEs ([redacted] patients). A total of [redacted] patients are ongoing in the trial.	N/A
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All the outcomes measured are reported in the CSR.	N/A

Appraisal	KONFIDENT-S [KVD900-302 OLE trial; NCT05505916]	EAG comments
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. The FAS included all enrolled patients who received at least 1 dose of IMP for a qualifying HAE attack. It was the population for efficacy analyses.	N/A

Source: Adapted from Table 14, CS Appendices[10]
AEs = adverse events; CS = company submission; CSR = Clinical Study Report; EAG = External Assessment Group; FAS = Full Analysis Set; HAE = hereditary angioedema; IMP = investigational medicinal product; ITT = intention-to-treat; N/A = not applicable; OLE = open-label extension

3.1.5 Evidence synthesis

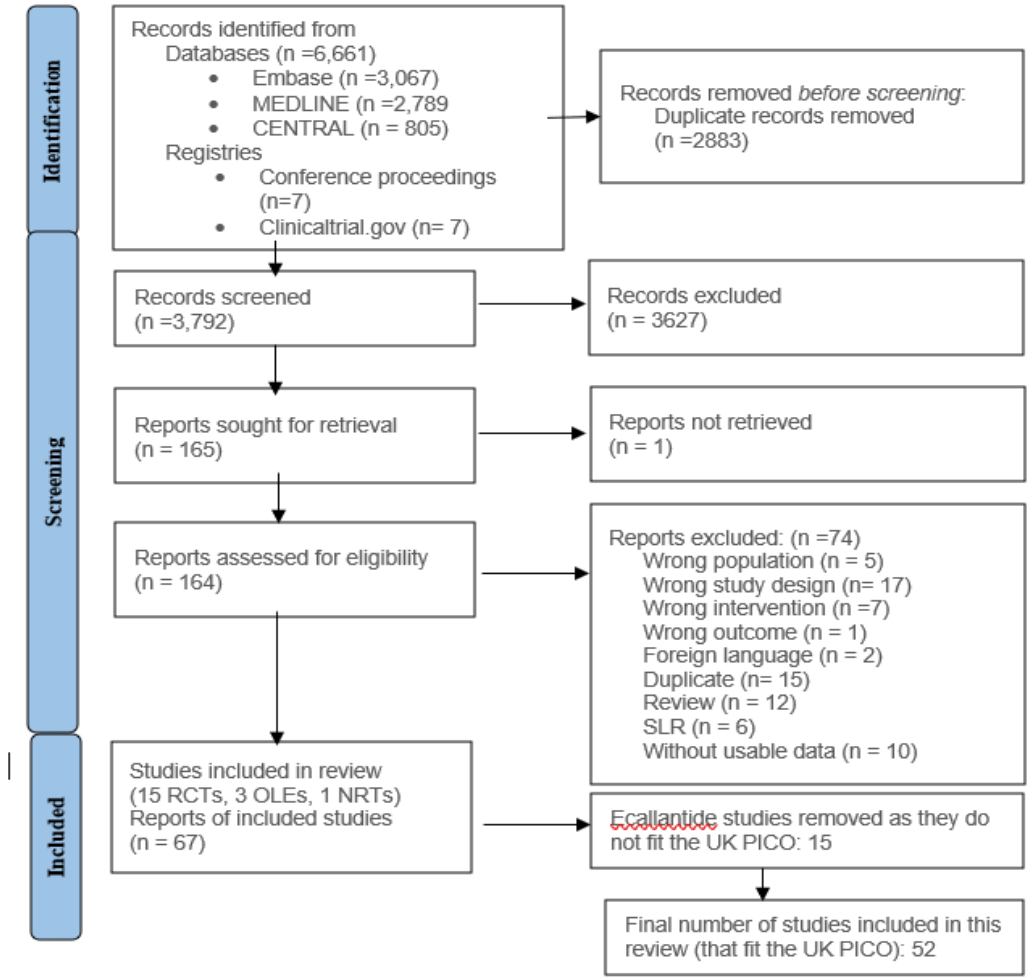
In the absence of a head-to-head trial comparing sebetralstat with other comparators, a SLR and matching-adjusted indirect comparison (MAIC) was conducted to determine the relative efficacy between sebetralstat and recombinant human C1 esterase inhibitor (rhC1-INH). Details and EAG's comments are provided in Sections 3.3 and 3.4 for the ITC.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Study retrieval

Study identification and retrieval is summarised with a Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRISMA) (see below). Six thousand, six hundred and sixty-one records (see Figure 3.1) were identified by the searches. After duplicates records were removed, 3,792 title and abstracts were screened. Of these 165 full texts were retrieved and following screening a total of 65 publications were included for data extraction. Three references were added from the grey literature searches, bringing the total number of included publications to 67. Of these 67 publications, 15 were unique RCTs, three were open label extension (OLE) studies and one was a non-randomised, open label, single arm study. Twenty-seven of the 67 publications were subgroup analyses, pooled from several trials and 26 were conference abstracts. Fifteen studies were removed since they included a sole focus of ecallantide which does not match the United Kingdom (UK) population, intervention, comparator and outcomes (PICO) for the sebetralstat NICE submission.[10] Fifty-two UK relevant studies were therefore included.

Figure 3.1: PRISMA flow chart



Source: Adapted from Figure 1, CS Appendices[10]
CS = company submission; NRT = non-randomised trial; OLE = open label extension; PICO = population, intervention, comparator, outcome; PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT = randomised controlled trial; SLR = systematic literature review; UK = United Kingdom

3.2.2 Trial summaries

This Section provides a summarised overview of included evidence as is presented in the CS.[6]

3.2.2.1 Summary of the KONFIDENT Phase 3 trial

KONFIDENT was a Phase 3 double-blind, randomised, placebo-controlled, three-way crossover trial 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 HAE attacks.[6] Table 3.4 provides an overview of trial characteristics.

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.

Table 3.4: KONFIDENT Phase 3 trial design

Trial number (acronym)	**NCT05259917 (KONFIDENT)**
Location	Australia, Bulgaria, Canada, France, Germany, Greece, Hungary, Israel, Italy, Japan, Netherlands, New Zealand, North Macedonia, Poland, Portugal, Puerto Rico, Romania, Slovakia, Spain, UK (included five UK sites*) and USA.
Trial design	A randomised, double-blind, placebo-controlled, Phase 3, three-way crossover trial to evaluate the efficacy and safety of two dose levels of sebetralstat, an oral plasma kallikrein inhibitor, for OD treatment of angioedema attacks in adolescent and adult patients with HAE Type I or II.
Eligibility criteria for participants	Inclusion criteria: • Male or female patients 12 years of age and older. • Confirmed diagnosis of HAE Type I or II at any time in the medical history. • Patient has access to and ability to use conventional OD treatment for HAE attacks (plasma-derived or recombinant C1-INH, icatibant, or ecallantide). • If a patient is receiving long-term prophylactic treatment with one of the protocol-allowed therapies (IV or SC plasma-derived C1-INH protein, lanadelumab, or berotralstat), they must be on a stable dose and regimen for at least 3 months immediately before and during the trial. Patient must be willing to remain on a stable dose and regimen for the duration of the trial. • Patient's last dose of attenuated androgens other than danazol was at least 28 days prior to randomisation. Patient: • Has had at least two documented HAE attacks within 3 months prior to screening or randomisation; or • Is a completer of the KVD824-201 trial within 3 months prior to randomisation and meets all other entry criteria to enrol in KVD900-301 KONFIDENT Phase 3 study. • Patients must meet the contraception requirements. • Patients must be able to swallow trial tablets whole. • Patients, as assessed by the Investigator, must be able to appropriately receive and store IMP, and be able to read, understand, and complete the electronic diary (eDiary). • Investigator believes that the patient is willing and able to adhere to all protocol requirements. • Patient provides signed informed consent or assent (when applicable). A parent or LAR must also provide signed informed consent when required.
Eligibility criteria for participants	Exclusion criteria: • Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1-INH deficiency, HAE with normal C1-INH (previously known as HAE Type III), idiopathic angioedema, or angioedema associated with urticaria.

Trial number (acronym)	NCT05259917 (KONFIDENT)
	• Attenuated androgens, antifibrinolytic agents, and other investigational long-term prophylactic agents were not permitted in most countries. Exclusion of attenuated androgens was due to safety concerns related to their mixed use across the countries included in KONFIDENT, with only danazol approved in the USA and a wide range of others used across other regions, many of which are not approved for use in HAE. Similarly, exclusion of tranexamic acid was due to its variable approval status across the countries included in KONFIDENT. • A clinically significant history of poor response to BR2 blocker, C1-INH therapy or plasma kallikrein inhibitor therapy for the management of HAE, in the opinion of the Investigator. • Use of ACE inhibitors after the Screening Visit or within 7 days prior to randomisation. • Any oestrogen containing medications with systemic absorption (such as oral contraceptives including ethinyloestradiol or hormonal replacement therapy) within 7 days prior to the screening visit or during the trial. • Patients who require sustained use of strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers. Inadequate organ function, including but not limited to: • ALT >2x ULN • AST >2x ULN • Bilirubin direct >1.25x ULN • INR >1.2 • Clinically significant hepatic impairment defined as a Child-Pugh B or C • Any clinically significant comorbidity or systemic dysfunction, which in the opinion of the Investigator, would jeopardise the safety of the patient by participating in the trial. • History of substance abuse or dependence that would interfere with the completion of the trial, as determined by the Investigator. • Known hypersensitivity to sebetralstat or placebo or to any of the excipients. • Prior participation in trial KVD900-201. • Participation in any gene therapy treatment or trial for HAE. • Participation in any interventional investigational clinical trial (with the exception of KVD824-201), including an investigational COVID-19 vaccine trial, within 4 weeks of the last dosing of investigational drug prior to screening. • Any pregnant or breastfeeding patient.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered)	Participants were randomly assigned in a ratio of 1:1:1:1:1:1 to one of six sequences. In each sequence, one or two doses of the first trial agent in the sequence was administered by the participant for the first eligible HAE attack, one or two doses of the second trial agent in the sequence was administered for the second eligible attack, and one or two doses of the third trial agent in the sequence was administered for the third eligible attack.

Trial number (acronym)	**NCT05259917 (KONFIDENT)**
Intervention(s) (n=[x]) and comparator(s) (n=[x]) Permitted and disallowed concomitant medication	Prior medications (including conventional HAE medications) are defined as those medications taken within 4 weeks prior to the Screening Visit up to the first dose of IMP. Concomitant medications are defined as those medications (including conventional HAE medications) ongoing at or started after the first dose of IMP.
Primary outcomes (including scoring methods and timings of assessments)	Evaluation of efficacy: • PGI-C: time to beginning of symptom relief defined as at least "a little better" (2 time points in a row) within 12 hours of the first IMP administration.
Other outcomes used in the economic model/specified in the scope	Key secondary outcomes: • PGI-S: time to first incidence of decrease from baseline (2 time points in a row) within 12 hours of the first IMP administration. • PGI-S: time to HAE attack resolution defined as "none" within 24 hours of the first IMP administration. Secondary endpoints: • PGI-C: proportion of attacks with beginning of symptom relief defined as at least "a little better" (2 time points in a row) within 4 hours and within 12 hours of the first IMP administration. • PGI-C: time to at least "better" (2 time points in a row) within 12 hours of the first IMP administration. • PGI-S: time to first incidence of decrease from baseline (2 time points in a row) within 24 hours of the first IMP administration. • Composite VAS: time to at least a 50% decrease from baseline (3 time points in a row) within 12 hours and within 24 hours of the first IMP administration. Exploratory endpoints: • GA-NRS: cumulative GA-NRS expressed as area under the curve over 12 and 24 hours of the first IMP administration. Outcomes modelled that are in the NICE scope. Severity of angioedema attacks. Reduction in symptoms of angioedema attacks. Mortality. Use of rescue medication. Adverse effects of treatment. HRQoL.
Pre-planned subgroups	Prespecified subgroup analyses of the primary and key secondary end points were performed according to: • Age group • Use of long-term prophylaxis (yes or no) • Baseline attack location and severity • Number of administrations of the trial agent (1 or 2) • Geographic region

Trial number (acronym)	NCT05259917 (KONFIDENT)
Source: Adapted from Table 5, CS[6] * The five UK sites and the associated number of subjects enrolled, include: Royal London Hospital, London (1 subject); Frimley Park Hospital, Surrey (2 subjects); St James University Hospital, Leeds (4 subjects); University Hospital Birmingham (1 subject); Immunodeficiency Centre for Wales, Cardiff (0 subjects) ACE = angiotensin-converting enzyme; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BR2 = bradykinin receptor 2; COVID-19 = coronavirus disease 2019; CS = company submission; GA-NRS = general anxiety - numeric rating scale; HAE = hereditary angioedema; HRQoL = health-related quality of life; IMP = investigational medicinal product; IV = intravenous; OD = on-demand; SC = subcutaneous; UK = United Kingdom; ULN = upper limit of normal; USA = United States of America; VAS = visual analogue scale	

The CS states that randomisation was stratified according to the use of long-term prophylaxis at enrolment.[6] Eligible attacks were those considered by the participant to meet the following criteria:

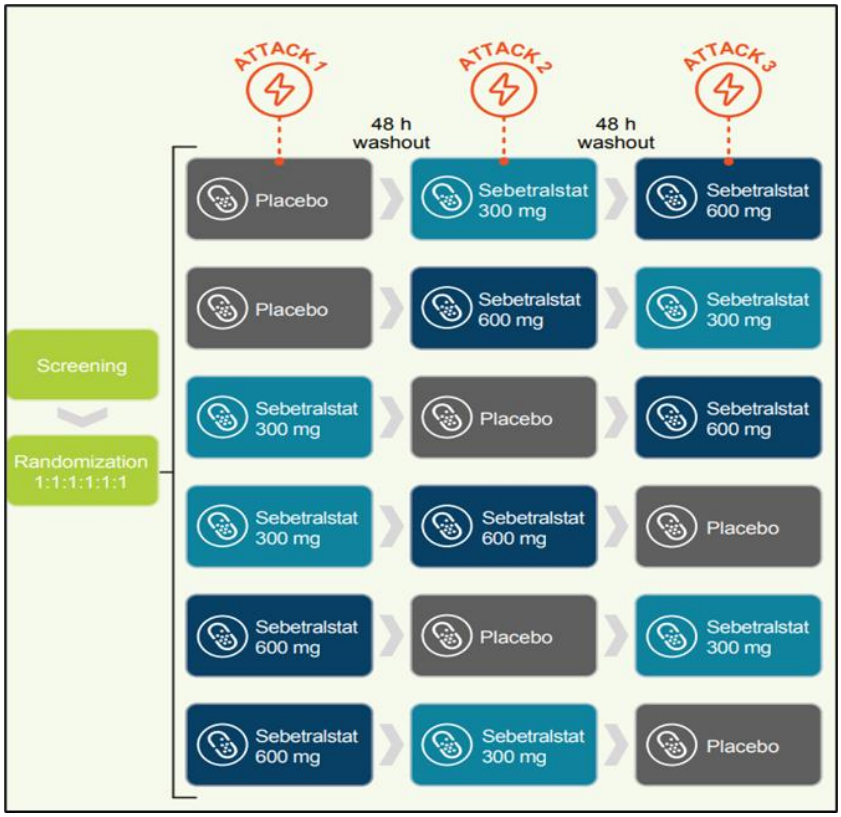
- the start of the attack could be identified, at least 48 hours had elapsed since the trial agent or conventional treatment was taken for a previous attack,
- the participant had the ability to enter attack information in an electronic diary during the initial 4 hours after first taking the trial agent,
- the attack involved any location and severity at baseline, excluding laryngeal attacks that were considered by the participant to be severe.

Patients were asked to self-administer a single dose of 300 mg sebetralstat (1 × 300 mg sebetralstat tablet plus 1 placebo tablet), 600 mg sebetralstat (2 × 300 mg sebetralstat tablets), or 2 matching placebo tablets in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours a second dose of the investigational medicinal product (IMP); the IMP may have been administered for each attack. The second dose of the IMP matched the initial dose administered.[6]

Due to the nature of the trial design EAG requested clarification of how treatment switching would be addressed in the analysis. The company in their response to clarification stated that '*The purpose of the crossover design was to enable the randomised evaluation of effect of the 3 different options (i.e. placebo and the 2 doses of sebetralstat) on the same individuals, essentially including each participant as their own control and maximizing data collection in patients with a rare disease. This type of trial design helps to minimise the impact of individual variability between participants and to ensure sufficient number of attacks were available for analysis.' They further stated that 'In any crossover trial, carryover effects should be considered. For the KONFIDENT trial, a minimum washout was required to ensure drug concentrations were eliminated by the end of the data collection period. The half-life of sebetralstat is approximately 3 hours. Because of the intermittent nature of attack frequency, median attacks actually occurred approximately every 21 days. The period and sequence were included in the primary analysis as a fixed effect to control for these effects, if any, and patients were nested within sequence as a random effect'*

EAG comment: In response to clarification letter, the company reproduced the following figure from the CS:

Figure 3.2: KONFIDENT Phase 3 trial design



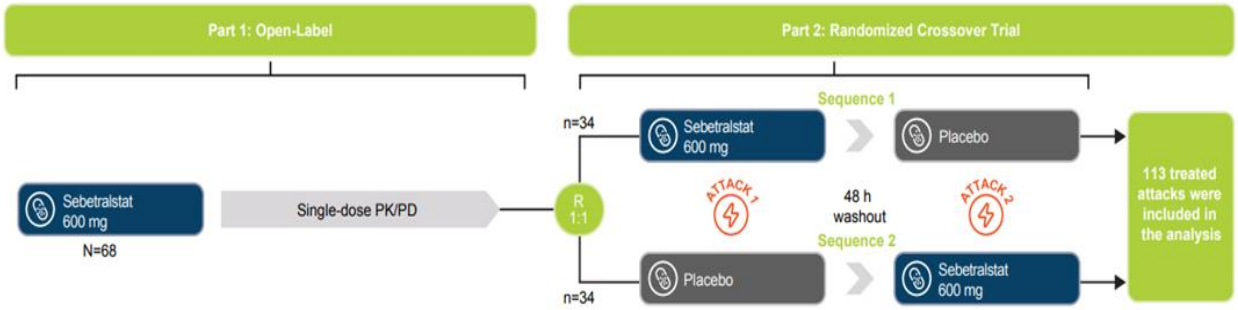
Source: Figure 3, CS, reproduced in clarification response
CS = company submission; h = hour

The EAG notes that this increased the efficiency of the trial i.e. by analysing attacks as opposed to patients and randomising the sequence of doses so that the probability of a patient being treated with any dose (or placebo) in any attack (1, 2 or 3) is the same. The EAG also considers that the washout period is sufficient to reduce any contamination by previous treatment, although any such bias is reduced by randomising patients to sequences of doses.

3.2.2.2 Summary of Sebetralstat Phase 2 Study

KVD900-201 was a randomised, cross-over Phase 2 trial run in two parts (NCT04208412) comparing sebetralstat with placebo as an on-demand (OD) treatment for patients with HAE Type I or HAE Type II. Part 1 assessed the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of a single 600 mg dose of sebetralstat, whilst Part 2 was a randomised, double-blinded, placebo-controlled, two-sequence, two-period (2 x 2) crossover trial to assess the efficacy, safety, and tolerability of a single dose of sebetralstat (600 mg).[6]

Figure 3.3: Phase 2 trial profile



Source: Adapted from Figure 2, CS Appendices[10]
CS = company submission; H = hour; R = randomisation; PK/PD = pharmacokinetic/pharmacodynamic

Table 3.5: Summary of KVD900-201 trial methodology design

Trial number (acronym)	**NCT04208412 (KVD900-201)**
Location	25 study centres in 10 countries (1 in Austria, 3 in the Czech Republic, 3 in Germany, 1 in Hungary, 3 in Italy, 1 in Macedonia, 2 in Poland, 1 in the Netherlands, 4 in the UK and 6 in the USA).
Trial design	A two-part, randomised, double-blind, crossover Phase 2 trial comparing sebetralstat versus placebo in patients with HAE Type I or II. In Part 1 of the trial, participants were given a single 600 mg open-label oral dose of sebetralstat to assess safety, PK and PD of the dose. Part 2 was a randomised, double-blind, placebo-controlled, two-sequence, two-period (2 × 2) crossover trial; participants were randomly assigned (1:1) to either sequence 1, in which they were given a single dose of 600 mg of sebetralstat to treat the first eligible attack and a second dose of placebo to treat the second eligible attack, or sequence 2, in which they were given placebo to treat the first eligible attack and then 600 mg of sebetralstat to treat the second eligible attack. Participants and investigators were masked to treatment assignment.[11]
Eligibility criteria for participants- Inclusion criteria	Individuals were eligible if they had experienced at least three HAE attacks in the past 93 days, were not on prophylactic therapy, and had access to and the ability to self-administer conventional attack treatment. [11] Key inclusion criteria: • Male or female adult subjects 18 years of age and older. • Confirmed diagnosis of HAE Type I or II at any time in the medical history. • At least three documented HAE attacks in the past 93 days, as supported by medical history. • Access to and ability to use conventional attack treatment for attacks of HAE. • Adequate organ functions. • Females of childbearing potential must agree to use highly effective birth control from the Screening visit until the end of the trial follow-up procedures. • Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months, do not require contraception during the study. • Males with female partners of childbearing potential must agree to be abstinent or else use a highly effective method of birth control as defined in inclusion 6 from the Screening Visit until the end of the trial follow-up procedures. • Provide signed informed consent and are willing and capable of complying with study requirements and procedures.

Trial number (acronym)	**NCT04208412 (KVD900-201)**
Eligibility criteria for participants- Exclusion criteria	Key exclusion criteria: • Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1-INH deficiency, HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or angioedema associated with urticaria. • Current use of C1-INH, androgens, or tranexamic acid for HAE prophylaxis. • Use of ACE inhibitors or any oestrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 93 days prior to initial study treatment. • Use of androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) or antifibrinolytics within 30 days prior to initial study treatment. • Use of lanadelumab within 10 weeks prior to initial study treatment. • Use of strong CYP3A4/CYP2C9 inhibitors and inducers during participation in the trial. • Clinically significant abnormal ECG at Visit 1 and pre-dose at Visit 2. This includes, but is not limited to, a QT interval by Fredericia, QTcF >470 msec (for women) or >450 msec (for men), a PR >220 msec or ventricular and/or atrial premature contractions that are more frequent than occasional and/or occur as couplets or higher in grouping. • Any clinically significant history of angina, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, or any other cardiovascular abnormality. • Any other systemic dysfunction (e.g., gastrointestinal, renal, respiratory, cardiovascular) or significant disease or disorder which, in the opinion of the Investigator, would jeopardise the safety of the subject by taking part in the trial. • History of substance abuse or dependence that would interfere with the completion of the study, as determined by the Investigator. • Known lactose allergy or intolerance. • Known hypersensitivity to KVD900 or placebo or to any of the excipients. • Participation in an interventional investigational clinical study within 93 days or within 5 half-lives of the last dosing of investigational drug (whichever is longer) prior to initial study treatment. • Any pregnant or breast-feeding subject.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x])	In Part 1 of the trial, participants were given: • A single 600 mg open-label oral dose of sebetralstat (n=68) For Part 1, assessment of vital signs and safety laboratory tests were done before and at 1 hour and 4 hours after study drug administration. Plasma samples were taken during Part 1 before, every 15 minutes for the first hour, and at 1.5, 2, 3, and 4 hours after study drug administration. In Part 2 participants were randomised (1:1) to receive either:

Trial number (acronym)	**NCT04208412 (KVD900-201)**
Permitted and disallowed concomitant medication	Sequence 1: a single 600 mg oral dose of sebetralstat to treat the first eligible attack and a second dose of placebo to treat the second eligible attack (n=34) OR Sequence 2: placebo to treat the first eligible attack and then 600 mg of sebetralstat to treat the second eligible attack (n=34). For Part 2, a minimum 48-hours washout period was required between each eligible attack and, therefore, each dose of study drug. Participants were required to identify the start of the HAE attack and notify the trial physician or qualified designee via telephone with a description of the attack. After telephone validation of attack eligibility, participants were advised to administer the study drug within 1 hour of onset and before the attack reached a severe level, as defined on the PGI-S scale.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was the time to use of conventional attack treatment (pdC1-INH or rhC1-INH IV or icatibant) within 12 hours after study drug.
Other outcomes used in the economic model/specified in the scope	The following Phase 2 details are provided for background; however, the economic model uses data from the Phase 3 KONFIDENT study. PGI-C 7-point transition question: Improvement: time to symptom relief ("a little better" or higher for 2 consecutive time points) within 12 hours of study drug. VAS improvement: Improvement: time to symptom relief (50% reduction from baseline in composite VAS for three consecutive time points) within 12 hours of study drug. PGI-S 5-point Likert scale: Worsening (including use of conventional attack treatment): Proportion of HAE attacks that (1) worsen by one level or more from baseline or (2) use of conventional attack treatment within 12 hours of study drug. Time to (1) worsening by one level or more from baseline or (2) use of conventional attack treatment, whichever comes first, within 12 hours of study drug.
Pre-planned subgroups	A subgroup analysis of the primary efficacy endpoint was performed by primary attack location at HAE attack onset.

Source: Adapted from Table 58, CS, Appendices[10]

ACE = angiotensin-converting enzyme; C1-INH = C1 inhibitor; CS = company submission; HAE = hereditary angioedema; IV = intravenous; PD = pharmacodynamic; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic; UK = United Kingdom; USA = United States of America; VAS = visual analogue scale

3.2.2.3 Summary of KONFIDENT-S OLE trial

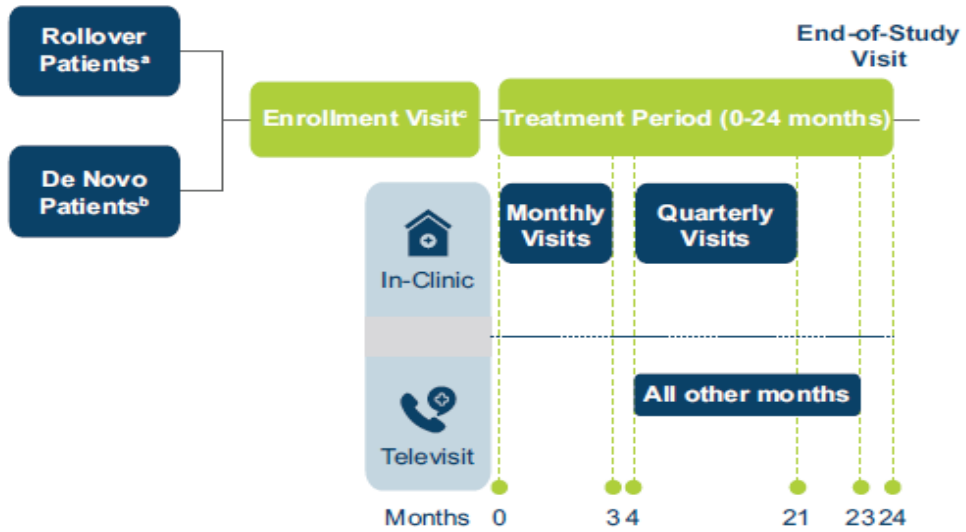
According to the CS[6] the KONFIDENT-S is an ongoing multicenter OLE trial to assess:

- The safety of long-term administration of sebetralstat in adolescent and adult patients with HAE Type I or II.
- The long-term efficacy of sebetralstat in the treatment of attacks in adolescent and adult patients with HAE Type I or II.
- The safety and efficacy of sebetralstat when used as short-term prophylaxis in adolescent and adult patients with HAE Type I or II prior to undergoing surgical, dental, or medical procedures. (Note: this study objective is not related to the DP of this appraisal).

Up to 150 patients (≥12 years of age) with a confirmed diagnosis of HAE-C1-INH (Type I or II) and at least two documented HAE-C1-INH attacks within 3 months were enrolled either after completing the KONFIDENT trial (rollover) or de novo (see Figure 3.4). It was stated in the CS that those receiving long-term prophylaxis (LTP) must be on a stable dose and regimen for ≥3 months immediately before and during the trial. However, in the factual accuracy check (FAC) the company stated that from January 2025 this was amended to allow patients to start, stop, or change long-term prophylactic treatment at the discretion of the PI during the trial. For up to 2 years, patients self-administer sebetralstat 600 mg (2 × 300 mg tablets) as early as possible after recognising the start of an attack. An optional second administration of sebetralstat is permitted ≥3 hours after the first administration.[6]

The CS also emphasises the following information of importance 'Please note that from January 2025 the dose in KONFIDENT-S will change from 600 mg to 300 mg. The study was designed with the original 600 mg dose before results from the Phase 3 KONFIDENT study were available. Since then, the 300 mg and 600 mg have been demonstrated to be dose equivalent so the open-label study will now change to 300 mg dosing from 2025'.[6]

Figure 3.4: KONFIDENT-S OLE trial design



Source: Adapted from Figure 10, CS[6]
CS = company submission
[a] Completed the Phase 3 KONFIDENT OLE trial.
[b] All other participants, including those who participated in the Phase 2 trial.
[c] For de novo participants, the Enrolment Visit is a Screening Visit.

Table 3.6: KONFIDENT-S OLE trial

Trial number (acronym)	**NCT05505916 (KONFIDENT-S)**
Location	Total of 72 trial sites. Australia (1 site), Austria (1 site), Bulgaria (1 site), Canada (1 site), France (4 sites), Germany (4 sites), Greece (2 sites), Hungary (1 site), Israel (4 sites), Italy (4 sites), Japan (9 sites), the Netherlands (1 site), New Zealand (1 site), North Macedonia (1 site), Poland (2 sites), Portugal (1 site), Romania (1 site), Saudi Arabia (1 site), Slovakia (1 site), South Africa (1 site), Spain (3 sites), UK*, USA (20 sites).[12]
Trial design	Open-label, multicentre extension trial to evaluate the long-term safety of sebetralstat in patients who are 12 years or older with HAE Type I or II. Patients must have a confirmed diagnosis of HAE-C1-INH (Type I or II) and at least two documented HAE-C1-INH attacks within 3 months. Approximately 150 patients (including a minimum of 12 adolescents) in total are planned to be enrolled in HAE centres worldwide. These patients will include rollover patients (those randomised in the KONFIDENT Phase 3 trial) and non-rollover patients (other patients including those randomised in the KVD900-201 Phase 2 trial or sebetralstat naïve).
Eligibility criteria for participants	Patients may roll over from Phase 3 KONFIDENT study (KVD900-301) as well as be recruited *de novo*. Inclusion criteria: • Confirmed diagnosis of HAE Type I or II at any time in the medical history. • Patient has had at least two documented HAE attacks within 3 months prior to the Enrolment Visit. • If a patient is receiving long-term prophylactic treatment with one of the protocol-allowed therapies, they must have been on a stable dose and regimen for at least 3 months prior to the Enrolment Visit (except for danazol, which requires a stable dose and regimen for at least 6 months prior to the Enrolment Visit). • Male or female patients 12 years of age and older. • Patients must meet the contraception requirements. • Patients must be able to swallow trial tablets whole. • Patients, as assessed by the Investigator, must be able to appropriately receive and store IMP, and be able to read, understand, and complete the eDiary. • Investigator believes that the patient is willing and able to adhere to all protocol requirements. • Patient provides signed informed consent or assent (when applicable). A parent or LAR must also provide signed informed consent when required. Exclusion criteria: • Discontinued from the KONFIDENT Phase 3 trial for reasons of noncompliance, withdrawal of consent, or safety. • Presence of any safety concerns that would preclude participation in the open-label trial as determined by the investigator.

Trial number (acronym)	NCT05505916 (KONFIDENT-S)
	• Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1-INH deficiency, HAE with normal C1-INH (previously known as HAE Type III), idiopathic angioedema, or angioedema associated with urticaria. • A clinically significant history of poor response to BR2 blocker, C1-INH therapy, or plasma kallikrein inhibitor therapy for the management of HAE, in the opinion of the Investigator. • Use of attenuated androgens (e.g., stanozolol, oxandrolone, methyltestosterone, testosterone), or anti-fibrinolytics (e.g., tranexamic acid) within 28 days prior to the Enrolment Visit. • Use of ACE inhibitors within 7 days prior to the Enrolment Visit. • Any oestrogen-containing medications with systemic absorption (such as oral contraceptives including ethinyloestradiol or hormonal replacement therapy) within 7 days prior to the Enrolment Visit. Inadequate organ function, including but not limited to: • ALT >2x ULN • AST >2x ULN • Bilirubin direct >1.25x ULN • INR >1.2 • Clinically significant hepatic impairment defined as a Child-Pugh B or C • Any clinically significant comorbidity or systemic dysfunction, which in the opinion of the Investigator, would jeopardise the safety of the patient by participating in the trial. • History of substance abuse or dependence that would interfere with the completion of the trial, as determined by the Investigator. • Known hypersensitivity to sebetralstat or to any of the excipients. • Participation in any gene therapy treatment or trial for HAE. • Participation in any interventional investigational clinical trial, including an investigational COVID-19 vaccine trial, within 4 weeks of the last dosing of investigational drug prior to the Enrolment Visit. • Any pregnant or breastfeeding patient.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x]) Permitted and disallowed concomitant medication	Oral sebetralstat 600 mg – changed to 600 mg in January 2025. Prior medications were defined as those medications taken within 4 weeks prior to the screening visit up to the first dose of IMP; concomitant medications were defined as those medications ongoing at or started after the first dose of IMP. Attacks that were not treated with IMP could be treated with conventional OD treatment per the patient's usual treatment regimen. Permitted therapies included conventional OD treatments, long-and short-term prophylactic treatment (berotralstat, lanadelumab, IV or SC plasma-derived C1-INH). Prohibited therapies during the trial included attenuated androgens, anti-fibrinolytics, investigational therapies for

Trial number (acronym)	NCT05505916 (KONFIDENT-S)
	HAE, ACE inhibitors, oestrogen-containing medications with systemic absorption, sustained use of strong CYP3A4 inhibitors and inducers.[13]
Primary outcomes (including scoring methods and timings of assessments)	• Frequencies and percentages of patients with AEs, AEs within 3 days of IMP administration, SAEs, and AEs causing premature discontinuation. • Number and percentage of patients with normal or abnormal laboratory results at each scheduled visit. • Number and percentage of patients with normal or abnormal vital sign results at each scheduled visit. • The primary estimand is the proportion of adolescents and adults with HAE Type I or II who take any sebetralstat dose, who experience any AEs (including fatal AEs) in the first 24 months, irrespective of uses of other medications and sebetralstat discontinuations for any reason.
Other outcomes used in the economic model/specified in the scope	Secondary efficacy outcomes in the KONFIDENT-S trial include: • PGI-C: time to beginning of symptom relief defined as at least "a little better" (2 time points in a row) within 12 hours of initial dose of IMP administration. • PGI-S: time to first incidence of 2 time points in a row decrease from baseline within 12 hours of initial dose of IMP administration. [Note: this reflects the time to reduction in severity] • PGI-S: time to HAE attack resolution defined as "none" within 24 hours of initial dose of IMP administration. • AE-QoL (exploratory): AE-QoL changes over time. • Time to first incidence of conventional OD attack treatment use within 12 hours and 24 hours.
Pre-planned subgroups	Prespecified subgroup analyses of the primary and key secondary end points will be performed according to sex, race, age, prophylactic treatment status, region, HAE Type, baseline primary attack location, attack severity at baseline based on PGI-S, number of doses received, time from onset of attack to the first IMP administration. Note: Subgroup analyses will be conducted and presented as part of the final clinical study report.
Source: Adapted from Table 18, CS[6] * The UK now has 6 trial sites. Of these, 5 sites have patients enrolled. A total of 8 patients were enrolled in the UK, Of the 8 UK patients, 7 are still ongoing. ACE = angiotensin-converting enzyme; AEs = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BR2 = bradykinin receptor 2; C1-INH = C1 inhibitor; COVID-19 = coronavirus disease 2019; CS = company submission; HAE = hereditary angioedema; IMP = investigational medicinal product; INR = international normalised ratio; IV = intravenous; LAR = legally authorised representative; OD = on-demand; OLE = open-label extension; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; QoL = quality of life; SC = subcutaneous; UK = United Kingdom; ULN = upper limit of normal; USA = United States of America; VAS = visual analogue scale	

The CS confirms[6] that the population sets analysed for this trial will include:

- Screened set: the screened set included all patients who signed the ICF.
- Safety Analysis Set (SAS): the SAF included all patients who received at least 1 dose of IMP.
- Short-Term Prophylactic (STP) safety set: The STP safety set included all the patients who received at least 1 dose of IMP as STP therapy.
- Full Analysis Set (FAS): the FAS included all enrolled patients who received at least 1 dose of IMP for a qualifying HAE attack. It is the population for efficacy analyses.

3.2.3 Baseline characteristics

The patient characteristics of the relevant trials are included below.

3.2.3.1 KONFIDENT Phase 3

Of the 110 participants who received at least one dose of double-blind treatment, 66 were female (60.0%), and 101 (91.8%) had HAE Type I. Overall, the median age was 39.5 years, and 30 participants (27.3%) were adolescents between 12 and 17 years of age with [redacted] adolescent patients evaluable for the primary analysis. The majority were white (83.6%), 9.1% were Asian and 0.9% were Black/African American (0.9%) with 0.9% as 'Other'. The median time since the diagnosis of HAE was 12 years (interquartile range, 7 to 22.) Only OD therapy at enrolment was received by 86 participants (78.2%) of the overall study population. Twenty-four participants (21.8%) of the overall population were receiving long-term prophylaxis. Of these 24 receiving LTP, by the following proportions: berotralstat in 9 (37.5%), lanadelumab in 8 (33.3%), C1-INH in 6 (25.0%), and both berotralstat and C1-INH replacement in 1 (4.2%).[6]

The characteristics were well matched between arms although some differences at the >5% level were evident. The EAG takes the view that where there appears to be differences in arms at a level of 5% or more, that this is noteworthy of comment, so should be highlighted for analysis and interpretation. This does not mean that the differences will be statistically or clinically meaningful, and of course large percentage differences can occur in small samples with minor numerical differences, however it is important that such imbalances are identified. Of note in Table 3.7 is that the sebetralstat 600 mg arm had more males (>5%) than the placebo arm (39.8% versus 34.4%) and also that the placebo arm had more patients who were resident in Europe than the sebetralstat 300 mg arm (50.6% versus 57.1%).

Table 3.7: KONFIDENT Phase 3 study baseline characteristics (full analysis population)

Characteristic	Sebetralstat 300 mg (N=87)	Sebetralstat 600 mg (N=93)	Placebo (N=84)	Overall (N=110, treating 264 attacks)
Age, years				
Median (IQR)	37.0 (25.0-49.0)	39.0 (25.0-49.0)	38.0 (25.0–49.0)	39.5 (25.0–49.0)
Sex, n (%)				
Male	33 (37.9)	37 (39.8)	29 (34.5)	44 (40.0)

Characteristic	Sebetralstat 300 mg (N=87)	Sebetralstat 600 mg (N=93)	Placebo (N=84)	Overall (N=110, treating 264 attacks)
Geographic region, n (%)				
Europe United States Asia-Pacific region	44 (50.6) 27 (31.0) 16 (18.4)	49 (52.7) 28 (30.1) 16 (17.2)	48 (57.1) 23 (27.4) 13 (15.5)	58 (52.7) 34 (30.9) 18 (16.9)
HAE-C1-INH Type — n (%)				
Type I	79 (90.8)	87 (93.5)	79 (94.0)	101 (91.8)
Type II	8 (9.2)	6 (6.5)	5 (6.0)	9 (8.2)
Current treatment regimen — no. (%)				
OD treatment only	68 (78.2)	72 (77.4)	66 (78.6)	86 (78.2)
Prophylaxis plus OD treatment	19 (21.8)	21 (22.6)	18 (21.4)	24 (21.8)
Race – no. (%)†				
White Asian Black Other Not reported	73 (83.9) 9 (10.3) 1 (1.1) 0 4 (4.6)	80 (86.0) 8 (8.6) 0 1 (1.1) 4 (4.3)	73 (86.9) 7 (8.3) 0 1 (1.2) 3 (3.6)	92 (83.6) 10 (9.1) 1 (0.9) 1 (0.9) 6 (5.5)
Median BMI (IQR)	26.3 (22.8–31.2)	26.2 (22.9–30.9)	26.2 (22.9–30.8)	26.2 (22.8–31.6)

Source: Adapted from Table 6, CS[6]

The full analysis population comprised participants who administered sebetralstat or placebo to themselves for at least one HAE attack.

Participants may be represented in multiple columns.

Percentages may not total 100% because of rounding. HAE-C1-INH denotes HAE due to C1-INH deficiency and IQR.

BMI = body mass index; CS = company submission; HAE-C1-INH = hereditary angioedema C1 inhibitor; IMP = investigational medicinal product; IQR = interquartile range; OD = on-demand

† Race was reported by the participant

EAG comment: Note that the N for each group is the number of attacks, as opposed to patients, which is consistent with the method of analysis i.e. by attack as opposed to by patient. As the KONFIDENT trial excluded patients with HAE Type III (HAE-nC1-INH) the EAG were concerned about possible issues with generalisability to the relevant clinical population in England and Wales. We requested clarification form the company on this matter who responded saying that '*the third subtype of HAE (HAE-nC1-INH) is extremely rare and the resultant swellings follow a different biochemical pathway from the common Type I and II swellings. Therefore, the inclusion of HAE Types I and II in the KONFIDENT trial is representative of the UK patients that would receive sebetralstat*' [8].

3.2.3.2 KONFIDENT-S OLE trial

The KONFIDENT-S OLE study utilised both de novo and rollover patients. Overall, the mean (standard deviation [SD]) age of patients was [redacted]) years and ranged from [redacted] years. [redacted] patients were ≥18 years of age. There were [redacted] female and [redacted] male with [redacted] of the patients being White, [redacted] Asian and [redacted] listed as 'other'. The mean (SD) body mass index (BMI) was [redacted] kg/m2[6].

There were [redacted] of patients who presented with Type I HAE and [redacted] were receiving an OD only HAE treatment regimen than were receiving a stable dose of prophylactic therapy ([redacted]), Of the prophylactic therapies, [redacted] patients used kallikrein-inhibiting treatments (including lanadelumab and berotralstat) and [redacted] of patients used other therapies.[6]

Table 3.8: KONFIDENT-S OLE demographics and baseline characteristics – overall (safety set) (September 2024 data cut-off)

Characteristic	Rollover [redacted]	Non-rollover [redacted]	Total [redacted]
Age			
Years, Mean (SD)	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Female Male	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Geographic region, n (%)			
North America Europe Rest of world	[redacted]	[redacted]	[redacted]

HAE-C1-INH Type — no. (%)			
Type I	[redacted]	[redacted]	[redacted]
Type II	[redacted]	[redacted]	[redacted]
BMI (kg/m^2)			
n Mean (SD)	[redacted]	[redacted]	[redacted]
Source: Adapted from Table 19, CS[6] [a] BMI was calculated as (body weight in kilograms)/(height in meters) BMI = body mass index; CS = company submission; HAE-C1-INH = hereditary angioedema C1 inhibitor; SD = standard deviation			

Generally, there was balanced matching of characteristics between the rollover and non-rollover patient characteristics although there were noticeable differences >5% between arms with regards to geographical origin and ethnicity. The rollover group had [redacted]% white participants versus [redacted]% in the non-rollover group. Additionally, there was [redacted]% undefined 'other' ethnicity versus [redacted]% in the non-rollover group. There were [redacted] % North American participants in the rollover group versus [redacted]% in the rollover, as well [redacted]% European versus [redacted]% in the non-rollover group, and [redacted]% of participants in the rollover group were from 'rest of world' versus [redacted]% in the non-rollover group.

The EAG again highlights that differences at the 5% level are highlighted for note when interpreting results and data and do not state that these necessarily will impact on clinically meaningful results. We are mindful that differences of 5% or more can occur in limited samples with very small numerical differences as is the case with the numbers of white participants in each group ([redacted] versus [redacted] participants equating to [redacted]% versus [redacted]%). Nonetheless such points should be borne in mind when interpreting and generalising.

3.2.4 External validity

The EAG were concerned about the relevance and generalisability of the included evidence to the relevant clinical population in England and Wales and raised this to the company. A primary issue of the EAG was around the exclusion of patients with HAE Type III (HAE-nC1-INH) from the KONFIDENT trial and how this would impact representativeness. The company dismissed this concern by emphasising the rarity of this subtype and that any swellings follow a '*different biochemical pathway from the common Type I and II swellings. Therefore, the inclusion of HAE Types I and II in the KONFIDENT trial is representative of the UK patients that would receive sebetralstat*'[8].

The nature of the trial design of KONFIDENT also raised questions for the EAG as it was not clear how the design and administration of interventions would reflect clinical treatment realities in England and Wales. We asked the company to clarify whether this trial design is reflective of treatment pathways in UK clinical practice or if not aligned, to discuss the potential impact on the generalisability of the trial results to National Health Service (NHS) patients. The company responded by summarising the nature of the trial three-way crossover design but also importantly stating that '*the crossover trial design does not reflect the treatment pathway and how patients would be treated in clinical practice (i.e. patients would not systematically switch between sebetralstat doses nor placebo in the real-life clinical setting). However, since the KONFIDENT results represent the treatment effect of sebetralstat in treating an acute HAE attack, the efficacy and safety findings from the trial*

are considered generalisable to NHS clinical practice, even though the crossover trial design does not reflect the NHS treatment pathway[8] .'

It is not clear to the EAG as to who considers it generalisable to the NHS treatment pathway. The company stated in their response to clarification that '*UK clinical experts engaged during the development of the submission validated the generalisability of the KONFIDENT findings to clinical practice. They highlighted that the proportion of patients receiving long-term prophylaxis (in addition to on-demand treatment) in clinical practice would likely be higher than the 21.8% in the KONFIDENT trial, however, they added that this would not affect the sebetralstat clinical findings'*[8].

To support the assertion of validation from UK clinical experts, the company provided a document.[14] This document summarises the input of clinicians on various aspects of this trial and its relevance to UK practice. The EAG has reviewed this document and while we do not have any reason to challenge its assertions, the fact that there is no mention of the identities of the UK clinical experts is a concern. If evidence from clinical expert opinion is to be used in support of a claim, the EAG needs to see an auditable information. As a minimum we would expect to see the names and positions of the clinical experts with an appropriate biography to justify the status as a clinical expert. If meetings or committees had taken place to formulate an official position, we would expect to see such minutes or summaries of these meetings. If any audit data or unpublished research had informed these clinical opinions, we would also expect the data to be submitted in support of the claim. As it stands this document does not provide any information on these matters and while we accept that the opinion seems to demonstrate a support for trial generalisability, we cannot accept this claim based on the presentation of the clinical opinion via this method.

3.2.5 Statistical analyses of included trials

The relevant statistical methods as described and presented in the CS[6] are included below, or summarised where possible, along with any comments or critique by the EAG.

3.2.5.1 KONFIDENT Phase 3 trial

The hypothesis of this trial was that each sebetralstat treatment group would be more effective than placebo for the OD treatment of HAE attacks.[6] This was to be based on a difference in survival distribution of the time to beginning of symptom relief defined by the PGI-C as at least "a little better" for 2 time points in a row within 12 hours of the first IMP administration.[6]

Approximately one hundred and fourteen patients were to be randomised to ensure approximately 84 patients completed the trial to ensure approximately 84 attacks were treated with placebo, 300 mg sebetralstat, and 600 mg sebetralstat. The trial population comprised 2 subsets: (1) patients who entered the trial taking only conventional OD treatment; and (2) patients who entered the trial on a stable dose and regimen of long-term prophylactic treatment. Following screening, 136 patients underwent enrolment in KONFIDENT.[6]

Based on results from the Phase 2 trial (KVD900-201), a sample size of 66 patients completing the trial would provide 90% power for testing each pairwise comparison (sebetralstat versus placebo) at the 2.5% alpha level (2-sided) for the primary endpoint of time to beginning of symptom relief of the HAE attack defined by PGI-C as at least "a little better" for 2 time points in a row within 12 hours of the first IMP administration.[6]

This sample size was derived using the assumption that median time to symptom relief of the HAE attack is 1.6 hours in active dose arm and 9 hours in placebo arm based on the Phase 2 KVD900-201

trial. It was assumed that patients begin the trial together and will be followed for the same period of time, 49% of patients in control group and 17% of patients in sebetralstat treatment group were assumed to be lost-to-follow-up (right-censored). Using conservative approach and simulation-based procedure for power calculations for a parallel group design, the two-sided two-group survival comparison Gehan-Wilcoxon test had approximately 90% power to detect a median time ratio of 5.6 (9/1.6) with a target 2-sided significance level of 2.5% for 66 patients in each treatment group.[6]

Two pairwise comparisons were performed: 300 mg sebetralstat versus placebo and 600 mg sebetralstat versus placebo. All statistical tests were 2-sided with an overall alpha of 0.05. The primary efficacy endpoint analysis and key secondary endpoints had Bonferroni multiplicity adjustment for multiple dose levels with a loop-back feature to allow two-way alpha passing. Within each pairwise comparison, fixed sequence closed testing procedure was followed. The fixed testing procedure was employed first on the primary and then on the key secondary endpoints 1 and 2, separately for each dose comparison to placebo. Specifically, key secondary endpoint 1 was tested only if the test on the primary endpoint was statistically significant. Key secondary endpoint 2 was tested only if the test on the primary and key secondary endpoint 1 were statistically significant. The loop-back feature allowed for retesting of unrejected hypotheses at 0.05 alpha level if all hypotheses were rejected within the other pairwise comparison[6].

The KONFIDENT study included the following analysis sets as presented in the CS:[6]

- SAS: included all patients who received at least one dose of trial medication. If one or more patient(s) received the incorrect trial medication, data summarised using the SAS were presented according to the actual treatment received. The SAS was the population for safety analyses.
- FAS: included all randomised patients who received trial medication from at least one period for the respective qualifying HAE attack. If one or more patient(s) received the incorrect trial medication, data summarised using the FAS were presented according to the randomised treatment. The FAS was the population for efficacy analyses.
- Per-Protocol Set: included all randomised patients who received trial medication from at least one period for the respective qualifying HAE attack and who did not have major protocol deviations that could affect the primary efficacy endpoint.
- OD FAS: included FAS patients who entered the trial taking only conventional OD treatment.
- Prophylaxis FAS: included FAS patients who entered the trial on a stable dose and regimen of long-term prophylactic treatment.

Efficacy data were summarised by randomised treatment. All efficacy analysis was performed using the FAS and primary and key secondary endpoints analysis was repeated using the Per Protocol Set (PPS). Statistical tests were 2-sided with an overall alpha of 0.05 unless otherwise specified. Treatment comparisons of interest were pairwise comparisons of 300 mg sebetralstat versus placebo and 600 mg sebetralstat versus placebo.[6]

Secondary endpoints in KONFIDENT were tested according to the fixed sequence closed testing procedure.[6]

- Time to first incidence of decrease within 12 hours: time to first incidence of decrease from baseline on the Patient Global Impression of Severity scale (PGI-S) for 2 time points in a row

(hours) = date/time of first incidence of decrease of symptom intensity from baseline for 2 time points in a row (with possible missing values in between) - date/time of first IMP administration. Note: this reflects the time to reduction in severity.

- Time to HAE attack resolution within 24 hours: time to HAE attack resolution (hours) = date/time of first PGI-S rating of "None"– date/time of first IMP administration.

Gehan score transformation tests were used to analyse efficacy endpoints. Least-squares means, and standard errors (SEs) were presented by treatment. P-values were calculated for the comparison of each sebetralstat dose group versus placebo, along with the least-square mean treatment difference and corresponding 95% confidence interval (CI) were presented. Additionally, adjusted p-values for each pairwise comparison was also presented with Bonferroni adjustment allowing alpha loop-back. The number and percentage of attacks that met both endpoints and the number censored were presented by treatment. Kaplan-Meier estimates of the 25th percentile (Q1), the median, and the 75th percentile (Q3) and corresponding 95% CI were presented by treatment. Kaplan-Meier survival curves were presented by treatment.[6]

Secondary endpoints as described in the CS also included:[6]

- Patient Global Impression of Change (PGI-C): number and percentage of attacks with beginning of symptom relief defined as at least "a little better" (2 time points in a row) within 2, 4, 6, 8, 10, 12, 24, and 48 hours of the first IMP administration.
- PGI-C: time to at least "better" (2 time points in a row) within 12 and 24 hours of the first IMP administration.
- Time to either (1) first incidence of PGI-C being rated 'a little worse' or lower for two time points in a row, or (2) use of conventional attack treatment, whichever comes first within 12 hours and 24 hours. Time to conventional attack treatment use (h) = date/time of first conventional attack treatment use – date/time of IMP administration.
- PGI-S: time to first incidence of decrease from baseline (2 time points in a row) within 24 hours of the first IMP administration.
- Time to either (1) first incidence of worsening in attack severity on the PGI-S by one level or more from baseline for two time points in a row, or (2) use of conventional attack treatment, whichever comes first within 12 hours and 24 hours.
- PGI-S: time to HAE attack resolution defined as "none" within 48 hours.
- Time to first incidence of conventional attack treatment use within 12 hours and 24 hours. Time to first incidence of conventional attack treatment use (hours) = date/time of first incidence of conventional attack treatment use – date/time of first IMP administration.
- Time to the second IMP administration within 12 hours and 24 hours. Time to the second IMP administration (hours) = date/time of the second IMP administration – date/time of first IMP administration.
- Number and percentage of attacks receiving second IMP administration within 4, 8, 12, 24, and 48 hours of the first IMP administration.
- Composite visual analogue scale (VAS): time to at least a 50% decrease from baseline (3 time points in a row) within 12 hours and within 24 hours of IMP administration. The Gehan

scores transformation statistics and p-value were provided for exploratory purposes for these endpoints. Kaplan-Meier estimates of the Q1, the median, and the Q3 and corresponding 95% CI were presented by treatment. Kaplan-Meier survival curves were presented by treatment.

Subgroup analyses of the primary and key secondary efficacy endpoints were performed by sex (if provided), race, age group, prophylactic treatment status, region, Type of HAE, baseline primary attack location, attack severity at baseline based on PGI-S, number of doses received, and time from onset of attack to the first IMP administration. Frequencies and survival estimates were presented for each subgroup. P-values were added for exploratory purposes. The examination of primary and key secondary endpoints, utilising both the OD FAS and the prophylaxis-FAS, is the same as the subgroup analyses comparing the 'On-Demand' subgroup with the 'On Prophylactic Treatment' subgroup.[6]

EAG comment: As stated in Section 3.2.2, the power calculation is based on increasing efficiency by analysing by attack with any order bias reduced by randomisation to any one of all possible sequences of treatment per attack.

3.2.5.2 Phase 2 study

The primary variable for statistical comparison between treatments in Part 2 of the study was time to use of conventional attack treatment within 12 hours of study drug. Primary analysis was analysed using a FAS population which was defined as all participants who were randomly assigned to a treatment sequence and received study drug for two attacks in Part 2 of the study. The time to conventional attack treatment use is listed with censored observations flagged. Frequencies (n, %) of subjects that used conventional attack treatment or were censored are presented. Kaplan-Meier estimates of the Q1, the median and corresponding 95% CI of time to conventional attack treatment use is presented by treatment (sebetralstat/placebo), along with Gehan's generalised Wilcoxon test p-value. Kaplan-Meier survival curves are also presented by treatment. Kaplan-Meier survival analysis was performed using the SAS LIFETEST procedure as was appropriate for right censored data.[6]

The SAS included all participants who received at least 1 dose of the study drug, starting with Part 1. Treatment-emergent adverse events (TEAEs) were summarised by study part and treatment, both active treatment periods combined and overall (all treatment periods combined). An overall summary of TEAEs was produced presenting the number of TEAEs reported and the number and percentage of subjects reporting TEAEs within categories (i.e. on-treatment TEAEs within 48 hours of dose, post-treatment TEAEs, severe TEAEs, serious TEAEs, drug-related TEAEs, serious drug-related TEAEs, TEAEs leading to withdrawal of study, TEAEs leading to death). The number of TEAEs and the number and percentage of subjects reporting at least one TEAE were tabulated by system organ class (SOC) and preferred term (PT). A subject reporting multiple episodes of a particular adverse event (AE) only contributed one count towards the corresponding SOC and PT. This summary was also repeated for serious TEAEs, on-treatment TEAEs and post treatment TEAEs. For the most frequently reported TEAEs (defined as AEs reported by ≥5% of subjects within a treatment), the number of TEAEs and the number and percentage of subjects reporting at least one TEAE were tabulated by PT, sorted in descending frequency by the number of subjects. Following determination of the most frequently reported TEAEs, a subset is presented for on treatment TEAEs.[6]

The PK analysis set included all participants who completed the PK measurements in Part 1. A one-way ANOVA with Fisher's least significant difference test was used for the PD analysis. Gehan's generalised Wilcoxon test was used as an extension of the Wilcoxon rank sum test, to do a non-parametric analysis of time-to-event data. This is a rank-based approach that is appropriate for crossover time-to-event data because it provides a test statistic in the presence of censoring, including

when the median is censored. Prescott's test was used to compare proportions between treatments. All these tests were prespecified. Patient-reported outcome measures (PROMs) were summarised overtime and explored using area under the curve (AUC) calculations. No imputations for missing values (e.g. missed assessments during sleep). Outcomes reported after conventional attack treatment were excluded from analyses. Time-to-event data was plotted using standard Kaplan-Meier methods.[6]

All randomised subjects who received both doses of study drug in Part 2 and did not incur a major protocol deviation that would invalidate or bias the results constituted the PPS. A secondary efficacy analysis of the primary and secondary endpoints was performed using the PPS. As mentioned above, the primary efficacy analysis was based on the FAS. For secondary efficacy analyses, frequencies (n, %) of the HAE attack severity and change in attack severity are presented by time point and treatment. Frequencies (n, %) of the time point of worsening in HAE attack severity on the PGI-S by one level or more by time point are also presented. The PGI-S scores were transformed into numeric values (recoded as 0 [none] to 4 [very severe]) and descriptive statistics (N, n, mean, SD, minimum, Q1, median, Q3 and maximum) of absolute and change from baseline values are presented by time point and treatment. The mean absolute and change from baseline values are also presented graphically over time. The PGI-C scores were transformed into numeric values (recoded as -3 [much better] to 3 [much worse]) and descriptive statistics (N, n, mean, SD, minimum, Q1, median, Q3 and maximum) are presented by time point and treatment. The mean values are also presented graphically over time. The descriptive statistics and plots over time of the recoded numeric values of the PGI-S and PGI-C results as described above were performed with and without the last observation carried forward (LOCF) method of imputation, such that any missing values prior to use of conventional attack treatment were imputed, as were values obtained post-use of conventional attack treatment. Descriptive statistics (N, n, mean, SD, minimum, Q1, median, Q3 and maximum) of absolute and change from baseline (pre-dose) HAE attack symptoms VAS scores were tabulated by time point and treatment. The descriptive statistics and plots over time of the VAS scores and the composite and index VAS scores as described above were performed with and without the LOCF method of imputation, such that any missing values prior to use of conventional attack treatment were imputed, as were values obtained post-use of conventional attack treatment.[6]

P values of less than 0·05 were considered to be significant. The statistical analysis plan was developed in compliance with the International Conference on Harmonisation E9 document Statistical Principles for Clinical Trials, and all analyses in Part 2 were done using SAS (version 9.3).[6]

3.2.6 Risk of bias assessments

The EAG appraised the included evidence to assess risk of bias (RoB) and study quality. EAG comments can be found in Section 3.1.4 of this report alongside the company conducted appraisals. Where the EAG appraisal differs from that of the company a comment will be made. Where no significant difference is identified, an 'N/A' is inserted.

3.2.7 Efficacy results of the included studies

3.2.7.1 Primary Efficacy Results

Section 2.6 of the CS included the following statements: "*There was a statistically significant improvement in the time to the beginning of symptom relief between 300 mg sebetralstat (adjusted p<0.0001) versus placebo group and between 600 mg sebetralstat (adjusted P=0.0013) versus placebo group. The median (95% CI) time to the beginning of symptom relief was 1.61 hours (95%*

CI: 1.28, 2.27) for 300 mg sebetralstat group, 1.79 hours (95% CI: 1.33, 2.27) for 600 mg sebetralstat group, and 6.72 hours (95% CI: 2.33, not evaluable) for placebo group."[6]

The company also stated that "*More attacks reached beginning of symptom relief within 12 hours of first IMP administration in the sebetralstat treatment groups than placebo group (300 mg sebetralstat group: 66 [75.9%] attacks and 600 mg sebetralstat group: 71 [76.3%] attacks versus placebo group: 41 [48.8%] attacks).*"[6] Further details can be found in Table 3.9 below.

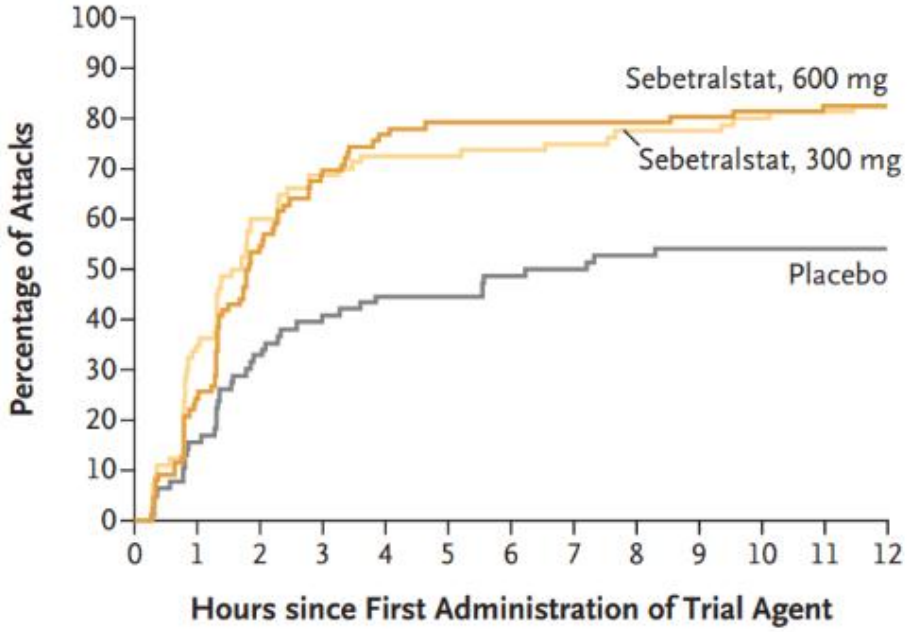
The company also reported that "*More attacks reached the beginning of symptom relief in the 300 mg sebetralstat and 600 mg sebetralstat treatment groups than placebo group.*"[6] More details can be found in the Kaplan-Meier plot below in Figure 3.5.

Table 3.9: KONFIDENT Phase 3 - primary endpoint results

	Sebetralstat 300 mg (N = 87)	**Sebetralstat 600 mg (N = 93)**	**Placebo (N = 84)**
Time to beginning of symptom relief within 12 hours (primary)*			
Participants: no. (%)			
Events	66 (75.9)	71 (76.3)	41 (48.8)
Censored	21 (24.1)	22 (23.7)	43 (51.2)
Censored at hour 0 due to underivable end point	7 (8.0)	7 (7.5)	8 (9.5)
Adjusted P value compared with placebo	<0.001	0.001	
Median (IQR)	1.61 (0.78-7.04)	1.79 (1.02-3.79)	6.72 (1.34->12)

Source: Based on Table 9 of the CS[6]
*Defined as a rating of at least "A Little Better" on the PGI-C scale for two or more consecutive time points.
CS = company submission; IQR = interquartile range; mg = milligram; PGI-C = Patient Global Impression of Change

Figure 3.5: Primary endpoint. Kaplan-Meier plot for time to beginning of symptom relief within 12 hours (FAS)



No. of Attacks													
Sebetralstat, 600 mg	93	65	39	26	20	18	18	18	18	17	16	15	15
Sebetralstat, 300 mg	87	52	32	25	22	22	21	20	18	18	16	15	14
Placebo	84	64	51	45	42	42	39	38	36	35	35	35	35

Source: Based on Figure 4 of the CS[6]
CS = company submission; FAS = Full Analysis Set; mg = milligram

3.2.7.2 Secondary Efficacy Results

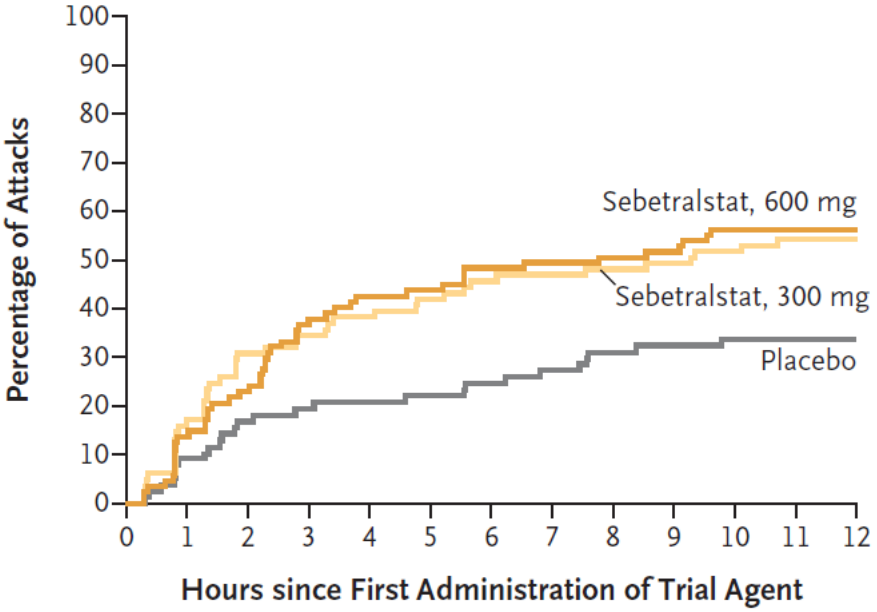
3.2.7.2.1 Key secondary efficacy results

The company reported that "*A reduction in attack severity (within 12 hours after the first administration) was reached faster than placebo with the 300 mg dose (P=0.004) and the 600 mg sebetralstat dose (P=0.003). Furthermore, the median time to a reduction in severity with the 300 mg dose was 9.27 hours (interquartile range, 1.53 to >12), 7.75 hours (2.19 to >12) with the 600 mg dose, and over 12 hours (6.23 to >12) with placebo.*

More attacks achieved the time to reduction in severity within 12 hours in the 300 mg sebetralstat (44 [50.6%] attacks) and 600 mg sebetralstat groups (49 [52.7%] attacks) than placebo group (26 [31.0%] attacks)."[6] Further details can be found in Figure 3.6 and Table 3.10 below.

The company also reported that "*Complete resolution of the attack was also reached faster with the 300 mg dose and the 600 mg dose than with placebo (P=0.002 and P<0.001, respectively). Furthermore, complete resolution of attacks within 24 hours of the first administration occurred in 42.5% of attacks for the 300 mg sebetralstat group, 49.5% of attacks for the 600 mg group, and 27.4% of attacks for those receiving placebo.*"[6] Further details can be found in Figure 3.7 and Table 3.10 below.

Figure 3.6: KONFIDENT Phase 3 key secondary endpoint results: reduction in severity of attack

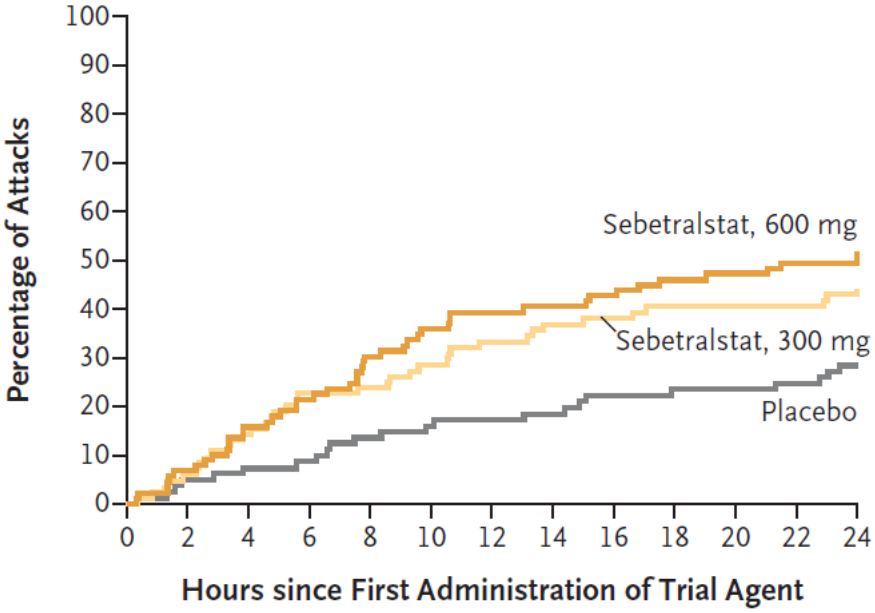


No. of Attacks													
Sebetralstat, 600 mg	93	75	67	54	50	49	45	44	43	42	38	38	38
Sebetralstat, 300 mg	87	67	56	53	50	47	44	43	42	41	39	37	37
Placebo	84	70	64	62	61	60	58	56	53	52	51	51	51

Source: Based on Figure 5 of the CS[6]
CS = company submission; mg = milligram; PGI-S = Patient Global Impression of Severity scale

Key secondary end point assessment in a time-to-event analysis: a reduction in the severity of the attack, defined as an improved rating on the 5-point PGI-S scale (ratings range from “none” to “very severe”) at two or more consecutive time points within 12 hours after the first administration.

Figure 3.7: KONFIDENT Phase 3 key secondary endpoint: complete resolution of the attack



No. of Attacks													
Sebetralstat, 600 mg	93	83	75	70	62	57	54	53	51	48	47	45	45
Sebetralstat, 300 mg	87	79	72	65	64	60	56	53	52	50	50	50	48
Placebo	84	77	75	74	70	68	67	66	63	62	62	61	58

Source: Based on Figure 6 of the CS[6]
CS = company submission; mg = milligram; PGI-S = Patient Global Impression of Severity scale

Key secondary end point assessment for complete resolution of the attack, defined as a rating of "none" on the PGI-S scale within 24 hours after the first administration

Table 3.10: KONFIDENT Phase 3 – key secondary endpoint results

	Sebetralstat 300 mg (N = 87)	**Sebetralstat 600 mg (N = 93)**	**Placebo (N = 84)**
Time to reduction in the severity of attack within 12 hours (key secondary)†			
Participants: no. (%)			
Events	44 (50.6)	49 (52.7)	26 (31.0)
Censored	43 (49.4)	44 (47.3)	58 (69.0)
Censored at hour 0 due to underivable end point	6 (6.9)	6 (6.5)	7 (8.3)
Adjusted P value compared with placebo	0.004	0.003	
Median (IQR)	9.27 (1.53->12)	7.75 (2.19->12)	>12 (6.23->12)
Time to complete resolution of the attack within 24 hours (key secondary)‡			
Participants: no. (%)			
Events	37 (42.5)	46 (49.5)	23 (27.4)
Censored	50 (57.5)	47 (50.5)	61 (72.6)
Censored at hour 0 due to underivable end point	3 (3.4)	4 (4.3)	3 (3.6)
Adjusted P value compared with placebo	0.002	<0.001	
Median (IQR)	>24 (8.58->24)	24.00 (7.54->24)	>24 (22.78->24)

Source: Based on Table 10 of the CS[6]
CS = company submission; IQR = interquartile range; mg = milligram; PGI-S = Patient Global Impression of Severity
† Defined as an improved rating from baseline in PGI-S for two or more consecutive time points
‡ Defined as a PGI-S rating of "None"

3.2.7.2.2 Other secondary efficacy results

The company reported that "*These secondary endpoint results also demonstrating improvement across a range of endpoints for patients treated with sebetralstat compared to placebo.*"[6] Further details can be found in Table 3.11 below.

Table 3.11: Linear mixed model of Gehan score and Kaplan-Meier estimates for other secondary endpoints within 12 and 24 hours (FAS)

		300 mg sebetralstat			600 mg sebetralstat			Placebo
Endpoint	**Number of patient events[a]**	**Median (95% CI)**	**Nominal p-value (sebetralstat versus placebo)**	**Number of patient events[a]**	**Median (95% CI)**	**Nominal p-value (sebetralstat versus placebo)**	**Number of patient events[a]**	**Median (95% CI)**
n	87			93			84	
Time to at least "better" on PGI-C within 12 and 24 hours								
Within 12 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Within 24 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to first incidence of PGI-C being rated 'a Little Worse' or lower or use of conventional attack treatment within 12 and 24 hours								
Within 12 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Within 24 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to first incidence of decrease on PGI-S within 24 hours								
Within 24 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to HAE attack resolution on PGI-S within 48 hours								
Within 48 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to first incidence of worsening in attack severity on the PGI-S or use of conventional attack treatment within 12 and 24 hours								
Within 12 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Within 24 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to first incidence of conventional attack treatment use within 12 and 24 hours								
Within 12 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Within 24 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to the second IMP administration within 12 and 24 hours								

		300 mg sebetralstat			600 mg sebetralstat			Placebo
Endpoint	**Number of patient events[a]**	**Median (95% CI)**	**Nominal p-value (sebetralst at versus placebo)**	**Number of patient events[a]**	**Median (95% CI)**	**Nominal p-value (sebetralst at versus placebo)**	**Number of patient events[a]**	**Median (95% CI)**
Within 12 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Within 24 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to at least 50% decrease on composite VAS from baseline within 12 and 24 hours								
Within 12 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Within 24 hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 11 of the CS[6]

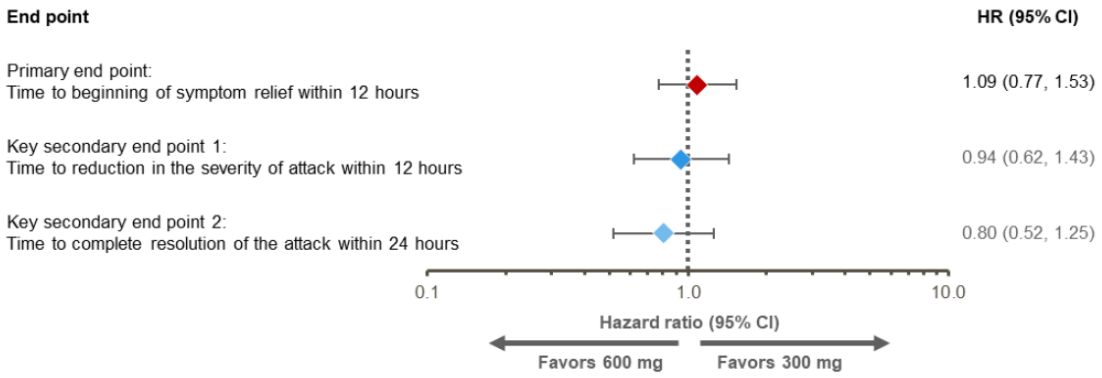
Notes:

- n is number of IMP-treated HAE attacks. The number of IMP-treated HAE attacks is equivalent to the number of patients in each group. Time to at least better at 2 time points in a row (hours) = date/time of first rating of "better" or higher immediately followed by another rating of "better" or higher (with possible missing values in between) – date/time of first IMP administration.
- Time to first incidence of symptom decrease from baseline at 2 consecutive time points (hours) = date/time of first incidence of decrease from baseline for 2 time points in a row (with possible missing values in between) – date/time of first IMP administration.
- Time to HAE attack resolution (hours) = date/time of first rating of "none"– date/time of first IMP administration.
- Time to first incidence of worsening in attack severity by 1 level or more from baseline on the PGI-S for 2 time points in a row (hours) = date/time of first incidence of increase from baseline on the PGI-S for 2 time points in a row (with possible missing values in between) – date/time of first IMP administration.

CI = confidence interval; CS = company submission; FAS = Full Analysis Set; HAE = hereditary angioedema; IMP = investigational medicinal product; mg = milligram; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity scale; VAS = visual analogue scale

EAG comment: One EAG concern with the KONFIDENT trial's three-way crossover design is the potential for carryover effects between treatment periods. In crossover trials, particularly those assessing treatments for acute conditions, it is essential to ensure that the effect of one treatment does not influence outcomes observed in subsequent periods. In response to clarification, the company notes that: *"…essentially including each participant as their own control…"*.[8] As stated above, the EAG is reassured that the crossover design combined with sufficient time between attacks permits an unbiased estimate of the effect of dose independent of attack number and treatment sequence. In addition, the company stated in the clarification response that the period and sequence were included as a fixed effect on the primary analysis.[8] In conclusion, the treatment effects of 600 mg or 300 mg versus placebo can be regarded as unbiased. The company then also conclude that there is equivalence between 300 mg and 600 mg, as shown in Figure 3.8 below:

Figure 3.8: KONFIDENT study: hazard ratios (HRs) of sebetralstat 300 mg and 600 mg doses for primary or key secondary endpoints



Source: Figure 11, CS[6]
CI = confidence interval; CS = company submission; HR = hazard ratio; mg = milligram

The EAG consider that this is a reasonable conclusion, and that any potential bias is negated by using only the 300 mg data in the indirect treatment comparison (ITC) (see Sections 3.3 and 3.4).

3.2.8 Adverse events

The company reported that "*Adverse events (AEs) occurred in 17 of 86 participants (19.8%) who received 300 mg of sebetralstat, in 14 of 93 (15.1%) who received 600 mg, and in 17 of 83 (20.5%) who received placebo.*"[6] The safety profile for sebetralstat was similar to placebo in the Phase 3 KONFIDENT study. Further details can be found in Table 3.12, Table 3.13 and Table 3.14 below.

Table 3.12: KONFIDENT Phase 3 safety results

Event	Sebetralstat 300 mg (N=86)		Sebetralstat 600 mg (N=93)		Placebo (N=83)	
	no. (%)	no. of events	no. (%)	no. of events	no. (%)	no. of events
Any AE						
Overall	17 (19.8)	20	14 (15.1)	18	17 (20.5)	24
Related to trial agent	2 (2.3)	2	3 (3.2)	4	4 (4.8)	5
Any SAE during treatment†						
Overall	1 (1.2)	1	2 (2.2)	2	0	0
Related to trial agent	0	0	0	0	0	0
Any SAE during treatment‡						
Overall	1 (1.2)	1	0	0	0	0
Related to trial agent	0	0	0	0	0	0
Any AE within 3 days after an administration						
Overall	5 (5.8)	5	6 (6.5)	6	10 (12.0)	13
Related to trial agent	2 (2.3)	2	2 (2.2)	2	4 (4.8)	5
Any AE that led to hospitalisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Event	Sebetralstat 300 mg (N=86)		Sebetralstat 600 mg (N=93)		Placebo (N=83)	
	no. (%)	no. of events	no. (%)	no. of events	no. (%)	no. of events
AE during treatment that led to trial discontinuation	0	0	0	0	0	0
AE during treatment that led to death	0	0	0	0	0	0
TRAEs within 3 days after an administration§						
Gastrointestinal disorders						
Dyspepsia	1 (1.2)	1	0	0	0	0
Nausea	0	0	1 (1.1)	1	1 (1.2)	1
General disorders and administration site conditions						
Fatigue	1 (1.2)	1	0	0	0	0
Nervous system disorders						
Headache	0	0	1 (1.1)	1	1 (1.2)	1
Dysgeusia	0	0	0	0	1 (1.2)	1
Reproductive system and breast disorders						
Menstruation irregular	0	0	0	0	1 (1.2)	1
Skin and SC tissue disorders						
Rash	0	0	0	0	1 (1.2)	1

Source: Based on Table 14 of the CS[6]

* Shown are data for 110 participants who administered the indicated dose of sebetralstat or placebo to themselves for at least one angioedema attack.

† SAEs during treatment were defined as any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, resulted in inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or substantial disability or incapacity, was a congenital anomaly or birth defect, or was considered to be an important medical event according to medical and scientific judgment. The three SAEs during treatment were the only AEs that resulted in hospitalisation.

‡ SAEs during treatment were defined as AEs of Grade 3 in severity as assessed qualitatively by the Investigator or as reported by the participant.

§ TRAEs are categorised according to MedDRA, version 26.0, system organ class and preferred term.

AEs = adverse events; CS = company submission; MedDRA = Medical Dictionary for Regulatory Activities; mg = milligram; SAEs = serious adverse events; SC = subcutaneous; TRAEs = treatment-related adverse events

Table 3.13: KONFIDENT study: safety summary by number of administrations

Event – no. (%)	Sebetralstat				Placebo	
	300 mg (N=58)	300 mg + 300 mg (N=28)	600 mg (N=60)	600 mg + 600 mg (N=34)	1 administration (N=44)	2 administrations (N=39)
Any AE	10 (17.2)	7 (25.0)	7 (11.7)	7 (20.6)	5 (11.4)	12 (30.8)
Treatment-related	2 (3.4)*	0	1 (1.7)*	2 (5.9)*	3 (6.8)*	1 (2.6)*
SAEs during treatment†	1 (1.7)‡	0	2 (3.3)	0	0	0
TRAE	0	0	0	0	0	0

Event – no. (%)	Sebetralstat				Placebo	
	300 mg (N=58)	300 mg + 300 mg (N=28)	600 mg (N=60)	600 mg + 600 mg (N=34)	1 administration (N=44)	2 administrations (N=39)
Severe AEs during treatment§	1 (1.7)‡	0	0	0	0	0
TRAE	0	0	0	0	0	0
AE during treatment that led to study discontinuation	0	0	0	0	0	0
AE during treatment that led to death	0	0	0	0	0	0

Source: Based on Table 15 of the CS[6]
*TRAEs were fatigue and indigestion with sebetralstat 300 mg, nausea with sebetralstat 600 mg, dyspepsia and hot flash with sebetralstat 600 mg + 600 mg, headache and nausea (same patient), rash, and dysgeusia with 1 administration of placebo, and irregular menstruation with 2 administrations of placebo.
†SAE was defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or substantial disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event by medical and scientific judgement.
‡The severe AE and SAE listed are the same event; lumbar disc herniation that required hospitalisation and was deemed severe by the Investigator.
§Severe AE was defined as a qualitative assessment of an AE of Grade 3 severity by the Investigator or as reported by the patient.
AEs = adverse events; CS = company submission; mg = milligram; SAEs = serious adverse events; TRAEs = treatment-related adverse events

Table 3.14: KONFIDENT AEs within 3 days after an administration

Event*	Sebetralstat 300 mg (N=86)		Sebetralstat 600 mg (N=93)		Placebo (N=83)	
	no. (%)	no. of events	no. (%)	no. of events	no. (%)	no. of events
Any AE within 3 days after an administration *,†						
Eye disorders	0	0	0	0	1 (1.2)	1
Eye hemorrhage	0	0	0	0	1 (1.2)	1
Gastrointestinal disorders	3 (3.5)	3	2 (2.2)	2	3 (3.6)	3
Vomiting	1 (1.2)	1	1 (1.1)	1	1 (1.2)	1
Nausea	0	0	1 (1.1)	1	1 (1.2)	1
Abdominal pain	0	0	0	0	1 (1.2)	1
Dyspepsia	1 (1.2)	1	0	0	0	0
Gingival bleeding	1 (1.2)	1	0	0	0	0
General disorders and administration site conditions	1 (1.2)	1	0	0	1 (1.2)	1
Fatigue	1 (1.2)	1	0	0	1 (1.2)	1
Infections and infestations	1 (1.2)	1	0	0	2 (2.4)	2

Event*	Sebetralstat 300 mg (N=86)		Sebetralstat 600 mg (N=93)		Placebo (N=83)	
	no. (%)	no. of events	no. (%)	no. of events	no. (%)	no. of events
Influenza	0	0	0	0	1 (1.2)	1
Pharyngitis bacterial	0	0	0	0	1 (1.2)	1
Pharyngitis streptococcal	1 (1.2)	1	0	0	0	0
Musculoskeletal and connective tissue disorder	0	0	0	0	1 (1.2)	1
Neck pain	0	0	0	0	1 (1.2)	1
Nervous system disorders	0	0	4 (4.3)	4	2 (2.4)	2
Headache	0	0	3 (3.2)	3	1 (1.2)	1
Dizziness	0	0	1 (1.1)	1	0	0
Dysgeusia	0	0	0	0	1 (1.2)	1
Reproductive system and breast disorders	0	0	0	0	1 (1.2)	1
Menstruation irregular	0	0	0	0	1 (1.2)	1
Respiratory, thoracic, and mediastinal disorders	0	0	0	0	1 (1.2)	1
Epistaxis	0	0	0	0	1 (1.2)	1
Skin and SC tissue disorders	0	0	0	0	1 (1.2)	1
Rash	0	0	0	0	1 (1.2)	1

Source: Based on Table 16 of the CS[6]
*Shown are data for 110 participants who administered the indicated dose of sebetralstat or placebo to themselves for at least one angioedema attack.
†Categorised by SOC and preferred term (coded using MedDRA, version 26.0)
AEs = adverse events; CS = company submission; MedDRA = Medical Dictionary for Regulatory Activities; mg = milligram; SOC = system organ class

The company also mentioned that "*Three serious adverse events were reported (all led to hospitalisation); none were related to the trial agent or occurred within 3 days after sebetralstat or placebo was taken. In the 300 mg group, one case of herniated lumbar vertebrae was reported. In the 600 mg group, one case of anisocoria related to lisdexamfetamine use and one case of exacerbation of a hereditary angioedema attack, in which the patient did not take the trial agent, were reported.*"[6]

The company also added that "*No deaths were reported in this trial and there were no on-treatment serious adverse events (SAEs) reported.*" [6]

Further details can be found in Table 3.15 below.

Table 3.15: SAEs by SOC and preferred term (SAS)

SOC preferred term	300 mg sebetralstat (N=86) n (%) E	600 mg sebetralstat (N=93) n (%) E	Placebo (N=83) n (%) E

Total number of SAEs	[redacted]	[redacted]	[redacted]
Congenital, familial, and genetic disorders	[redacted]	[redacted]	[redacted]
HAE	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]
Anisocoria	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Intervertebral disc protrusion	[redacted]	[redacted]	[redacted]

Source: Based on Table 17 of the CS[6]

Notes: At each level of patient summarisation, a patient was counted once if the patient reported 1 or more events.

n represents the number of patients at each level of summarization.

N is the number of patients randomised using a permuted-block randomisation method to ensure a balanced assignment to each of the 6 treatment sequences, to receive that received 300 mg KVD900, 600 mg KVD900, or matching placebo for the analysed IMP-treated HAE attacks, according to the actual treatment received.

[E] represents the number of events at each level of summarisation.

CS = company submission; HAE = hereditary angioedema; IMP = investigational medicinal product; mg = milligram; SAE = serious adverse event; SAS = Safety Analysis Set; SOC = system organ class

EAG comments: The AEs results are considered reliable.

3.3 Critique of trials identified and included in the ITC and/or multiple treatment comparison

The company provided the results from a recently published ITC[15,16] with the objective of demonstrating the method-of-administration comparability between an oral OD treatment with an IV treatment in the CS.[6]

The company made the following statement:[6]

- *"ITC was based on the primary endpoint ('time to beginning of symptom relief') and safety outcomes, between oral sebetralstat and intravenous rhC1-INH.*
- *ITC found no significant differences in time to beginning of symptom relief and overall treatment-related adverse events between sebetralstat and IV rhC1-INH. Although this ITC does not inform the economic analyses, it has been included in Appendix L for completeness.*
- *In the absence of robust and feasible ITC to capture comparative effectiveness between sebetralstat and its comparators for utilisation in the cost-effectiveness model [developed for the purpose of this sebetralstat appraisal (see Section 3)]; the cost-effectiveness model considers that earlier on-demand treatment administration is associated with a shorter total attack duration.*
- *To alleviate the absence of direct or indirect evidence, the cohort State-Transition Model (cSTM) incorporates a statistical sub-model to estimate the effect moderation of TTA (time to treatment administration) on TTAR, to obtain an adjusted TTAR (time to attack resolution) for each treatment."*

Given that the company stated in the Appendix L that the ITC used propensity score weighting (PSW) to enhance the comparability between included trials, the EAG asked the company to clarify which baseline characteristics were used to estimate the propensity score (PS). The EAG also asked the company to provide a table showing which baseline characteristics were included from the systematic review, which were by the clinical experts, and which were available in the individual patient data (IPD) for the ITC. In addition, the EAG also asked the company to provide a list of prognostic variables (which were identified via systematic review and/or by clinical experts) that were not adjusted for in the MAIC analysis. In responding to the EAG's request, the company made the following statement:[8]

- *"The company has conducted a systematic literature review and found no evidence suggesting potential treatment effect modifiers for HAE on-demand therapies. In the best effort to evaluate potential confounders, we assessed the list of potential prognostic factors outlined in a recent publication on the indirect comparison of HAE prophylactic treatments, in addition to data availability in KONFIDENT. Two scenarios were considered with regarding to the matching variables:*
- *Scenario 1: match on disease severity, measured by the baseline visual analogue scale (VAS)*
- *Scenario 2: match on baseline disease severity and selected demographic variables (age, sex, race)."*

Table 3.16 presents potential prognostic factors, confounders and/or treatment effect modifiers.

Table 3.16: Potential prognostic factors, confounders and/or treatment effect modifiers

Potential prognostic factors, confounders and/or treatment effect modifiers	Watt et al (2024)	Available in KONFIDENT IPD	Used for matching
Disease severity	x	x	x (Scenarios 1 & 2)
Age	x	x	x (Scenario 2 only)
Sex	x	x	x (Scenario 2 only)
Race (White/Caucasian versus other)	x	x	x (Scenario 2 only)
HAE Type (Type I versus Type II)	x	x	
Presence of family history	x		
Comorbidity categories	x		
Route of administration	x		
Follow-up time	x	x	
Baseline attack frequency	x		
Smoking habit	x		
Alcohol consumption	x		
Source: Table 1 of company response to clarification letter[8] HAE = hereditary angioedema; IPD = individual patient data			

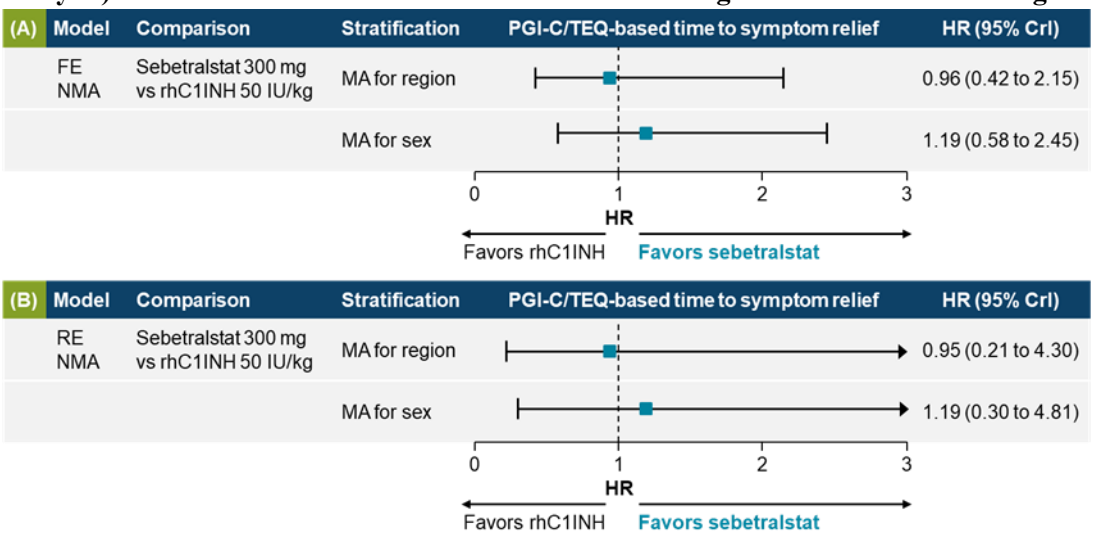
The company also stated that the remaining potential prognostic factors, confounders and/or treatment effect modifiers could not be adjusted for because either they were not available in the KONFIDENT trial and/or not reported in the Ruconest studies.[8]

3.4 Critique of the ITC and/or multiple treatment comparison

3.4.1 Time to beginning of symptom relief

There was no significant difference in time to beginning of symptom relief between sebetralstat 300 mg and rhC1-INH 50 international units (IU)/kg in the fixed-effects models for region (hazard ratio [HR], 0.96; 95% credible interval [CrI], 0.42–2.15; see Figure 3.9 [A]) or sex (HR, 1.19; 95% CrI, 0.58–2.45; Figure 3.9 [B]). There were no differences being observed in the random-effects models (sensitivity analysis) for region (HR, 0.95; 95% CrI, 0.21–4.30) or sex (HR, 1.19; 95% CrI, 0.30–4.81). Because of the simplicity of the network meta-analysis (NMA) for time to beginning of symptom relief (only two comparisons from two trials) and similar DIC for the fixed-effects and random-effects model, the fixed-effects model was considered appropriate as the main analysis.[10]

Figure 3.9: Time to beginning of symptom relief per (A) FEs (base-case) and (B) REs (sensitivity analysis) models. HR values >1 favour sebetralstat 300 mg over rhC1-INH 50 IU/kg.



Source: Figure 17 of CS Appendix[10]

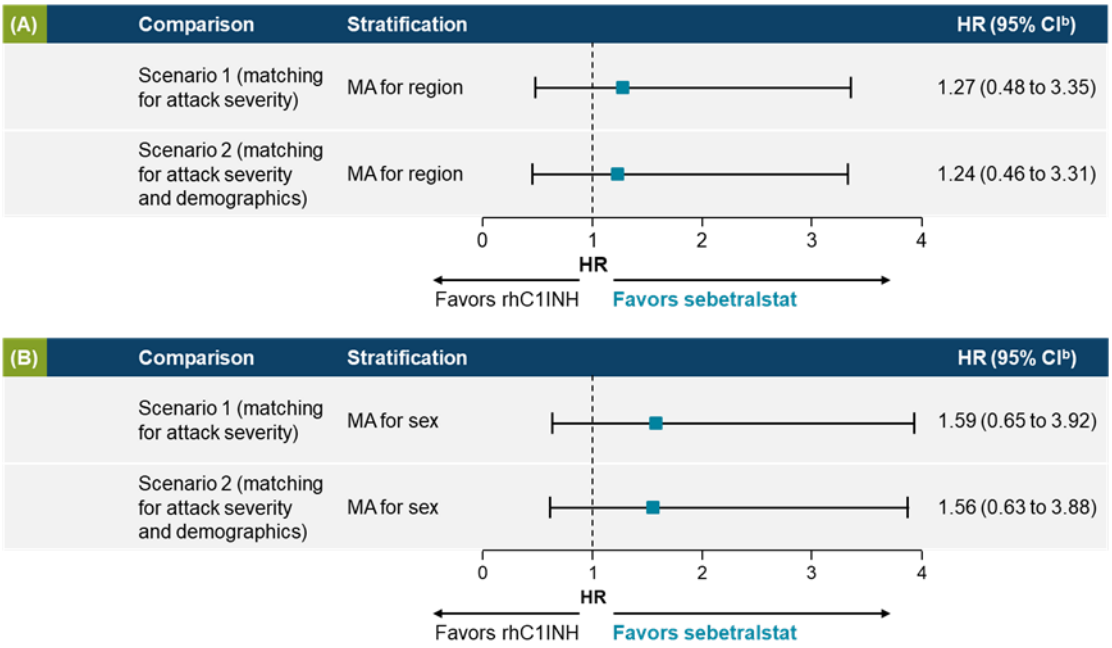
CrI = credible interval; CS = company submission; FEs = fixed effects; HR = hazard ratio; IU = international units; MA = meta-analysis; mg = milligram; NMA = network meta-analysis; PGI-C = Patient Global Impression of Change; REs = random effects; rhC1-INH = recombinant human C1 esterase inhibitor

3.4.2 Time to beginning of symptom relief

MAICs were performed for time to beginning of symptom relief, because the differences in baseline disease severity and demographics may have affected time to beginning of symptom relief. Two MAICs were conducted under each of the two match-adjustment scenarios (baseline severity only and baseline attack severity plus demographics) because HRs were only available for region and sex in the rhC1-INH C1-1310 trial.[10]

There was no statistically significant difference in time to beginning of symptom relief between sebetralstat 300 mg and rhC1-INH 50 IU/kg in either scenario.[10] In Scenario 1, after matching for baseline attack severity, time to beginning of symptom relief numerically favoured sebetralstat 300 mg compared with rhC1-INH 50 IU/kg (region: HR, 1.27 [95% CI, 0.48–3.35]; sex: HR, 1.59 [95% CI, 0.65–3.92]; see Figure 3.10 [A]). In Scenario 2, after matching for baseline severity and patient demographics, the results did not materially change (region: HR, 1.24 [95% CI, 0.46–3.31]; sex: HR, 1.56 [95% CI, 0.63–3.88]; Figure 3.10 [B]).[10]

Figure 3.10: Time to beginning of symptom relief matched for (A) baseline attack severity[a] only and (B) baseline attack severity,[a] age, sex, and race



Source: Based on Figure 18 of CS Appendices[10]
[a] Maximum of three baseline overall severity VAS scores.
[b] HR values >1 favour sebetralstat 300 mg over rhC1-INH 50 IU/kg.
CI = confidence interval; CS = company submission; HR = hazard ratio; IU = international units; rhC1=INH = recombinant human C1 esterase inhibitor; MA = meta-analysis; MAIC = matching-adjusted indirect comparison; VAS = visual analogue scale

3.4.3 Additional data

The EAG asked the company to provide the mean and SD of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm before matching. The EAG also asked the company to provide the sample size for each arm and provide standardised mean difference (SMD) for the comparison of the intervention arm and the comparator arm before matching. In responding to the EAG's request, the company provided relevant data in the clarification response document.[8] Table 3.17 presents mean and SD of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm before matching, and SMD before matching.

Table 3.17: Mean and SD of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm before matching, and SMD

Baseline variables	KONFIDENT (N=169)	Riedl et al 2014[17] (N=75)	SMD
Attack severity, VAS mean (SD)	46.6 (25.4)	75.1 (13.5)	-1.401
Age, mean (SD)	37.5 (14.9)	40.2 (15.1)	-0.180
Female sex, n (%)	107 (63.3%)	47 (63.3%)	0.000
White race, n (%)	144 (85.2%)	72 (95.8%)	-0.368
Source: Based on Table 2 of CS response CS = company submission; MAIC = matching-adjusted indirect comparison; SMD = standardised mean difference; SD = standard deviation; VAS = visual analogue scale			

Furthermore, the EAG asked the company to provide mean and SD of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm after matching. The EAG also asked the company to provide the effective sample size for each arm and provide the SMD for the comparison of the intervention arm and the comparator arm after matching. In responding to the EAG's request, the company provided relevant data in the clarification response document.[8]

Table 3.18 presents mean and SD of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm after and SMD after matching.

Table 3.18: Mean and SD of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm after matching, and SMD

Scenario 1	**Used for matching**	**Baseline variables**	**KONFIDENT (ESS = 62)**	**Riedl 2014[17] (N=75)**	**SMD**
	Yes	Severity, VAS mean (SD)	75.1 (21.1)	75.1 (13.5)	0.000
	No	Age, mean (SD)	37.8 (15.2)	40.2 (15.1)	-0.158
	No	Female sex, n (%)	39 (62.4%)	47 (63.3%)	-0.019
	No	White race, n (%)	54 (86.7%)	72 (95.8%)	-0.326
Scenario 2	Used for matching	Baseline variables	KONFIDENT (ESS = 58)	Riedl 2014 (N=75)	SMD
	Yes	Severity, VAS mean (SD)	75.1 (20.7)	75.1 (13.5)	0.000
	Yes	Age, mean (SD)	40.2 (13.6)	40.2 (15.1)	0.000
	Yes	Female sex, n (%)	37 (63.3%)	47 (63.3%)	0.000
	Yes	White race, n (%)	56 (95.8%)	72 (95.8%)	0.000

Source: Based on Table 3 of CS response
CS = company submission; ESS = effective sample size; MAIC = matching-adjusted indirect comparison; SD = standard deviation; SMD = standardised mean difference; VAS = visual analogue scale

EAG comments:

- For ITC, the company provided the results from a recently published ITC with the objective of demonstrating the method-of-administration comparability between an oral OD treatment with an IV treatment in the evidence submission.
- However, the EAG noted that a recent paper relating to this ITC was not included in the CS. The EAG asked the company to provide an explanation why this recent paper relating to the ITC was not included in the CS. In responding to the EAG request, the company stated that the Li et al 2025[15] manuscript is the full publication for the same body of work as the Li et al 2024 (ACAAI 2024 poster)[18] and Wang et al 2024 (ACAAI 2024) conference abstract.[16] The CS Appendix L content was a detailed version of the ITC based on the Li et al 2025 manuscript, which was a draft (unpublished) item at the time of submission development, so the omission of Li et al 2025 as a final reference in the CS was an oversight by the company. The EAG considers that the explanation provided by the company appears to be reasonable.
- The EAG asked the company to provide the mean and SD of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm before matching. The

EAG also asked the company to provide the sample size for each arm and provide SMD for the comparison of the intervention arm and the comparator arm before matching. In responding to the EAG's request, the company provided relevant data before matching.

- Furthermore, the EAG asked the company to provide mean and SD of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm after matching. The EAG also asked the company to provide the effective sample size for each arm and provide the SMD for the comparison of the intervention arm and the comparator arm after matching. In responding to the EAG's request, the company provided relevant data after matching.
- The EAG considers that based on the additional data provided by the company during the clarification response stage, the distributions of these covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm were generally balanced after matching.
- Given that the company stated in the Appendix L that the ITC used PSW to enhance the comparability between included trials, the EAG asked the company to clarify which baseline characteristics were used to estimate the PS. The EAG also asked the company to provide a table showing which baseline characteristics were included from the systematic review, which by clinical experts and which were available in the IPD for the ITC analysis. In addition, the EAG also asked the company to provide a list of prognostic variables (which were identified via systematic review and/or by clinical experts) that were not adjusted for in the MAIC analysis.
- In responding to the EAG's request, the company stated that the company has conducted a systematic review and found no evidence suggesting potential treatment effect modifiers for HAE OD therapies. The company further stated that in the best effort to assess potential confounders, the company assessed the list of potential prognostic factors outlined in a recent publication on the ITC of HAE prophylactic treatments, in addition to data availability in the KONFIDENT trial. In the MAIC analyses, two scenarios were considered relating to matching variables. In Scenario 1, match based on disease severity that was assessed by the baseline VAS was performed. In Scenario 2, match based on baseline disease severity and a number of selected demographic variables (age, sex, race) was performed.
- It should be noted that a number of important prognostic variables (HAE Type [Type I versus Type II], comorbidity categories and baseline attack frequency) were not adjusted for in the MAIC analysis due to unavailability of data. Due to the lack of adjustment for these important prognostic variables in the MAIC analyses, this issue may have compromised the validity of results from the MAIC analyses.

3.5 Additional work on clinical effectiveness undertaken by the EAG

Not applicable**.**

3.6 Conclusions of the clinical effectiveness Section

The CS, Appendix B and response to clarification[6,8,10] provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence on the efficacy and safety of sebetralstat for treating acute attacks of HAE. Searches were conducted in February 2024 and updated in November 2024. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of bibliographic databases, conference proceedings and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted.

The study selection criteria for PICOs in the SLR of clinical effectiveness generally encompassed those specified by the NICE Final Scope. The data extraction process was satisfactory and in line with recommended good practice in SLRs. The process for the assessment of RoB in the included studies was satisfactory. The process of assessing RoB, and the number of reviewers involved were described. The number of studies retrieved, screened and included was clear based on the PRISMA flow chart.

One pivotal RCT was identified as being relevant to the SLR: one RCT (KONFIDENT Phase 3 trial) provided the main source of evidence. KONFIDENT was a Phase 3 double-blind, randomised, placebo-controlled, three-way crossover trial 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 OD treatment of patients with HAE attacks. The EAG rated the KONFIDENT trial being at low RoB. The Phase 2 trial (KVD900-201) was a randomised, double-blind, crossover trial comparing sebetralstat versus placebo for the treatment of patients with HAE Type I or II. The OLE study (KONFIDENT-S trial) provided data on the long-term clinical efficacy and safety of sebetralstat for the treatment of patients with HAE Type I or II.

The results of the KONFIDENT trial showed that there was a statistically significant improvement in the time to the beginning of symptom relief between 300 mg sebetralstat and the placebo group (adjusted p<0.0001) and between 600 mg sebetralstat and the placebo group (adjusted P=0.0013). The median (95% CI) time to the beginning of symptom relief was 1.61 hours (95% CI: 1.28, 2.27) for 300 mg sebetralstat group, 1.79 hours (95% CI: 1.33, 2.27) for 600 mg sebetralstat group, and 6.72 hours (95% CI: 2.33, not evaluable) for the placebo group.[6] Furthermore, a statistically significant reduction in attack severity (within 12 hours after the first administration) was reached with the 300 mg dose (P=0.004) and the 600 mg sebetralstat dose (P=0.003) compared with placebo. The median time to a reduction in severity with the 300 mg dose was 9.27 hours (IQR, 1.53 to >12), 7.75 hours (2.19 to >12) with the 600 mg dose, and over 12 hours (6.23 to >12) with placebo. [6]

In terms of ITC, the company provided the results from a recently published ITC with the objective of demonstrating the method-of-administration comparability between an oral OD treatment with an IV treatment the evidence submission. Given that the company stated in the Appendix L that the ITC used PSW to enhance the comparability between included trials, the EAG asked the company to clarify which baseline characteristics were used to estimate the PS. The EAG also asked the company to provide a table showing which baseline characteristics were included from the systematic review, which by clinical experts and which were available in the IPD for the ITC. In addition, the EAG also asked the company to provide a list of prognostic variables (which were identified via systematic review and/or by clinical experts) that were not adjusted for in the MAIC analysis.

In responding to the EAG's request, the company stated that the company has conducted a SLR and found no evidence suggesting potential treatment effect modifiers for HAE OD therapies. The company further stated that in the best effort to evaluate potential confounders, the company assessed the list of potential prognostic factors outlined in a recent publication on the indirect comparison of HAE prophylactic treatments, in addition to data availability in the KONFIDENT trial. Two scenarios were considered with regarding to the matching variables. In Scenario 1, match based on disease severity that was measured by the baseline VAS was performed. In Scenario 2, match based on baseline disease severity and a number of selected demographic variables (age, sex, race) was performed.

It should be noted that a number of important prognostic variables (HAE Type [Type I versus Type II], comorbidity categories and baseline attack frequency) were not adjusted for in the MAIC analysis

due to unavailability of data. Because of the lack of adjustment for these important prognostic variables in the MAIC analyses, this issue may have compromised the validity of results from the MAIC analyses.

4. Cost-effectiveness

4.1 Critique of the review of CE evidence

This Section pertains mainly to the review of CEA studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to CE presented in the CS. Therefore, the following Section includes searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for the CE Section

The following paragraphs contain summaries and critiques of all searches related to CE, HRQoL and resource use identification presented in the CS.[6] The CADTH evidence-based checklist for the PRESS, was used to inform this critique.[9] The EAG has presented only the major limitations of each search strategy in the report.

Appendices E, F and G of the CS provide details of SLRs conducted to identify relevant studies on CE, HRQoL and cost/healthcare resource use (HCRU) in the treatment of HAE.[10] Both the CE searches and HRQoL searches were conducted in March 2024 and updated in November 2024.

EAG comments:

- A single set of searches was undertaken to identify relevant studies on the economic evidence and HCRU in HAE. An additional set of searches was conducted to identify relevant HRQoL data. The CS, Appendices E, F and G and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[6, 8, 10]
- The following databases were searched for the economic evidence and HCRU SLR: Embase, MEDLINE, EconLit, the Health Technology Assessment (HTA) database, the NHS Economic Evaluation Database (NHS EED) and the Cost Effectiveness Analysis registry. Conference abstract searches included the Professional Society for Health Economics and Outcomes Research (ISPOR) proceedings. The MEDLINE, Embase and EconLit searches were documented as being conducted on 12 February 2024 in the CS,[6] however the response to clarification states that the MEDLINE and Embase searches were conducted on 15 March 2024.[8] Update searches were conducted on 15-18 November 2024.
- The HRQoL SLR searches were conducted on 15 March 2024, and included the following databases: Embase, MEDLINE, EconLit, the HTA database, the NHS EED and the Cost Effectiveness Analysis registry. Conference proceedings were searched for ISPOR, the European Academy of Allergy and Clinical Immunology, the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma & Immunology. Searches were updated on 15 November 2024.
- No publication date or language limits were applied to any of the CE/HRQoL searches.
- The economic evidence/HCRU searches contained a population facet for HAE. This was then combined with a study design filter containing terms for costs and economic evaluations. The HRQoL searches contained the same population facet for HAE which was combined with a study design filter containing terms for HRQoL.
- All searches were well structured, transparent and reproducible.
- Searches contained a good range of search terms, synonyms and subject headings. None of the study design filters used were referenced, however all contained an extensive combination of subject heading terms and free text terms, and the EAG considered them appropriate. However, as

the EconLit database contains only references to economic studies, and given the low number of references found by the search, the EAG felt additional filters were unnecessary for this resource.
- The update searches were conducted by applying a 2024 publication year limit to the original searches. The EAG believed that the use of additional database fields (such as record entry date or update date) would have increased the chance of retrieving records with a pre-2024 publication date which had been added to the database since the date of the original search.

4.1.2 Inclusion/exclusion criteria

In- and exclusion- criteria for the review on CE studies, utilities and costs and resource use are presented by the company in Appendices E, F and G of the CS.[10] The EAG agrees that the in- and exclusion- criteria are suitable to fulfil the company's objective to identify relevant CE studies in general. The searches were restricted to the English language, and the resource use outcomes were limited to studies from 2013 onwards (justified as "to focus on studies that best reflect current practice", but the date selected seems arbitrary). Thus, it is possible that relevant studies might have been missed.

4.1.3 Findings of the CE review

The original searches were conducted on 15 March 2024 and updated searches were conducted on 15 November 2024 (MEDLINE and Embase) and 18 November 2024 (Econlit).

The PRISMA flow diagrams for the original and updated CE and resource use SLR can be found in Figure 25 and 26 of Appendix E of the CS, respectively.[10] The original search identified a total of 1,640 records from database searches and 26 from the grey literature, from which a total of 119 were included for data extraction. Since 12 of these were without useable data for extraction, and eight were SLR reports, the total number of articles included in review was 99. The updated searches identified a total of 181 records from database searches, from which eight were included for data extraction. Of the 107 studied in the review, 30 were CE studies, and 77 cost and HCRU studies.

Additionally, the PRISMA flow diagrams for the original and updated HRQoL SLR can be found in Figures 27 and 28 of Appendix F of the CS, respectively.[10] The original search identified 349 records from database searches and six from ClinicalTrials.gov, from which 49 were included for data extraction (including one trial from ClinicalTrials.gov). Six records were added from conference proceedings, two more from reference explosion and six from the economic SLR, with HRQoL outcomes. The total number of included records were therefore 63. The updated searches identified a total of 33 records from database searches, from which 15 were included for data extraction.

4.1.4 Conclusions of the CE review

The CS, Appendices E, F and G and response to clarification[6, 8, 10] provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant studies on CE, HRQoL and cost/HCRU in HAE. Searches were conducted in March 2024 and updated in November 2024. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of databases and conference proceedings were searched. Overall, the EAG has no major concerns about the literature searches conducted. No economic models to address the current DP were identified by the company. Therefore, a de novo model was built, which is discussed in the remainder of this Section.

4.2 Critique of the submitted economic evaluation

4.2.1 NICE reference case checklist

Table 4.1: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	As per the reference case
Perspective on costs	NHS and PSS	As per the reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	The company defined SoC as a basket comparator reflecting current OD treatments. The EAG prefers a fully incremental analysis as per the reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	As per the reference case
Synthesis of evidence on health effects	Based on systematic review	Post-hoc statistical model to estimate TTAR from TTA using KONFIDENT trial data.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Acute attack disutilities derived from a vignette study.[19] Treatment-related utility decrements derived from a DCE vignette study.[20]
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Vignettes describing health states during acute attacks were based on interviews with patients, caregivers and clinical experts. The DCE study for treatment-related utilities was developed based on interviews with patients and caregivers.

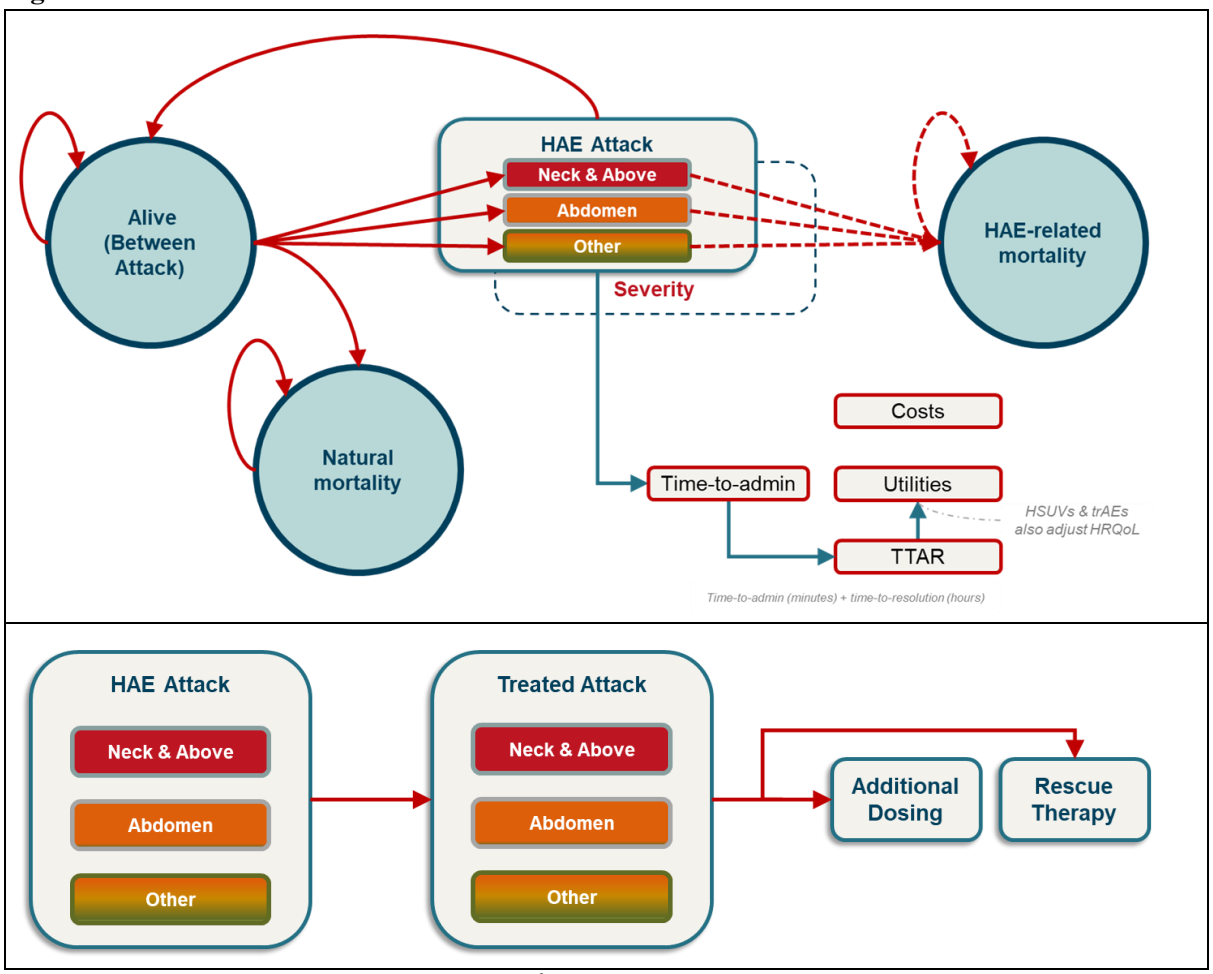
Element of HTA	Reference case	EAG comment on CS
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	100 members of the general public valued the vignettes for health states during acute attacks. The DCE vignettes were valued by both HAE patients and general population samples from the UK and the US.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	As per the reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	As per the reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	As per the reference case

CS = company submission; DCE = discrete choice experiment; EAG = External Assessment Group; EQ-5D = EuroQoL-5 Dimensions; HRQoL = health-related quality of life; HTA = Health Technology Assessment; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OD = on-demand; PSS = Personal Social Services; QALY = quality-adjusted life year; SoC = standard of care; TTA = time to treatment administration; TTAR = time to attack resolution; UK = United Kingdom; US = United States

4.2.2 Model structure

The company developed a de novo cohort state-transition model in Microsoft Excel® 365, selected as the most appropriate structure for capturing the clinical and economic burden of HAE. The model includes two health states: Alive and Dead (Natural Mortality). Attacks are modelled as acute transient events within the Alive state, with a constant cycle-level risk over time. All attacks are assumed treated in line with WAO guidelines and previous models evaluating the CE of OD treatments for HAE.[21, 22] A schematic representation of the model structure is described in Figure 4.1.

Figure 4.1: Model structure



Source: Based on Figure 12 and 13 of the CS[6]
CS = company submission; HAE = hereditary angioedema; HRQoL = health-related quality of life; HSUV = health-state utility value; trAE = treatment-related adverse event; TTAR = time to attack resolution

Attack-related utilities and costs are applied per model cycle. Utilities account for disutility from attack location (not severity), side effects, and health state. Costs related to HAE attacks include acquisition, administration and HCRU, and AEs. However, AEs are assumed to be resolved without incurring additional costs to the NHS.

In the base case, attack location is used to estimate the impact of HAE attacks on HRQoL, rather than attack severity. This choice reflects the high subjectivity and variability associated with severity, which is influenced by individual experiences, psychological factors, and functional impairment.[19, 23-28] In contrast, location provides a more consistent and reliable proxy for disutility, as supported by expert opinion. The model assumes attacks occur in one of three body regions: Neck and Above, Abdominal, or Other, with disutility applied accordingly. Use of severity as an alternative indicator is explored in scenario analysis. However, to avoid double counting, location and severity are treated as mutually exclusive due to the lack of studies reporting disutilities by both dimensions.

Disutility is adjusted by time to attack resolution (TTAR), which is the preferred efficacy outcome. Due to lack of comparative TTAR evidence, the company used a post-hoc statistical model to estimate TTAR from time to treatment administration (TTA) using KONFIDENT data.[29-31] Pairwise indirect comparisons were limited by heterogeneity in endpoints and trial designs.[16, 32-37]

The model accounts for additional dosing and rescue therapy, which contribute costs but not TTAR adjustments. The company assumed that the adjusted TTAR of each treatment includes adjustment for the TTA of the first dose, any additional doses, and rescue therapy use. Due to a lack of data on the conditional use of rescue therapy, the model assumes that the proportions of patients requiring additional doses and those using rescue therapy are modelled independently. The sequencing of these treatment-steps could not be captured.

Hospitalisation risk is modelled by administration Type (self versus health care practitioner [HCP]) and is associated with a cost per event, drawing from assumptions in Technology Appraisal 606 (TA606).[38] While Accident and Emergency costs for Neck and Above attacks were not included, this was justified due to equal attack distribution across comparators.

General population mortality is applied, and HAE-related mortality is excluded from the base-case due to its rarity in diagnosed patients,[22, 39] though it is considered in scenario analysis.

The economic analysis is conducted from the NHS and PSS perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is 21 days with a lifetime time horizon and a half-cycle correction applied.

4.2.3 Population

The CS defines the modelled population as individuals aged 12 years and over with Type I and Type II HAE. As no clinical or economic differences between subtypes were identified, these are modelled as a single homogeneous population.[22,29] Baseline characteristics were derived from the KONFIDENT Phase III RCT,[29] its OLE,[30] and published literature where applicable. The mean age at baseline was 37.7 years, with 60% female.[29] Weight was modelled using general population distributions adjusted for age and gender.[40]

The cohort was split into 45% receiving LTP plus OD treatment, and 55% receiving OD only.[41] These subgroups differ in annual attack rates, resulting in a cohort average of 14.7 attacks per year. Clinical and economic outcomes per attack are assumed equal across both subgroups.

EAG comment: In response to clarification question B1c,[8] the company reiterated that participants in the KONFIDENT study were considered broadly representative of the global HAE population. UK clinical experts consulted by the company advised that, in practice, the proportion of patients using LTP plus OD treatment is likely higher than the 21.8% reported in KONFIDENT. The KONFIDENT-S OLE trial showed similar patient demographics to the main trial and, according to the company, is also regarded as representative of the UK HAE population.

In addition, in response to clarification question B16a,[8] the company explained that the average cohort attack rate was calculated as 11×45% + 17.74×55% = 14.71. The sources for these estimates can be found in the economic model: Mendivil et al 2023 - Table 5 for the LTP + OD rate (11.0) and Longhurst et al 2018 for the OD rate (17.78).[42, 43]

The clinical experts consulted by the EAG estimated that between 50% and 70% of patients use LTP + OD in clinical practice. All experts indicated that OD treatment remains necessary due to breakthrough attacks, which may be milder in patients on prophylaxis.[3]

The EAG explored the impact of the proportion of patients receiving LTP + OD (50% - 70%) and the cohort attack rates as per company's clarification report B16 (11.0 and 5.49 per year) on the model results through different scenario analyses in Section 5.2 of this report.

4.2.4 Interventions and comparators

The economic analysis defines sebetralstat 300 mg as the intervention. The comparator is SoC, modelled as a basket comparator reflecting current OD treatments, regardless of being SC or IV options. According to the company, this approach aligns with WAO guidelines and reflects clinical practice, where treatment is individualised.[22] Comparator treatments included as part of SoC in the economic model are icatibant (SC), ruconest (IV), and berinert (IV). Incremental outcomes for SoC are calculated as a weighted average based on each treatment's market share. The economic model also allows comparison with cinryze (IV), and pairwise comparisons between sebetralstat and each OD treatment are presented as scenario analyses.

EAG comment: The EAG's main concern relates to the definition of SoC as a basket of current OD treatments. The company reiterated that the basket comparator is more reflective of NHS clinical practice. In response to clarification question B4,[8] the company referred to Section 4.2.17 of the NICE manual for health technology evaluations: "*if the technologies form part of a class of treatments, and evidence is available to support their clinical equivalence, estimates of QALYs gained for the class as a whole can be shown*".[44] The company omitted though that a class (or basket, as used by the company) of treatments is used in "*exceptional circumstances*", and did not provide further justification as to why the comparators should be included in the same class. The definition of a class (of drugs) that can be found in the NICE Glossary indicates that a class is a "*group of drugs with the same or similar mechanisms of action. They may or may not have the same basic chemical structure. There may be differences between drugs in a class, such as the side effects associated with them*".[45] It is the EAG's understanding that there are two types of comparator treatments considered in this submission, C1-INHs (including berinert, ruconest and cinryze – which could indeed be considered as a class) and bradykinin B2 receptor (BR2) antagonists (icatibant), but that these two do not have the same mechanism of action. Thus, C1-INHs and BR2 antagonists do not meet NICE definition of class of treatments. In addition, the company have not presented evidence to support clinical equivalence. The evidence provided by the company in the CS shows that icatibant (BR2 antagonist) has shorter time to attack resolution than any of the C1-INHs (see e.g., Table 4.4 of this report), due to its faster time to administration, which is the only driver of differential efficacy in the regression model included in the present economic analyses. Therefore, the EAG considers that clinical equivalence (between BR2 antagonists and C1-INHs) cannot be assumed in this case. Based on this, the EAG concludes that the definition of SoC as a basket of current OD treatments is not justified since there is no similar mechanism of action and no clinical equivalence.

Regarding the previously discussed concern the EAG would also like to point out the following: in response to clarification question B4,[8] the company indicated that while OD HAE treatments can differ in mechanism of action (acknowledging therefore that this criterion is not met), all treatments are "*functionally substitutable*". The EAG thinks that considering functionally substitutable treatments as belonging to the same class could be problematic. This approach would imply that all treatments available for a given indication would belong to the same class of treatments, thereby eliminating the need for pairwise comparisons. However, in many cases treatments indicated for the same condition do not mean that these treatments belong to the same class. Furthermore, this assumption would suggest that patients can switch from one treatment option to another "at will", which does not seem to align with clinical practice in this case. When patients receive icatibant for example, patients would stay on that treatment and would receive other options only on exceptional circumstances (e.g., as rescue therapy), as confirmed by clinical experts consulted by the EAG.[3]

To justify defining SoC as a basket of current OD treatments, in response to clarification question B4,[8] the company cited previous NICE TAs. Specifically, the company mentioned that in TA1051, in which although pairwise comparisons were initially provided, the EAG and Appraisal Committee (AC) requested the company to present results using a basket of comparators.[46] However, it is the EAG's understanding that the key issue in TA1051 was not the choice between pairwise or basket comparison analyses, but rather the exclusion of relevant comparators including extended half-life treatments and the whole class of the standard half-life treatments based on projected market share data. The company in later stages of the appraisal provided both Types of analysis (pairwise and basket comparisons), assuming equal efficacy within classes. Regarding TA1054,[47] the company claimed that the EAG did not raise major objections towards the use of the basket approach. However, the EAG disagrees with the company here. In the EAG's report of TA1054, it was highlighted that using a basket comparator for all treatments could bias clinical and CE estimates. This was a key issue in the appraisal that was in fact discussed by the AC. However, in the absence of appropriate comparative data, the AC accepted the approach, but emphasised that "*a lack of data did not imply a lack of difference between the treatments*".[48] NICE TA995 is yet another example where the relevant comparators include gonadotropin-releasing hormone (GnRH) agonists and GnRH antagonists and these are not grouped together as a basket because they are not the same Type of treatment.[49] Consequently, the EAG does not consider these previous NICE appraisals as valid precedents for using a basket of OD treatments in the current assessment.

A direct consequence of not defining SoC as a basket of current OD treatments is that, in line with the NICE reference case,[44] the economic evaluation results should be presented in a fully incremental analysis with technologies that are dominated and extendedly dominated removed from the analysis. This has major implications for this submission as shown through Section 5.2 of this report.

In case the AC for the current TA accepts the company's approach to defining the comparator technology as a basket of current OD treatments, the EAG would like to highlight the sensitivity to the model results to changes in the market shares assumed by the company. This is discussed in detail in Section 4.2.7 of this report.

4.2.5 Treatment effectiveness and extrapolation

Due to the absence of direct or indirect evidence comparing TTAR between sebetralstat and comparators, clinical inputs are based on attack characteristics and TTA. These were sourced from the KONFIDENT Phase III RCT and OLE and relevant literature.[29, 30] Where applicable, TTAR inputs were also derived from KONFIDENT and supplemented by a post-hoc statistical model estimating the relationship between TTA and TTAR.[31]

4.2.5.1 Attack-related inputs

HAE attack inputs include TTA for each OD treatment and the distribution of attack locations, with a constant cohort attack rate over time. The latter assumption is considered reasonable by the company, as OD treatments do not affect long-term attack frequency and there is limited evidence supporting changes in attack rates by age or other patient characteristics.[22] This was also supported by the clinical experts consulted by the EAG.[3] The distribution of attack severity is used in scenario analyses but not in the company's base-case.

Data show meaningful differences in average TTA across treatments, largely influenced by route of administration.[27,50] Delayed TTA is associated with poorer treatment response and longer attack duration, consistent with HAE pathophysiology and pharmacodynamics.[22, 27, 51-53]

TTA for sebetralstat is sourced from KONFIDENT OLE,[30] where a mean TTA of ~[redacted] hours was reported. While icatibant has a UK average of ~2.9 hours,[42] for IV–administered treatments, the average TTA ranges from 6–7 hours in facility-based settings,[54, 55] although the company's model applies an average of ~3.8 hours based on Christiansen et al 2024 across all IV OD treatments.[27] A summary of the HAE attack-related input parameters is provided in Table 4.2.

Table 4.2: HAE attack-related input parameters used in the economic model

Parameter definition	Mean value	Source
Duration of HAE attack (hours)	96	SMC No. (476/08)[56]
TTA sebetralstat (minutes)	[redacted]	Post-hoc analysis. Data on file[31]
TTA icatibant (minutes)	174	Longhurst et al 2018[42]
TTA ruconest (minutes)	228	Christian et al 2024[27]
TTA berinert (minutes)	228	
TTA cinryze (minutes)	228	
Attack location – neck and above (%)	13.74	KONFIDENT[29]
Attack location – abdominal (%)	40.08	
Attack location – other (%)	46.18	
Attack severity – severe (%)	16.47	KONFIDENT[29]
Attack severity – moderate (%)	41.18	
Attack severity – mild (%)	42.35	
Source: Based on Table 27 of the CS[6] CS = company submission; HAE = hereditary angioedema; SMC = Scottish Medicines Consortium; TTA = time to treatment administration		

4.2.5.2 Attack resolution

Attack resolution is modelled via TTAR, which is adjusted per treatment using a statistical function incorporating the relationship between TTA and TTAR. This relationship is estimated using a Cox proportional hazards model, based on KONFIDENT data.[29,31] The model accounts for treatment sequence, attack number, baseline severity, and attack location, with robust SEs used to adjust for within-subject clustering. The company used a FEs model with robust SEs to account for within-subject correlation. This approach was preferred over a random effects model due to the focus on estimating coefficient hazards and the negligible difference in results between the two methods.[31,57] It also simplified interpretation and reduced model complexity without compromising validity. Full model coefficients and results from the Cox regression are provided in Table 4.3.

Table 4.3: Results from the Cox regression model

Explanatory variable	Ln (HR)	95% CI	Robust SE	p-value
Treatment sequence (ref. group 6)				
6	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]

Explanatory variable	Ln (HR)	95% CI	Robust SE	p-value
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
HAE attack number (ref. group 3)				
3	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
Baseline attack severity (ref. group None or Mild)				
None or Mild	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe or Very Severe	[redacted]	[redacted]	[redacted]	[redacted]
Baseline attack location (ref. group Other)				
Other	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal	[redacted]	[redacted]	[redacted]	[redacted]
Neck and Above	[redacted]	[redacted]	[redacted]	[redacted]
Time to administration				
TTA	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 28 of the CS[6]
CI = confidence interval; CS = company submission; HAE = hereditary angioedema; HR = hazard ratio; NE = not estimated; SE = standard error; TTA = time to treatment administration

A Cox regression model based on Table 4.3 can be expressed as follows:

$$h(t \mid X) = h_0(t)\exp\left(\beta_1 X_{i,1} + \beta_2 X_{i,2} + \cdots + \beta_{12} X_{i,12}\right) \quad [eq.1]$$

where $h(t \mid X)$ is the hazard function at time t conditional on the covariates X, $h_0(t)$ is the baseline hazard function, and $\beta_1, \ldots, \beta_{12}$ are the coefficients for $X_{i,1}, \ldots, X_{i,12}$ (the categorical covariates treatment sequence, attack number, baseline attack severity, baseline attack location and the continuous covariate TTA), for individual i.

After adjusting for treatment sequence, attack number, baseline attack severity, and baseline attack location, the coefficient estimated by the Cox regression model for the relationship between TTA and TTAR is [redacted]. Note that a negative relationship between TTA and TTAR is in line with literature and clinical expert opinion.[22, 27, 50, 52, 53, 58, 59] The company further estimated the average association between TTA and TTAR as follows:

$$TTAR_{adjusted} = \phi + \exp(-\beta_{12}) \cdot (t_j - \bar{t}) + \exp(-\beta_k) \cdot X_k \quad [eq.2]$$

where ϕ is the baseline TTAR, i.e., the average TTAR, $exp(-\beta_{10})$ is the HR estimating the relationship between TTA and TTAR, t_j is the average TTA for treatment j (in hours), $\bar{t}$ is the mean cohort TTA (obtained from the KONFIDENT data which are used to inform the statistical model), $exp(-\beta_k)$ is the hazard ratio for attack location k, and X_k is the attack location covariate.

In the economic model, the HR is intended to indicate how increases in TTA reduce the hazard of reaching the TTAR endpoint (i.e., attack resolution). Therefore, to obtain the appropriate model input, the inverse HR from the Cox model is taken, [redacted]. An inverse HR of [redacted] indicates that for each unit increase in TTA, the hazard of not reaching the TTAR endpoint increases by a factor of roughly [redacted], i.e., the hazard of an attack not resolving within the period increases. The same logic applies to the attack location (or severity) HRs. Additionally, the company applied a MD to TTA, i.e., $(t_j - \bar{t})$, to centre the expected TTA of each treatment. This allows for a relative comparison for the TTA of each treatment. In the economic model, the predictive function is therefore defined as:

$$\mathrm{TTA}R_{adjusted} = \phi + \mathrm{HR}_{\mathrm{TTA}}{}^{-1} \cdot \left(\frac{t_j}{60} - \bar{t}\right) + HR_{Location}^{-1} \cdot X_k \quad [eq.3]$$

where $HR_{TTA}{}^{-1}$ is the inverse HR for TTA (i.e., [redacted]), $HR_{Location}^{-1}$ is the inverse HR for the specific attack location, and X_k is the proportion of patients experiencing an attack at location k. The company provide the following example to illustrate how the function calculates an adjusted TTAR within the economic model. Assuming an average baseline TTAR of [redacted] hours, a TTA HR of [redacted] an average TTA of [redacted], a TTA of [redacted], a HR of [redacted] for Neck and Above attacks, and that 13.74% of attacks occur in this area, we calculate an adjusted TTAR as follows:

[redacted]

A summary of the adjusted TTAR calculated for each treatment and other TTAR related input parameters can be found in Table 4.4.

Table 4.4: Time to attack resolution input parameters

Variable	Value			Reference
Baseline TTAR (hours)	[redacted]			Post-hoc analysis[31]
TTA ~ TTAR (HR)	[redacted]			
Attack location hazard (base-case)				
Neck and Above	[redacted]			Post-hoc analysis[31]
Abdominal	[redacted]			
Other	[redacted]			
Attack severity hazard (scenario)				
Severe	[redacted]			Post-hoc analysis[31]
Moderate	[redacted]			
Mild	[redacted]			
Adjusted TTAR (hours) by treatment and attack location				
	Neck and Above	Abdominal	Other	
Sebetralstat	[redacted]	[redacted]	[redacted]	Calculated by the company
Icatibant	[redacted]	[redacted]	[redacted]	

Variable	Value			Reference
Ruconest, berinert and cinryze	[redacted]	[redacted]	[redacted]	
Source: Based on Table 29 of the CS[6] CS = company submission; HR = hazard ratio; TTA = time to treatment administration; TTAR = time to attack resolution				

EAG comments: There are several methodological concerns associated to the way the company have incorporated in the economic model time to attack resolution as main clinical effectiveness input. However, it should be noted that, despite these, the whole analysis results in the estimation of two HRs (one for TTA and one for attack location – see [eq. 3]), which are included in the model as input parameters, which in practice have a minor/moderate impact on the model results. These concerns are summarised below.

The first issue is related to the source of evidence being a post-hoc analysis conducted by the company, using TTA and attack location as predictors for TTAR. In terms of evidence hierarchy, well-conducted ITCs usually rank higher than company-conducted post-hoc analyses and should be preferred for estimating relative treatment effects (i.e., differences in TTAR between different treatment options). However, the company noted difficulties in conducting ITCs due to heterogeneity of trial criteria and endpoints. The precariousness of ITCs within the context of the current HAE OD evidence landscape was also highlighted by NICE experts during Early Scientific Advice. The company's post-hoc Cox proportional hazards model is based on IPD from a single-arm trial (sebetralstat) and therefore, sits lower in the hierarchy of evidence than published ITCs, including MAICs or simulated treatment comparisons (STCs). While the Cox model offers analytic flexibility (e.g., incorporate covariates to adjust for their influence on the outcome) and uses IPD, it is retrospective (applied after trial completion, using data not collected for this purpose: the choice of model, variables, or functional forms may be influenced by observed results [i.e., data-driven modelling]), non-comparative (single arm trial: without a comparator, the model relies on assumptions [e.g., adjusting for TTA] to estimate relative effects, which may not fully account for confounding or effect modification), and not pre-specified (in the protocol or analysis plan – so its design and assumptions may have been influenced by knowledge of the outcomes and there is greater risk of selective reporting or choosing favourable results), potentially increasing the RoB. In contrast, published ITCs, particularly those using pre-specified methods and comparing interventions across placebo-controlled trials, provide adjusted comparative estimates and are generally considered more robust.

In response to clarification question B14, the EAG requested that the company incorporate results from the ITC analysis conducted by Li et al 2025 into the economic model.[8, 15] The company clarified that the ITC focused on comparing oral sebetralstat with IV rhC1-INH using time to onset of symptom relief and safety as the primary outcomes. The results of the ITC indicated no statistically significant differences between the two treatments on these measures. However, the company stated that the ITC results could not be incorporated into the economic model, as the outcomes assessed in Li et al 2025 do not correspond to the key clinical inputs used in the model to estimate CE.

Regarding the Cox regression analysis and the equation to estimate the effect on TTAR [eq. 3], the EAG considers that the Cox regression model should be re-estimated using TTA and attack location as the only covariates, and use the results of this revised Cox model to inform the TTAR adjustment formula [eq. 3] in the economic model. This approach avoids disconnect between the statistical and economic analyses: if the economic model does not include treatment sequence, number of attacks, or

severity, then these covariates should not be part of the Cox model used to generate the modelled treatment effect. This ensures that the clinical and economic components are aligned. Other concerns with this approach include the following:

- The transformation of HRs from the Cox regression model into additive effects on mean TTAR in [eq. 3] assumes a direct and linear relationship between the (logarithm of the) hazard and the mean TTAR. However, in proportional hazards models, HRs relate to the hazard function, not directly to mean time, and this conversion introduces a parametric assumption not derived from the model.
- The baseline TTAR (ϕ) is derived from the KONFIDENT cohort mean TTAR, and it is used as a base value that anchor all treatment effects to one trial population, which could reduce generalisability. Moreover, if $\bar{t}$ is the mean TTA from the same KONFIDENT cohort, and t_j represents other treatments' TTA (e.g., from external sources), [eq. 3] assumes external validity of the TTA ~ TTAR relationship.
- The inclusion of non-significant or clinically irrelevant covariates may introduce unnecessary complexity and potential noise into the Cox model, especially if they have no meaningful effect on TTAR. As show in Table 4.4, only TTA is a significant predictor for TTAR. Parsimonious models that retain only covariates with a clear prognostic or predictive effect are preferred. Retaining non-significant predictors can inflate uncertainty and bias estimated treatment effects, particularly if their estimated coefficients are unstable or inconsistent. Removing non-significant covariates not only reduces model complexity, but it may also improve the precision (narrower CIs) and goodness of fit (e.g., lower Akaike Information Criterion [AIC]). For example, attack location might be retained as covariate in the Cox model, despite being non-significant, provided that its use is relevant in [eq. 3] and supported by external evidence (e.g., with expert opinion).
- In addition, the Cox model captures the impact of OD treatments on TTAR solely through the TTA of the *first* dose. This may overestimate the benefit of sebetralstat, as the model does not account for reduced effectiveness when additional doses or rescue therapy are required. In response to clarification question B9,[8] the company acknowledged this is due to limitations in the KONFIDENT trial data. Specifically, because TTAR is censored when rescue therapy is used, the company could not accurately estimate TTAR using trial data from patients needing rescue therapy. Including rescue therapy as a covariate caused model convergence issues. To address this, the company provided a subgroup analysis excluding patients that used rescue therapy. This reduced the TTA HR (from [redacted] to [redacted]), increasing the base-case ICER by 1.01%. However, the EAG noticed that in this subgroup analysis where patients who used rescue therapy were excluded, the number of observations increased compared to the model used in the base-case, which was unexpected. Due to time constraints the EAG could not explain why this happens and, therefore, prefers not using these results in the economic model.
- A similar limitation applies to additional OD dosing. As highlighted in clarification question B12, the EAG considers it reasonable that requiring an additional dose reflects suboptimal response and longer TTAR.[8] In contrast, the company maintain that not adjusting TTAR for additional dosing or rescue therapy is a valid approach, by arguing that HAE attacks vary significantly, and the need for an additional dose does not necessarily imply treatment failure or longer TTAR. Additional dosing in the KONFIDENT trial was at patient discretion, and no data were collected on reasons for second dose use. The EAG was not convinced by this response and sought additional information from clinical experts, who indicated that an additional dose is typically given when the first dose fails to control symptoms or upon further development of angioedema, thereby in lack of treatment response at first dose.[3] This further supports the EAG's view that the

current approach based on projecting first-dose TTA differences onto TTAR, likely overestimates the benefits of oral treatment, but by how much it is unknown.

4.2.5.3 Other clinical inputs

During an HAE attack, patients may receive an additional dose of the same OD treatment or rescue therapy with an alternative.[22, 29] The proportion of attacks requiring additional dosing or rescue therapy is fixed per cycle and treatment specific. The number of such events per cycle is calculated as the product of the number of attacks and the treatment-specific proportion requiring each Type of intervention.

The model includes hospitalisation as the only AE, modelled as an annual probability dependent on whether treatment is self-administered (5.8%) or HCP-administered (12.5%).[38] Other treatment-related side effects (e.g., injection site reactions, pain during injection, nausea, headache or indigestion) are included with administration-specific risks, based on published sources.[27, 59, 60]

Mortality is applied using UK general population life tables,[39] adjusted by cycle, age, and gender. HAE-related mortality is excluded from the base-case, reflecting its rarity in diagnosed patients.

A summary of other treatment-related input parameters is provided in Table 4.5.

Table 4.5: Other treatment-related input parameters used in the economic model

Parameter	Sebetralstat	Icatibant	Ruconest	Berinert	Cinryze
Additional dosing (% per attack)	24.10[30]	12.70[42]	18.18[61]	1.11[55]	18.18*
Rescue therapy (% per attack)	8.10[30]	16.67[60]	7.32[54]	7.32*	7.32*
Injection skin reaction (% per administration)	N/A	97.22[60]	10.00[27]	24.78[59]	24.78**
Injection painful burning, stinging (% per administration)	N/A	50.90[27]	20.00[27]	12.50[27]	12.50**

Source: Based on Table 30 of the CS.[6]
* Assumption equivalent to ruconest
** Assumption equivalent to berinert
CS = company submission; N/A = not applicable

EAG comments: In response to clarification question B20, the company acknowledged an error in the model and report due to the incorrect use of the 12.7% value as the rate of additional dosing rather than rescue therapy for icatibant.[8] Following this, the model was updated to reflect that 12.7% of icatibant-treated attacks should be used for rescue therapy, replacing the previously used 16.67% from Cicardi et al 2010.[60] For estimating the rate of additional dosing, data from Aberer et al 2017 were used, given this study differentiates between attacks requiring additional doses and those requiring rescue medication.[2] A weighted average of the reported rates from LTP + OD and OD-only groups was applied to derive the final estimate of 8.91% (instead of 12.7% in the original base-case). Specifically, the company used the data reported for LTP + OD (93/973 attacks) and OD only (189/2255 attacks) patients, and applied a weighted average to calculate the expected proportion of patients requiring additional doses as follows:

$$\%\ icatibant\ treated\ attacks\ using\ additional\ doses\ = \frac{93}{973} \times \%\ on\ LTP\ and\ OD\ + \frac{189}{2255} \times \%\ on\ OD\ only$$

Note that while the updated electronic model correctly implemented changes, the clarification response reported incorrect figures (95 instead of 93 and 221 instead of 189).

The EAG noticed that Aberer et al 2017 also reported data on use of rescue therapy.[2] Given that Aberer et al 2017 distinguishes data by LTP + OD and OD-only groups, the EAG estimated the proportion of rescue medication in icatibant patients at 9.78% instead of 12.70% as following:

$$\%\ icatibant\ treated\ attacks\ using\ rescue\ therapy\ = \frac{95}{973} \times \%\ on\ LTP\ and\ OD\ + \frac{221}{2255} \times \%\ on\ OD\ only$$

Although not requested by the EAG, in clarification response B20, the company stated that the percentages of additional dosing and rescue therapy for sebetralstat were also updated based on interim data from the KONFIDENT-S OLE study. The updated input values for sebetralstat were changed from 24.10% to 22.25% (85/382) for additional dosing and from 8.10% to 5.25% (20/382) for rescue therapy.[8]

The current modelling approach treats additional doses and rescue therapy as independent events; potentially overestimating rescue therapy use and related costs. That is because additional dosing would be expected to reduce the need for rescue therapy. The company in clarification response B10 justified this approach mentioning that it was necessary due to limited data on their conditional relationship.[8]

Additionally, inputs from the company, EAG clinical experts, and the KONFIDENT trial data (clarification question B12),[8] indicate that the decisions to administer an OD treatment during an attack lie with patients. Given the ease of administration, the EAG considers it reasonable to expect higher rates of additional dosing with oral treatments compared to SC/IV OD therapies, which may not be appropriately captured in a trial setting. This expectation was also supported by the EAG clinical experts.[3] However, this assumption remains uncertain: it cannot be ruled out that, conversely, rates of additional dosing with oral OD treatments may be lower (over time) in the real world, especially once patients become accustomed to the new treatment, compared to trial settings.

In the absence of data on the use or rescue therapy conditional on additional dosing and on the frequency of additional dosing with oral OD treatments (except the trial data), the EAG explored the impact of these uncertainties through different scenario analyses.

4.2.6 Health-related quality of life

Since HRQoL data were not collected in the KONFIDENT trial, utility values were sourced from literature and a commissioned study.[29] For details on the HRQoL SLR, we refer to Appendix F of the CS.[10]

The company identified Aygoren-Pursun et al 2016 as the only study using European Quality of Life-5 Dimensions (EQ-5D) to estimate the burden of acute HAE attacks, applying UK population utility weights.[62] However, this study used an indirect, non-validated method for EQ-5D estimation and did not distinguish utility by attack location, limiting its relevance in the current appraisal.

The UK-based study by Lo et al 2022 assessed HRQoL in HAE using the time trade-off (TTO) method with vignette-based health states.[19] While EQ-5D is the preferred tool for generating utility

values in HTAs in the UK, the company highlighted that its limited sensitivity to short-term health fluctuations makes it less suitable for capturing the burden of acute HAE attacks. Vignette-based TTO studies, where health states are valued by patients or the public, might be acceptable alternatives in such contexts.[63]

The Lo et al 2022 vignette study aimed to capture disutility for patients and caregivers across attack locations. It involved interviews with 15 patients, five caregivers, and one clinician to develop health state descriptions. These were then valued by 100 members of the general public through TTO tasks.[19]

HAE patients also face a chronic burden due to the unpredictability of the condition and treatment administration challenges, especially with injectable therapies. These are seen as difficult to use, inconvenient in public, and are often associated with side effects and delayed treatment initiation due to portability issues.[20] However, quantifying these process-related disutilities is challenging.

To estimate the process disutilities of oral versus injectable OD treatments, the company commissioned a Discrete Choice Experiment (DCE).[20] That is because, firstly, collecting such process-related HRQoL data through a randomised trial would present feasibility challenges due to the difficulty of blinding participants to injectable versus oral OD treatments. Secondly, there is currently no other oral OD treatment on the market that would allow for the collection of observational data. Thirdly, the company considered the EQ-5D tool unlikely to be sufficiently sensitive to capture differences in utility specifically associated with modes of treatment administration.

The DCE study elicited preferences from both HAE patients and the general public. Preferences were analysed using logit models to estimate utility decrements for administration route and side effects.[20] The DCE method was selected for its flexibility across stakeholder groups and its ability to generate precise, independent utility estimates within an experimental framework. Further details are available in the CS, Appendix M.[10]

4.2.6.1 Health state utility values

The base-case model uses Lo et al 2022 to inform disutility values for acute HAE attacks by location.[19] The attack-free utility was 0.783, while utility values for attacks in the Neck and Above, Abdominal, and Other locations were 0.305, 0.345, and 0.582 respectively, yielding annual disutilities of -0.478, -0.438, and -0.201 (see Table 4.6). These disutilities were scaled by attack duration and cycle length and further adjusted by treatment-specific TTAR values. For attacks in the Neck and Above, disutility was calculated as the average decrement from facial and laryngeal attack states, as reported in Lo et al 2022. A full summary of disutilities by location is provided in Table 4.6.

UK general population health state utility values were applied for baseline health states across all treatments. These were adjusted over time using age- and gender-specific norms based on Ara and Brazier 2010 in the original CS.[64]

In addition, treatment-related utility decrements derived from the commissioned DCE study,[20] were used to express patient preferences related to route of treatment administration and side effects. DCE values used in the base-case were sampled from HAE patients (n=285) and rescaled by duration. The model does not apply the utility difference between SC and oral administration in the base-case, as the result was not statistically significant (95% CI included 0), in line with expert advice.[20] Further methodological details are in Appendix M of the CS.[10]

Table 4.6: Utilities used in the base-case analysis

State/event	Mean value (SE)	95% CI
Type of treatment (duration-rescaled)		
Oral tablet	[redacted]	[redacted]
Self-administered injection under skin	[redacted]	[redacted]
Self-administered infusion into the vein	[redacted]	[redacted]
HCP-administered infusion into the vein	[redacted]	[redacted]
Side effects (duration-rescaled)		
None	[redacted]	[redacted]
Skin reaction to the injection	[redacted]	[redacted]
Painful burning or stinging sensation when medication is administered	[redacted]	[redacted]
Headaches, diarrhoea, nausea and/or indigestion	[redacted]	[redacted]
Attack disutility (prior to duration adjustment in model)		
Neck and Above	-0.478 (0.049)	N/A
Abdominal	-0.438 (0.046)	N/A
Other	-0.201 (0.038)	N/A
Source: Based on Table 31 of the CS[6] CI = confidence interval; CS = company submission; HCP = health care practitioner; N/A = not applicable; SE = standard error		

EAG comments: There are several concerns related to the utility estimates incorporated by the company into the economic model. However, it is important to note that, despite these limitations, changes in the QoL inputs appear to have only a minor to moderate impact on the overall model results. A summary of the key concerns is provided below:

In the original base-case, the company used general population utilities derived from Ara and Brazier et al 2010.[64] To align with the NICE reference case, these were replaced by those derived from Hernandez-Alava et al 2022,[65] in response to clarification question B24.[8]

The EAG considers the decision not to include the EQ-5D in the clinical studies as a missed opportunity to assess the validity of this instrument on HAE.

The company did not include preference utility between oral and SC treatments in the base-case referring to the non-significant coefficient in the regression results from the DCE analysis. The rationale for the exclusion was twofold: first, the company referred to NICE TA973 (atogepant for preventing migraine), where the EAG removed a disutility for monthly SC injection compared to oral medicine due to non-significance (clarification question B28).[8] Second, they argued that HRQoL differences between SC and oral OD treatments are already captured through differences in HRQoL attributed to injection-related side effects (e.g. injection site reactions, pain, or stinging sensations during treatment administration). In their response the company acknowledged that the non-significant outcome contradicted both qualitative patient feedback, which indicated a preference for oral administration, and clinical expert expectations, as SC treatments were frequently associated with HRQoL burden during and between attacks.[8]

The EAG noted that the DCE analyses were conducted separately using two distinct samples: 285 patients (UK = 76, US = 209) and 599 members of the general population (UK = 300, US = 299), with results reported in Table 108 of Appendix M in the CS.[10] These results show that the utility difference between for SC versus oral treatment was [redacted] when using the patient sample and [redacted] when using the general population sample. When using the general population sample, the coefficients estimating the (dis)utility values for mode of administration were reversed in magnitude for the self-administration of infusion into the vein versus the HCP-administration. The estimated (dis)utilities for injection-related side effects, were slightly higher in the general population sample compared to the patient-based estimates. The EAG recognises that oral administration may offer HRQoL advantages over SC administration that may not be captured in disutility due to injection-related side effects. Therefore, a scenario analysis was included using the utility values estimated from the general population sample.

At the request of the EAG (questions B29 of the clarification letter),[8] the company tried to validate the utility values obtained through the DCE study for mode of treatment administration. In their response, the company mentioned that there was no study found to compare self-administered versus HCP-administered IV treatment.

Regarding the home-based administration compared to the hospital-based administration, the company described studies showing higher satisfaction, better adherence, and small utility gains for self-administered SC injections at home compared to SC/IV administrations at hospital settings. A TTO study from the general population found SC injections at home were associated with a small utility gain compared to SC injections at hospital of 0.011 (clarification question B29).[8]

Few studies have indicated that IV administration is less preferred, with greater utility decrements compared to SC or oral routes. In HAE, NICE TA606 used TTO data to show a utility gain of 0.024 when switching from IV to SC administration, based on the difference between two utility estimates: oral treatment versus SC injection (0.0151) and oral versus IV infusion (0.0304).[8]

Studies in HAE show that self-administered IV infusions at home are feasible and preferred over hospital-based treatment, improving outcomes and HRQoL. These supported DCE findings that HCP-administered IV has greater utility decrement, reinforcing that an oral alternative may offer further HRQoL benefits.

In general, the EAG noted that these studies showed a lower range of utilities associated with the mode of administration compared to the range of utility values in the current submission.

At the request of the EAG (questions B30 of the clarification letter),[8] the company tried to validate the utility values obtained through the DCE study for the treatment-related side effects of SC/IV OD treatments. The company responded that utility values derived from the DCE study are broadly consistent with published literature in other therapeutic areas. For injection site reactions published utility values ranged from 0.011 for daily injections to 0.02 for monthly injections. For headaches, diarrhoea, nausea and/or indigestion, the company acknowledged that utility decrements in other studies were generally lower (0.03-0.04) than those in the commissioned DCE ([redacted]), likely because values in other studies assess individual symptoms, while the DCE reflects the combined impact of multiple side effects. The company did not identify any study reporting a utility decrement for burning or stinging caused by medication.

The DCE study elicited preferences from both HAE patients and the general public. While the general population samples from the UK and US were demographically representative, the patient sample

included a higher-than-expected proportion of females (77%).[20] The EAG is uncertain about the impact of this on the HRQoL estimates. However, general caution is warranted, as the DCE study has not undergone peer review.

4.2.6.2 Disutility due to adverse effects

As no consistent Grade 3 or higher treatment-related adverse events (TRAEs) were observed across OD treatments, utility decrements associated with AEs were not incorporated into the economic model.

4.2.7 Resources and costs

Since the CEA was conducted from the UK NHS and PSS perspective, only direct costs were considered in the base-case analysis. These comprised the drug acquisition costs of each OD treatment. Health state costs were not included in the economic model, whereas costs of certain AEs (that is, the risk of hospitalisation) were included. Sections 4.2.7.2 to 4.2.7.4 describe how resource use and costs were determined for the drug acquisition costs and the AE costs and explain the company's rationale for excluding health state costs.

4.2.7.1 Resource use and costs data identified in the review

As explained in Section 4.1.3 of this report, the company SLRs included 107 studies in the review, 30 were CE studies, and 77 cost and HCRU studies.

4.2.7.2 Treatment and acquisition costs

Drug acquisition costs of each OD treatment were calculated as a cost per attack. These costs comprised the initial OD drug administration cost (which is the first dose of OD treatment administered at the start of an attack), additional dosing costs, and rescue therapy costs. The cost of OD treatment per attack was dependent upon the dose required per attack, and the cost calculations accounted for drug wastage.

In the cost calculations, assumptions were made regarding the market share of the comparators included in the treatment basket (see Table 4.7). This was sourced from a Hospital Pharmacy Audit for OD HAE treatments conducted by the company.[66] The same distribution was also applied for the treatments used as rescue therapy, except that sebetralstat was assumed to never be used as rescue therapy. Finally, it was assumed that sebetralstat was always self-administered, while the rate of self-administration for the comparators ranged from 61% (ruconest, berinert, and cinryze) to 95.8% (icatibant).

Table 4.7: Treatments comprising SoC (comparator) and treatments used as rescue therapy

	Value	Source
Market share of comparators comprising SoC		
Icatibant	[redacted]	Hospital Pharmacy Audit for OD HAE treatments[66]
Ruconest	[redacted]	
Berinert	[redacted]	
Cinryze	[redacted]	
Treatments used as rescue therapy		
Sebetralstat	0.00%	Assumption
Icatibant	[redacted]	Assumption (equivalent to baseline market share)
Ruconest	[redacted]	
Berinert	[redacted]	
Cinryze	[redacted]	
Treatment self-administration (%)		
Sebetralstat	100%	Assumption
Icatibant	95.80%	Longhurst et al 2018[42]
Ruconest	61.00%	Yong et al 2023[41]
Berinert	61.00%	
Cinryze	61.00%	
Source: Based on Table 32 of the CS[6] CS = company submission; HAE = hereditary angioedema; OD = on demand; SoC = standard of care		

The cost of OD treatment per attack depended on the dose required per attack for each OD treatment, the treatment pack size, and the drug acquisition cost per pack (see Table 4.8). For treatments that require weight-based dosing, the dosage was calculated as the treatment's dose strength multiplied by the cohort weight, which was age-and gender-dependent derived from the UK general population weight distribution,[40] and then divided by the treatment's pack size. In addition, for weight-based treatments, the base-case model assumed drug wastage. Assuming no drug wastage in the model can be applied as a scenario. Since patients use the same OD treatment for any additional doses during an attack, the drug costs for additional dosing were applied in the same way as the initial administration cost. However, the per-cycle cost of additional dosing was conditional on the number of attacks requiring an additional dose per cycle.

The cost of rescue therapy was a weighted average cost, calculated using the costs of each treatment used for rescue therapy, multiplied by their expected frequency of use. Over the modelled time horizon, the average cost of rescue therapy was £1,403 (see Table 4.8). For weight-based treatments, the cost of rescue therapy can vary over the time horizon because the average cohort weight is age-dependent. Administration costs were calculated per HAE attack and applied to the proportion of patients requiring HCP-assisted administration. A full hour cost of HCP time was applied for both SC and IV treatments. In the company's base-case, the cost per working hour of an HCP was assumed equivalent to a Band 6 nurse, sourced from the Personal Social Services Research Unit (PSSRU).[67] Oral treatments were assumed to not incur HCP-assisted administration costs. The cost of HCP-assisted administration was also added to the rescue therapy costs and estimated at £11.76.

Table 4.8: Drug acquisition costs, administration costs, rescue therapy costs, and AE costs

	Value	Source
Treatment pack size and dosing assumptions		
Sebetralstat	1800 mg (pack size) / 300 mg (dosing)	Assumption
Icatibant	30 mg (pack size) / 30 mg (dosing)	BNF[68]
Ruconest	2100 IU (pack size) / 50 IU/kg (dosing)	
Berinert	500 IU (pack size) / 20 IU/kg (dosing)	
Cinryze	500 IU (pack size) / 1000 IU (dosing)	
Treatment acquisition cost (per pack)		
Sebetralstat	[redacted]	Assumption (for an updated price after clarification see Section 5.1.3)
Icatibant	£837	BNF[68]
Ruconest	£750	
Berinert	£670	
Cinryze	£668	
Rescue therapy costs		
Drug costs	£1,403	Assumption (average of lifetime distribution)
HCP administration costs	£11.76	Assumption (weighted average of assisted administration costs)
Total	£1,414.76	
Assisted administration costs		
Oral	£0.00	Assumption
Subcutaneous	£57.00	PSSRU Unit Costs[67]
Intravenous	£57.00	
Adverse event costs		
Hospitalisation	£582.00	NICE TA606[38]

Source: Based on Table 32 of the CS[6]
AEs = adverse events; BNF = British National Formulary; CS = company submission; HCP = health care practitioner; IU = international units; mg = milligram; NICE = National Institute for Health and Care Excellence; PSSRU = Personal Social Services Research Unit; TA = Technology Appraisal

EAG comments: There are several concerns related to some of the input parameters used to estimate resource use and treatment costs. However, it should be noted that while some of these are particularly relevant when comparing the intervention against SoC as a basket of treatments, they become less relevant in the context of pairwise comparisons, which the EAG considers more appropriate for the base-case analysis. The main EAG's concerns are summarised below.

The model results are highly sensitive to changes in the market shares assumed by the company when the comparator is defined as a basket of treatments. The larger the proportion of patients using IV

options, as opposed to SC options, the more cost-effective sebetralstat becomes. Increasing the proportion of patients using IV options in the comparator, quickly results in sebetralstat becoming the dominant strategy. Market shares are derived from a study commissioned by the company, and they are not completely in line with the values reported by clinical experts consulted by EAG. Therefore, the EAG is uncertain whether the current values used for the market share are representative of UK clinical practice. A larger share for the SC option icatibant would be expected according to the input from the EAG clinical experts estimating that about 75%-85% of patients use icatibant treatment, which was used in the EAG scenario analyses that considered SoC as a basket of treatments.[3]

This uncertainty regarding market shares is combined with that associated to the proportion of patients requiring additional dosing and rescue therapy, as discussed in Section 4.2.5.3 of this report. Taken together, these factors make the model results, under the company's assumptions of a comparator defined as a basket of treatments, extremely sensitive, where small changes in these parameters could result in sebetralstat dominating SoC or in an ICER well-above the common CE thresholds used by NICE for decision making. Examples of this can be seen in Section 5.2.2 of this report where the EAG presents the results of the exploratory analyses conducted using the company's base-case assumptions.

The company assumed that sebetralstat was never used as rescue therapy. However, rescue therapy is defined, according to the company, as the administration of an alternative OD treatment. Based on this, the EAG wonders whether sebetralstat could be used as rescue therapy for those patients not having sebetralstat as main treatment. A scenario assuming 5% usage of sebetralstat as rescue therapy was explored by the EAG in Section 5.2.2.

Administration costs were calculated per HAE attack and applied to the proportion of patients requiring HCP-assisted administration (for first doses, additional doses, and rescue medication). A full hour cost of HCP time was applied for both SC and IV treatments, while oral treatments were assumed to not incur HCP-assisted administration costs. In response to clarification question B36,[8] the company stated that this assumption was applied in the absence of evidence. The EAG considers however that SC administration probably requires substantially less time from a HCP than IV administration. This expectation is supported by clinical experts consulted by the EAG, all of whom agreed that SC injections are easier to administer and require less preparation time.[3] For this reason, the EAG assumed SC administration would take about 20 minutes to administer in the EAG base-case, while the impact of alternative administration times for both SC and IV was explored in the scenario analyses.

Finally, to account for drug wastage, the company applied a ceiling function to the weight-based dose, rounding the total required dose up to the nearest 0.2-vial increment. In response to clarification question B34, the company provided an example to illustrate the calculations: "*To illustrate, Ruconest requires a dosage of 50 IU/kg, up to a maximum dosage of 4200 IU. The standard pack size of Ruconest is 2100 IU. Assuming a patient weight of 77.86 kg, the expected dose is calculated as (77.86×50)/2100≈1390 units. The ceiling function rounds the dose to the nearest multiple of 0.2. Using the same Ruconest example, the expected dose for Ruconest is hence rounded to 1500 IU*".[8] However, based on the model calculations, the EAG believes that the company's explanation may not be correct. Using the ruconest example, a patient weight of 77.86 kg corresponds to a dose of 77.86*50 = 3,983 IUs (not 1,390). Given the vial size of 2,100 IU, this equates to 1.85 vials. Rounding up to the nearest multiple of 0.2 results in 2.0 vials, leading to a total cost of 2 * £750 = £1,500 (not 1,500 IU as per company's response above). This approach assumes that partial vials can be used in 20% increments. For example, for the lowest patient weight in the model (59.45 kg), the

required dose is approximately 1.41 vials, which the model rounds to 1.6 vials, rather than two full vials. While rounding to 0.2-vial increments reduces estimated wastage as compared to a full-vial wastage approach, the EAG questions the clinical plausibility of this assumption as the company has not provided a clear justification in response to question B34.[8] In the absence of evidence confirming that 0.2-vial dosing is feasible and standard practice, the EAG explored alternative scenarios no wastage and full vial wastage in Section 5.2.2 of this report.

4.2.7.3 Health state costs

Health state costs were not included in the economic model, as OD treatments do not influence the frequency of routine HCRU or reduce health state costs associated with HAE. There are no known differences in routine costs between OD HAE treatments, and, therefore, no direct costs were associated with time spent in any health state within the model.

4.2.7.4 Adverse event costs

No consistent Grade 3 or higher TRAEs were identified across OD treatments. As such, these events were not costed in the economic model. All other treatment side effects were assumed to spontaneously resolve without incurring additional costs to the NHS.

However, risk of hospitalisation was included as an AE, based on the assumption that patients are at risk of being hospitalised whenever an attack occurs. In response to clarification question B8,[6, 8, 10] the company explained that this typically only involves observation at an Accident & Emergency unit for a period of up to 24 hours, with approximately 5-10% of patients having an Accident & Emergency visit per year.

The risk varied depending on whether treatment was self-administered or administered by an HCP: HCP-assisted administration was assumed to have a greater delay in treatment administration and thus to carry a higher risk of hospitalisation due to delayed treatment, compared to self-administration. Consequently, the risk of hospitalisation following HCP administration was estimated at 12.5% per year, versus 5.8% per year for self-administration. From Table 30 of the CS,[6] it seems that these percentages were based on NICE TA606 on lanadelumab.[38] From the electronic model, it appeared that these percentages were taken from Mendivil et al 2023,[43] and Longhurst et al 2018,[42] respectively.

As shown in Table 4.8, the cost of hospitalisation was set at £582. Based on these inputs, the discounted costs of hospitalisation over the model's time horizon were calculated at £647 for sebetralstat, compared to £811 for SoC, as reported in the company's model.

EAG comments: The EAG considers that there is some uncertainty surrounding the risk of hospitalisation following either HCP administration (12.5% per year) or self-administration (5.8% per year). One reason for this is that these percentages were derived from studies in the literature with relatively small UK sample sizes - 24 patients in the study by Mendivil et al 2023,[43] and 52 patients in the study by Longhurst et al 2018.[42] The company varied these percentages in their one-way sensitivity analyses. These parameters appeared to have a relatively modest impact on the CE results: they were not among the most sensitive parameters in the tornado diagram presented in Figure 17 of the CS.[6]

Furthermore, the risk of hospitalisation could depend on the need for additional dosing. The experts consulted by the EAG suggested that the need for an additional dose may signal a more severe attack, increasing thus the risk of hospitalisation.[3] This means that hospitalisation costs could be higher for

treatments requiring a higher frequency of additional dosing. As noted in Table 30 of the CS,[6] sebetralstat was associated with a greater proportion of patients needing additional doses when an attack occurs compared to the comparators, potentially implying a higher risk of hospitalisation. This potential relationship is currently not captured in the company's economic model. The EAG feels however that this probably has a minor effect on the overall outcomes, given that the risk of hospitalisation itself appears to have a modest impact on the CE results, as already mentioned above.

5. Cost-effectiveness results

5.1 Company's CE results

5.1.1 Company's base-case

In Section 3.9 of the CS, the company presented their discounted CE results using the list price for sebetralstat 300 mg compared to SoC.[6] Table 5.1 results indicated that sebetralstat was more costly and more effective than SoC. The ICER was £[redacted] per QALY gained, which is above the common CE thresholds used by NICE for decision-making.

Table 5.1: Company base-case deterministic CE results (sebetralstat 300 mg versus SoC, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Sebetralstat	[redacted]	22.01	18.35	-	-	-	-
SoC	556,122	22.01	18.24	[redacted]	0.00	0.1109	[redacted]

Source: Based on Table 35 of the CS[6]
CE = cost effectiveness; CS = company submission; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYG = life years gained; mg = milligram; QALY = quality-adjusted life year; SoC = standard of care

Disaggregated discounted costs and QALYs are shown in Table 5.2 and 5.3, respectively. Overall, based on the company's base-case results, where the comparator is SoC, the new technology is modelled to affect QALYs by increasing total QALYs by reducing TTA (and thus TTAR) and avoiding TRAEs. Also, the technology is modelled to affect costs by reducing costs in all categories except those associated with additional dosing.

Table 5.2: Disaggregated cost results (sebetralstat 300 mg versus SoC, discounted)

	Sebetralstat (£)	SoC (£)	Increment (£)
First dose costs	[redacted]	[redacted]	[redacted]
Additional dosing costs	[redacted]	[redacted]	[redacted]
Rescue therapy costs	[redacted]	[redacted]	[redacted]
Total drug costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Rescue administration costs	[redacted]	[redacted]	[redacted]
Total administration costs	[redacted]	[redacted]	[redacted]
Hospitalisation costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Source: Based on the economic model[69]
mg = milligram; SoC = standard of care

Table 5.3: Disaggregated QALY results (sebetralstat 300 mg versus SoC, discounted)

Total disutility by location	Sebetralstat	SoC	Increment
Neck & Above disutility	-0.0382	-0.0458	0.0076
Abdomen disutility	-0.1047	-0.1250	0.0203

Total disutility by location	Sebetralstat	SoC	Increment
Other disutility	-0.0538	-0.0645	0.0107
Total disutility by treatment-related side effects	**-0.1967**	**-0.2352**	**0.0385**
Injection skin reaction	0.0000	-0.0167	0.0167
Injection painful burning, stinging	0.0000	-0.0129	0.0129
Total TRAEs disutility	**0.0000**	**-0.0296**	**0.0296**
Total disutility for IV treatments (self-/HCP- administered)	**0.0000**	**-0.0428**	**0.0428**
Total QALYs	**18.3465**	**18.2357**	**0.1109**

Source: Based on the economic model[69]
HCP = health care practitioner; IV = intravenous; mg = milligram; QALY = quality-adjusted life-year; SoC = standard of care; TRAE = treatment-related adverse event

EAG comment: As explained in Section 4.2.4, the EAG considers that a fully incremental analysis applies in this situation. See Section 5.2.2 for the impact on CE results.

5.1.2 Company's sensitivity and scenario analyses

5.1.2.1 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) where all relevant input parameters were sampled simultaneously from their corresponding probability distributions over 3,000 iterations. The input parameters and the probability distributions used in the PSA can be found in the "Parameters" sheet of the economic model. The average PSA results when sebetralstat is compared to SoC are presented in Table 5.4 and are overall in line with the deterministic ones shown in Table 5.1.

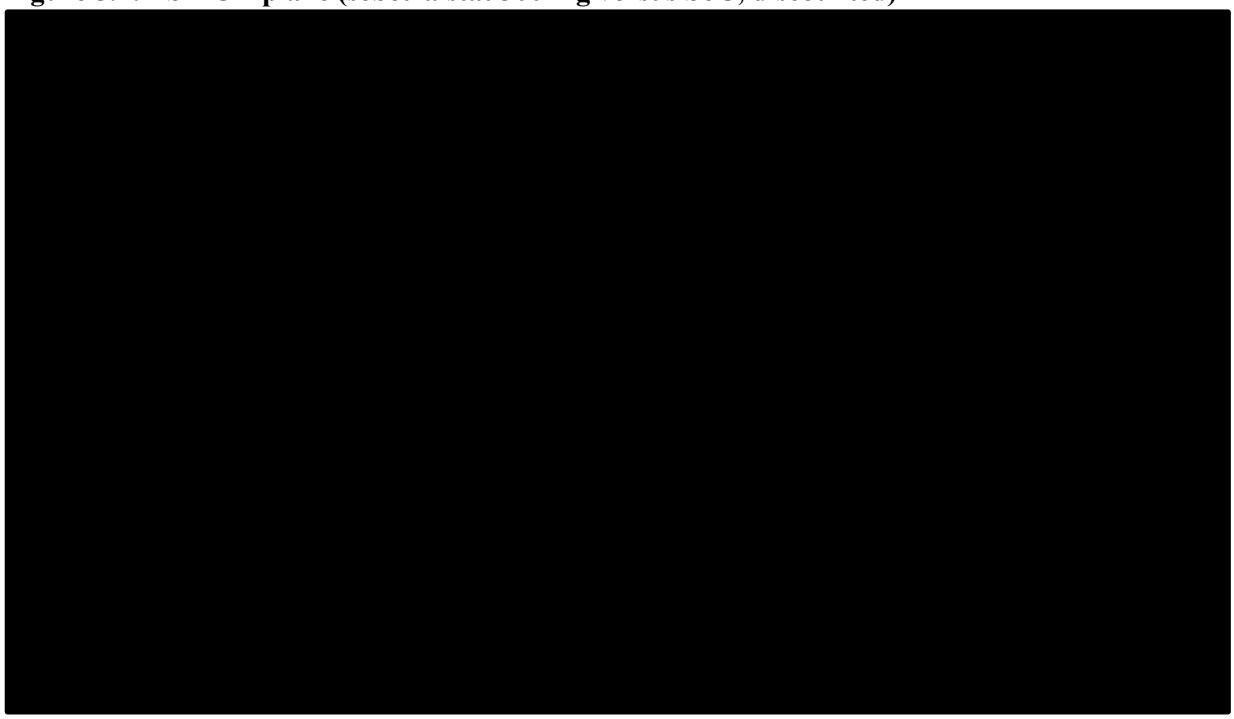
Table 5.4: Company base-case probabilistic CE results (sebetralstat 300 mg versus SoC, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Sebetralstat	[redacted]	NR	18.34	-	-	-	-
SoC	555,692	NR	18.23	[redacted]	NR	0.1109	[redacted]

Source: Based on the economic model[69]
CE = cost effectiveness; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYG = life years gained; mg = milligram; NR = not reported; QALY = quality-adjusted life year; SoC = standard of care

The company also plotted the outcomes from the PSA on a CE-plane (Figure 5.1). All outcomes reported positive incremental QALYs for sebetralstat compared to SoC. Cost outcomes were approximately equally spread across North-East and South-East quadrants. A cost-effectiveness acceptability curve (CEAC) was also calculated (Figure 5.2). The CEAC plot indicates that at the common thresholds of £20,000 and £30,000 per QALY gained, the estimated probability that sebetralstat is a cost-effective alternative to SoC was [redacted]% and [redacted]%, respectively.

Figure 5.1: PSA CE-plane (sebetralstat 300 mg versus SoC, discounted)



Source: Based on Figure 15 of the CS[6]
CE = cost effectiveness; CS = company submission; mg = milligram; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; SoC = standard of care; WTP = willingness to pay

Figure 5.2: PSA CEAC (sebetralstat 300 mg versus SoC, discounted)

Source: Based on Figure 16 of the CS[6]
CS = company submission; CEAC = cost-effectiveness acceptability curve; mg = milligram; PSA = probabilistic sensitivity analysis; SoC = standard of care

EAG comment: As discussed in Section 5.1.1, in a fully incremental analysis both IV options, ruconest and berinert, are dominated by the SC option icatibant. The latter is thus the only relevant

comparator. The PSA results comparing sebetralstat against icatibant only are in line with the deterministic results shown in Table 5.4. All PSA outcomes were in the North-East quadrant of the CE-plane, well above the common thresholds used by NICE for decision making (figure not shown). The CEAC plot indicates that for all the thresholds included in the economic model, the estimated probability that sebetralstat is a cost-effective alternative to SoC was [redacted]% (figure not shown).

5.1.2.2 Deterministic sensitivity analysis

The company also conducted a deterministic sensitivity analysis (DSA) where all input parameters were varied using a lower and upper bound value of the mean ± SE. A tornado diagram for the incremental net money benefit (INMB) at a threshold of £30,000/QALY is presented in Figure 5.3. In general, the INMB was most sensitive to input parameters related to the use of additional dosages and rescue therapy. At the base-case settings the INMB was negative, these parameters have the potential of resulting in positive INMB and thus changing decision making, but they can also make the INMB very negative.

Figure 5.3: DSA tornado diagram for INMB (sebetralstat 300 mg versus SoC, discounted)

[redacted]

Source: Based on the economic model[69]
DSA = deterministic sensitivity analysis; HSUV = health state utility value; INMB = incremental net monetary benefit; mg = milligram; SoC = standard of care; TTA = time to treatment administration; TTAR = time to attack resolution

EAG comment: The tornado diagram for the INMB at a threshold of £30,000/QALY, comparing sebetralstat against icatibant only, results in large negative INMB values, which are never positive (figure not shown).

5.1.2.3 Scenario analysis

The company presented the results of nine scenario analyses to assess the robustness of the model against alternative inputs and assumptions. In these scenarios, different assumptions were made regarding the definition of the comparator (pairwise comparisons instead of basket SoC), sebetralstat

TTA, the proportion of sebetralstat patients requiring an additional dose, the proportion of females in the population, baseline age and caregiver disutility, and using severity of attack instead of location for HRQoL impact. The results of these scenario analyses are shown in Table 5.5.

EAG comments: The scenarios with the largest impact on the model results were those where the comparator is not defined as a basket SoC: sebetralstat dominates the IV comparator options, but results in an extremely high ICER when compared to icatibant (SC). The model was also sensitive to changes in the proportion of patients requiring sebetralstat additional dose and the exclusion of caregiver disutilities. Sebetralstat is also dominant compared to SoC when the proportion of females in the patient population is approximately halved. The EAG is unclear whether this should be expected or not and more detailed explanation from the company and/or clinical experts would be required.

The EAG repeated scenarios 2-6 in Table 5.5 assuming icatibant as the only relevant comparator, the ICERs obtained were [redacted] per QALY gained, respectively. This highlights again, that, according to the EAG, the uncertainties present in the current version of the model are relevant for decision making only when the comparator SoC is defined as a basket of comparators (and this approach is not preferred by the EAG). In a fully incremental analysis, the remaining uncertainties basically have no impact on decision making.

Table 5.5: Company scenario analysis results (sebetralstat 300 mg versus SoC, discounted)

Scenario number	Scenario description	Base-case assumption	Incr. costs (£)	Incr. QALYs	ICER
0. Base-case	N/A	N/A	[redacted]	0.11	[redacted]
1. Pairwise comparisons	Comparator is icatibant	Comparator is SoC	[redacted]	0.08	[redacted]
	Comparator is ruconest		[redacted]	0.15	[redacted]
	Comparator is berinert		[redacted]	0.15	[redacted]
	Comparator is cinryze		[redacted]	0.15	[redacted]
2. Sebetralstat TTA	9 minutes	56 minutes	[redacted]	0.12	[redacted]
3. Sebetralstat additional dose (%)	12.7	24.1	[redacted]	0.11	[redacted]
4. Female (%)	33.3	60	[redacted]	0.11	[redacted]
5. Baseline age and caregiver disutility	12 years Caregiver disutility included (up to 18 years)	37.7 years Caregiver disutility excluded	[redacted]	0.25	[redacted]
6. Indicator for HRQoL impact of acute attack	Severity of the attack	Location of the attack	[redacted]	0.10	[redacted]

Source: Based on Table 37 of the CS[6]

CS = company submission; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; Incr. = incremental; mg = milligram; QALY = quality-adjusted life year; N/A = not applicable; SoC = standard of care; TTA = time to treatment administration

5.1.3 Updated company's CE results

Together with the response to the EAG's clarification questions, the company presented updated base-case results reflecting the following model changes:

- A new Patient Access Scheme (PAS) price for sebetralstat, which changed from £[redacted] per pill in the original CS to £[redacted] now.
- The proportion of icatibant patients requiring additional dosing was based on an erroneous interpretation of data from Longhurst et al 2018.[42]. The original CS inputted an additional dosing value of 12.7%. However, this has now been amended to a value 8.91%, sourced from Aberer et al 2017.[2]
- Likewise, the proportion of icatibant patients using rescue therapy were corrected from 16.67% to 12.7%.
- Market shares were updated to include a 1% share of cinryze. The updated market shares are now the following: [redacted]% icatibant; [redacted]% ruconest; [redacted]% berinert: [redacted]% cinryze.
- The proportion of patients using sebetralstat additional dosing was updated based on latest KONFIDENT-S OLE data cut. It was changed from 24.1% in the original CS to 22.25% now.
- The proportion of sebetralstat patients using rescue therapy was also updated based on latest KONFIDENT-S OLE data cut. It was changed from 8.1% in the original CS to 5.24% now.
- General population utilities sourced from Hernández-Alava et al 2022,[65] in line with the NICE reference case.[44]

The updated results after addressing these changes are presented in Table 5.6, showing the cumulative impact of the step-by-step changes made by the company.

Table 5.6: Updated company base-case deterministic CE results (sebetralstat 300 mg versus SoC, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Company's original base case (pre-clarification)							
Sebetralstat	[redacted]	22.01	18.35	-	-	-	-
SoC	556,122	22.01	18.24	[redacted]	0.00	0.1109	[redacted]
Step 1: updated sebetralstat PAS price (from £[redacted] to £[redacted] per pill)							
Sebetralstat	[redacted]	22.01	18.35	-	-	-	-
SoC	556,122	22.01	18.24	[redacted]	0.00	0.1112	[redacted]
Step 2: Change 1 + icatibant updated % of additional dosing (from 12.7% to 8.91%)							
Sebetralstat	[redacted]	22.01	18.35	-	-	-	-
SoC	550,686	22.01	18.24	[redacted]	0.00	0.1112	[redacted]
Step 3: Changes 1, 2 + icatibant updated % of rescue therapy (from 16.67% to 12.7%)							
Sebetralstat	[redacted]	22.01	18.35	-	-	-	-
SoC	540,768	22.01	18.24	[redacted]	0.00	0.1112	[redacted]
Step 4: Changes 1–3 + market shares updated to include 1% of cinryze							
Sebetralstat	[redacted]	22.01	18.35	-	-	-	-
SoC	540,881	22.01	18.24	[redacted]	0.00	0.1112	[redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Step 5: Changes 1–4 + sebetralstat updated % of additional dosing (from 24.10% to 22.25%)							
Sebetralstat	[redacted]	22.01	18.35	-	-	-	-
SoC	540,881	22.01	18.24	[redacted]	0.00	0.1112	[redacted]
Step 6: Changes 1–5 + sebetralstat updated % of rescue therapy (from 8.1% to 5.24%)							
Sebetralstat	[redacted]	22.01	18.35	-	-	-	-
SoC	540,881	22.01	18.24	[redacted]	0.00	0.1112	[redacted]
Step 7: Changes 1–6 + general population utilities Hernández-Alava et al 2022[65] (company's updated base case post-clarification)							
Sebetralstat	[redacted]	22.01	18.49	-	-	-	-
SoC	540,881	22.01	18.38	[redacted]	0.00	0.1112	[redacted]

Source: Based on the economic model after clarification[4]
CE = cost effectiveness; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYG = life years gained; mg = milligram; PAS = Patient Access Scheme; QALY = quality-adjusted life year; SoC = standard of care

EAG comment: The company's base-case results have changed significantly, since now sebetralstat dominates SoC. This is mostly caused by the updated proportions of sebetralstat and icatibant patients needing an additional dose and rescue therapy and their impact on incremental costs. The EAG noted the sensitivity of the model results to changes in these parameters. Therefore, the EAG presented the results of several scenario analyses in Section 5.2.2.

5.2 EAG's additional analyses

5.2.1 Model validation and face validity check

In the validation Section of the CS (3.13),[6] the company indicated that internal, face, and external validation of the de novo CE model was undertaken. Internal validation included independent verification of model inputs and calculations, a line-by-line audit of the Visual Basic for Applications (VBA) code by an independent researcher. The model structure, assumptions and input data were reviewed by experienced health economists.

The model's conceptual structure was reviewed by four clinicians to ensure clinical relevance for HAE patients using OD treatment.[70] However, external validation was limited due to variability in HAE and inconsistencies in TTAR definitions across sources. A comparison was made to the Scottish Medicines Consortium (SMC) appraisal of icatibant, which reported an incremental QALY gain of 0.0000852 versus berinert using a 96-hour time horizon (i.e., representing a single acute attack).[56] Incremental costs were not reported. The sebetralstat model was adjusted to match these assumptions for external comparison and the estimated QALY gain between icatibant versus berinert was 0.0000476. Based on this, the company concluded that the current model may underestimate the value gained from an oral treatment and is possibly conservative compared to the icatibant SMC model. However, it was suggested to interpret this with caution due to the differences in the modelled clinical outcomes and between model structures.

The validation efforts performed on the model, as presented by the company, are categorised according to the Types of validation used in the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool,[71] and summarised in Table 5.7.

EAG comments: The EAG acknowledges the company have performed various validation efforts. Nonetheless, the EAG considers that the model produces some counterintuitive results that, due to time constraints, could not be fully explained. In their base-case, the company assumed 45% of patients use LTP + OD treatment. However, it was noted that increasing this percentage improved the ICER for sebetralstat versus SoC, which is counterintuitive as greater prophylaxis use would be expected to reduce the need for OD treatments, thereby worsening its CE. This improvement is also unjustified, given the LTP + OD proportion of patients is applied across all treatments. In response to clarification question B15, the company justified this outcome by stating that "*the total average cost per attack is inflated by the proportion of patients using additional doses and rescue therapy"*.[8, 10] This reasoning was brief and unclear. The EAG tested whether setting these proportions to 0% would resolve the issue, but the ICER improvement persisted.

More critically, the proportion of patients using LTP + OD therapy informs the baseline attack rate calculated at 14.7 per year (see Section 4.2.3). Upon further validation, the EAG observed that reducing the annual attack rate (i.e., lowering disease burden) improved the ICER, which is also considered a counterintuitive outcome associated to the previous issue. Normally, a higher disease burden would lead to more attacks avoided and greater QALY gains, thus improving CE. In the economic model, however, it seems as if incremental costs rise faster than QALYs with increasing attack rates, reducing the CE of sebetralstat. This pattern persisted even when assuming cost per attack depending on the drug costs for the first doses only, excluding additional doses and rescue therapies. While such behaviour could result from non-linear QALY gains, discounting, mortality assumptions, or cost structures, the EAG could not determine the exact cause in this setting. Further investigation is warranted to understand this model artifact and address the structural or computational cause strengthening confidence in the results.

Table 5.7: Validation efforts performed on the company's model

Validation Type	Sub-Type	Description of company's activities	EAG comments
Conceptual model	Face validity	Validated via four clinicians[70] and health economists.	Expert-informed; details scattered across documents
	Cross validity	Through economic SLR. Summary of studies, including model structure in CS Table 24.[6]	Conceptual alignment confirmed; differences justified
Input data	Face validity	Data reviewed by health economists.	Details not provided.
	Model fit testing	Regression model estimating relationship between TTA and TTAR.[31]	Post-hoc analysis conducted by the company, not published or peer reviewed. Goodness-of-fit not discussed. ITC superior to post-hoc analysis in evidence hierarchy but not available.
Computerised model (technical verification)	External review	All source inputs and calculations in the Excel model verified by independent researcher.	Details not provided. No further errors identified by the EAG.
	Extreme value testing	Not explicitly mentioned.	Details not provided.
	Trace testing	Available in "Model Engine" sheets (hidden).	Trace testing evident.
	Unit testing	Quality control included a line-by-line audit of the VBA code.	Details not provided.
Model outcomes	Face validity	Assumed outcomes were reviewed by experts during advisory processes.	Not explicitly confirmed. Some counterintuitive results observed by the EAG. Further exploration needed.
	Cross validation	Compared with model used in the SMC appraisal of icatibant.[56]	Limited validity due to differences in modelling approaches: SMC model applied a 96-hour time horizon with 1 cycle, representing a single acute HAE attack.[56]

Validation Type	Sub-Type	Description of company's activities	EAG comments
	Alternative input data	Not reported beyond scenario analyses.	Details not provided.
	Empirical data (dependent)*	Not reported.	Details not provided.
	Empirical data (independent)*	Not reported.	Details not provided.

Source: compiled by the EAG from the CS.[6] * The distinction between dependent and independent validation of model outcomes against empirical data, refers to whether the empirical data used for validation were employed to develop the model (dependent) or not (independent).

CS = company submission; EAG = External Assessment Group; HAE = hereditary angioedema; ITC = indirect treatment comparison; SLR = systematic literature review; SMC = Scottish Medicines Consortium; TTA = time to (treatment) administration; TTAR = time to attack resolution; VBA = Visual Basic for Applications

5.2.2 EAG's exploratory analyses using company's base-case

Table 5.8 shows the results of the EAG's exploratory analyses changing one assumption from the company's base-case (after clarification) individually. All scenarios presented are deterministic. The scenarios explored by the EAG are the following:

- The proportion of patients receiving LTP + OD treatment was varied to 50% and 70% aligning with the input from the clinical experts consulted by the EAG (Section 4.2.3).
- Baseline attack rates per company's clarification question B16 were set at 11.0 and 5.49 per year (Section 4.2.3).
- The base-case uses an average TTA of ~2.9 hours for SC treatment, as reported in Longhurst et al 2018, and ~3.8 hours for IV treatments based on Christiansen et al 2024.[27, 42] The EAG run alternative scenarios using lower and upper bounds for these inputs. For TTA of SC treatment, given the right-skewed distribution (SD: 4.8 hours; median [IQR]: 0.8 [0.4–3.0] hours), the EAG considered 0.4 hours (Q1) as a lower-bound scenario, and 3.0 hours (Q3) as an upper-bound scenario to reflect more typical variation.[42] Similarly, for TTA of IV treatments, the EAG considered 1.0 (Q1) as the lower bound and 5.0 (Q3) as the upper bound given the right-skewed distribution (SD: 6.3 hours; median [IQR]: 2.0 [1.0–5.0] hours).[27] Details can be found in Section 4.2.5.1.
- Given that Aberer et al 2017 distinguishes data by LTP + OD and OD-only groups, the EAG conducted a scenario analysis estimating the proportion of rescue medication in icatibant patients at 9.78% instead of 12.70%.[2] (Section 4.2.5.3) The updated input values for sebetralstat, were also changed to their pre-clarification Phase input values in other scenarios from 24.10% to 22.25% (85/382) for additional dosing and from 8.10% to 5.25% (20/382) for rescue therapy. Additionally, the EAG ran more extreme scenarios assuming 0% rescue therapy and 0% for additional dosing of all treatments (Section 4.2.5.3).
- Utility differences for the mode of treatment administration as estimated from the general population sample (Section 4.2.6.1).
- Based on input from the clinical experts consulted by the EAG,[3] the share for icatibant was increased at 75%. That would then translate to a share of [redacted]%, [redacted]%, and [redacted]% for ruconest, berinert, and cinryze (keeping their relative shares the same and summing up to 100%). (Section 4.2.7.2)
- The EAG explored the impact of using sebetralstat as rescue therapy at a rate of 5%. That would then translate to a share of [redacted]% for icatibant, [redacted]%, [redacted]%, and [redacted]% for ruconest, berinert, and cinryze, respectively (keeping their relative shares the same and summing up to 100%). Details are in Section 4.2.7.2.
- The time of HCP-assisted administration were assumed to be 10 and 20 minutes for SC injections (Section 4.2.7.2). For IV HCP-assisted administration the time was assumed to be 30 minutes.
- The impact of medication wastage for weight-based treatments was explored through two scenario analyses: one assuming full vial wastage and the other assuming no wastage.
- The price of icatibant was based on the most recent, public electronic Market Information Tool (eMIT) price (i.e., £172.32, instead of the price of £837).

Table 5.8: Results of EAG's exploratory analyses using company's base-case (comparator is SoC)

Exploratory analysis number	Scenario applied to company's base-case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
0	Company's base-case (after clarification)	[redacted]	0.1112	[redacted]
1	LTP + OD set to 50% (from 45%)	[redacted]	0.1103	[redacted]
2	LTP + OD set to 70% (from 45%)	[redacted]	0.1068	[redacted]
3	Annual attack rate set to 11.0 (from 14.71)	[redacted]	0.1015	[redacted]
4	Annual attack rate set to 5.49 (from 14.71)	[redacted]	0.0870	[redacted]
5	TTA for SC treatment 0.8 hrs (from 2.9 hours)	[redacted]	0.0936	[redacted]
6	TTA for SC treatment 3.0 hrs (from 2.9 hours)	[redacted]	0.1121	[redacted]
7	TTA for IV treatment 1.0 hrs (from 3.8 hours)	[redacted]	0.0898	[redacted]
8	TTA for IV treatment 5.0 hrs (from 3.8 hours)	[redacted]	0.1204	[redacted]
9	Rescue therapy icatibant: 9.78% (from 12.70%)	[redacted]	0.1112	[redacted]
10	Rescue therapy sebetralstat: 8.10% (from 5.25%)	[redacted]	0.1112	[redacted]
11	Additional dosing sebetralstat: 24.10% (from 22.25%)	[redacted]	0.1112	[redacted]
12	Rescue therapy all treatments: 0%	[redacted]	0.1112	[redacted]
13	Additional dosing all treatments: 0%	[redacted]	0.1112	[redacted]
14	Treatment-related utility values from the general population (Table 108 in Appendix M of the CS)[10]	[redacted]	0.1453	[redacted]
15	Market shares: 75% (from [redacted]%) icatibant; [redacted]% (from [redacted]%) ruconest; [redacted]% (from [redacted]%) berinert; [redacted]% (from [redacted]%) cinryze	[redacted]	0.0952	[redacted]

Exploratory analysis number	Scenario applied to company's base-case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
16	Shares of rescue therapy: 5% sebetralstat (from 0%); [redacted]% icatibant (from [redacted]%); [redacted]% ruconest (from [redacted]%); [redacted]% berinert (from [redacted]%); [redacted]% cinryze (from [redacted]%)	[redacted]	0.1112	[redacted]
17	HCP-assisted administration time for SC: 20 minutes (from 1 hour)	[redacted]	0.1112	[redacted]
18	HCP-assisted administration time for SC: 10 minutes (from 1 hour)	[redacted]	0.1112	[redacted]
19	HCP-assisted administration time for IV: 30 minutes (from 1 hour)	[redacted]	0.1112	[redacted]
20	Full vial wastage for IV treatments (from 0.2 increments)	[redacted]	0.1112	[redacted]
21	No wastage for IV treatments (from 0.2 increments)	[redacted]	0.1112	[redacted]
22	Icatibant eMIT price (£172.32 from £837.0)	[redacted]	0.1112	[redacted]

Source: Based on the economic model after clarification[6]
CS = company submission; EAG = External Assessment Group; eMIT = electronic Market Information Tool; HCP = health care practitioner; ICER = incremental cost-effectiveness ratio; LTP = long term prophylaxis; IV = intravenous; OD = on demand; QALY = quality-adjusted life year; SC = subcutaneous; SoC = standard of care; TTA = time to treatment administration

Finally, as explained in Section 4.2.4, the EAG considers that a fully incremental analysis applies in this appraisal, since the definition of SoC as a basket comparator is not justified. The results of this analysis can be seen in Table 5.9 and indicate that all IV options, ruconest, berinert, are dominated by the SC option icatibant. This is expected due to the larger costs associated to IV treatments and the additional gain in QALYs due to SC delivery compared to IV. Therefore, in a full incremental analysis, the only relevant comparator is icatibant. Sebetralstat was also more costly and more effective than icatibant alone, with an ICER of £[redacted] per QALY gained.

Table 5.9: Company base-case deterministic CE results (fully incremental analysis, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Sebetralstat	[redacted]	22.01	18.49	-	-	-	-
Icatibant	356,827	22.01	18.41	[redacted]	0.00	0.0775	[redacted]
Ruconest	612,962	22.01	18.34	[redacted]			
Berinert	753,743	22.01	18.34	[redacted]			
Cinryze	555,437	22.01	18.34	[redacted]			

Source: Based on Table 35 of the CS[6]
CE = cost effectiveness; CS = company submission; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYG = life years gained; QALY = quality-adjusted life year

EAG comments: For the current assessment, it is crucial to determine whether the definition of the comparator as a basket of treatment options is appropriate or not. Under a fully incremental analysis, where the only relevant comparator is icatibant, none of the uncertainties identified by the EAG are relevant for decision-making, given the magnitude of the ICER estimated in Table 5.9.

The uncertainties explored by the EAG on the company's base-case illustrate that this is extremely sensitive to changes in several parameters such as the proportion of patients needing additional treatment doses or rescue therapy, market shares or comparator treatment prices. However, as mentioned above, for decision-making purposes, these are only relevant if the comparator is SoC (basket of treatments), or if the ICER is brought down to values closer to the thresholds used by NICE.

The EAG's view is that the definition of the comparator as a basket of treatments is not appropriate and that a fully incremental analysis should be conducted. Based on the results presented in this Section, the EAG will only present their preferred base-case in the next Section of this report but will not explore additional scenario analyses based on the EAG's preferred assumptions, given that, at the current estimated ICERs, these are irrelevant for decision making purposes.

5.2.3 EAG's preferred assumptions

The changes made by the EAG (to the model received with the response to the clarification letter) can be subdivided into the following categories (according to Kaltenthaler et al 2016):[72]

- Fixing errors ([FE]; correcting the model where model was unequivocally wrong).
- Fixing violations ([FV]; correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to).
- Matters of judgement ([MJ]; amending the model where the EAG considers that reasonable alternative assumptions are preferred).

After the proposed changes were implemented in the company's model, additional scenario analyses were also explored by the EAG in order to assess the impact of alternative assumptions on the CE results.

The adjustments made by the EAG, to define the EAG base-case (using the base-case after clarification as starting point) are listed below.

5.2.3.1.1 Fixing errors

No errors were found by the EAG in the model provided in response to the clarification letter.

5.2.3.1.2 Fixing violations

1. Icatibant price based on most recent eMIT public price (£172.32).[1]

5.2.3.1.3 Matters of judgement

2. Life tables (before COVID-19) based on 2016-2018 (Section 4.2.6.3).
3. Proportion of rescue medication in patients using icatibant set at 9.78% as in Aberer et al 2017.[2]
4. HCP-time for SC assisted administration set at 20 minutes in line with experts consulted by the EAG.[3]
5. The EAG prefers using a fully incremental analysis as explained in Section 4.2.4 of this report.

5.2.3.2 EAG base-case results

The step-by-step changes made by the EAG to derive its base-case and the cumulative impact of each change can be seen in Table 5.10. The change with the largest impact on the results was removing the assumption that the comparator SoC can be defined as a basket of treatments. This is expected since the only comparator that is not dominated is icatibant (SC); all the IV options are dominated due to their higher costs.

Table 5.10: Cumulative impact of EAG's preferred assumptions (deterministic)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
CS base-case					
Sebetralstat	[redacted]	18.35	-	-	-
SoC	556,122	18.24	[redacted]	0.1109	[redacted]
Company base-case after clarification					
Sebetralstat	[redacted]	18.49	-	-	-
SoC	540,881	18.38	[redacted]	0.1112	[redacted]
EAG Step 1 – icatibant eMIT price (£172.32)					
Sebetralstat	[redacted]	18.49	-	-	-
SoC	406,938	18.38	[redacted]	0.1112	[redacted]
EAG Step 2 – Step 1 + life tables based on 2016-2018 (before COVID-19)					
Sebetralstat	[redacted]	18.58			
SoC	408,994	18.47	[redacted]	0.1118	[redacted]
EAG Step 3 – Step 1, 2 + proportion of rescue medication in patients using icatibant set at 9.78%					
Sebetralstat	[redacted]	18.58			
SoC	403,466	18.47	[redacted]	0.1118	[redacted]

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
EAG Step 4 – Step 1-3 + HCP-time for SC assisted administration set at 20 minutes					
Sebetralstat	[redacted]	18.58			
SoC	403,147	18.47	[redacted]	0.1118	[redacted]
EAG Step 5 – Step 1-4 + comparator not defined as SoC (fully incremental analysis) – EAG's base-case					
Sebetralstat	[redacted]	18.58	-	-	-
Icatibant	97,474	18.50	[redacted]	0.0779	[redacted]
Ruconest	607,764	18.43	[redacted]		
Berinert	749,248	18.43	[redacted]		
Cinryze	550,003	18.43	[redacted]		

Source: Based on the model submitted following the clarification[4]
COVID-19 = coronavirus disease 2019; CS = company submission; EAG = External Assessment Group; eMIT = electronic Market Information Tool; HCP = health care practitioner; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SC = subcutaneous; SoC = standard of care

As shown in Table 5.10, implementing all these changes, which defined the EAG's base-case, yielded an ICER of £[redacted] when sebetralstat is compared to icatibant, while all IV treatments, including ruconest, berinert and cinryze are dominated. The probabilistic EAG base-case results (discounted) are comparable to the deterministic results, with an ICER of £[redacted], compared to icatibant. The CE-plane obtained from the PSA (not shown) indicated that all simulations were in the South-East quadrant, well above the £30,000 per QALY gained threshold. Based on the CEAC (not shown), the probability that sebetralstat is cost-effective compared to icatibant, at a willingness-to-pay (WTP) threshold of £30,000 per QALY gained, was [redacted]%.

5.2.4 Scenario analyses using EAG's preferred assumptions

The EAG considers that no additional scenario analyses using the EAG's preferred assumptions are needed. The main reason for this is that, seeing the magnitude of the EAG's base-case ICER, no plausible scenario would result in an ICER within the range of those used by NICE for decision-making.

5.2.4.1 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

5.2.5 Overview of the EAG key issues related to the CEAs

Table 5.11 summarises the CE key issues categorised according to the sources of uncertainty as defined by Grimm et al 2020:[73]

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide CIs, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g., there is a mismatch between the DP and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight).

Identifying the sources of uncertainty can help determine whether additional clarifications, evidence and/or analyses might help to resolve the key issue. Table 5.11 also includes suggested alternative approaches, expected effects on the CE, whether it is reflected in the EAG exploratory analyses, and if additional evidence or analyses might help to resolve the identified key issues.

Table 5.11: Overview of key issues related to the CE

Key issues	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
The EAG disagrees with the definition of the comparator technology as a basket of available treatments	4.2.4	Methods Transparency	Conduct a fully incremental analysis in line with the NICE reference case, provided that the definition of SoC as basket of treatments is not warranted.	+	Yes	Determine whether the definition of SoC as a basket of comparator treatments is appropriate or not.
Under the assumption that the definition of the comparator as a basket of treatments is appropriate, the model results are extremely sensitive to changes in some key cost input parameters	4.2.5.3 4.2.7.2	Imprecision	Additional scenario analyses were explored by the EAG.	+/-	No	Collect additional data on parameters such as the proportion of patients needing additional treatment doses or rescue therapy, or market shares.
Lack of comparative data to determine clinical effectiveness	4.2.5	Bias & indirectness Unavailability	Additional scenario analyses explored by the company, but not really based on comparative data.	+/-	No	Conduct or identify additional studies to incorporate clinical effectiveness comparative data in the

Key issues	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
						economic analyses.
The model results are counterintuitive for some scenario analyses	5.2.1	Transparency Bias & indirectness	Additional scenario analyses were explored by the EAG.	+/-	No	Investigate further these outcomes to clarify the modelling artefact(s) and resolve potential structural or computational issues.

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator
[b] Explored
CE = cost effectiveness; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; SoC = standard of care

5.3 Decision modifiers

5.3.1 QALY weighting for severity

The company has not presented a case for a QALY weighting for severity. The EAG agrees with this approach.

5.3.2 Uncaptured benefits

No uncaptured benefits have been proposed by the company.

5.3.3 Health inequalities

The company has not presented any information about health inequalities related to this submission.

5.4 Confidential comparator and subsequent treatment prices

A confidential appendix to this EAG report includes analyses using confidential comparator prices. The treatments that have commercial arrangements can be seen in Table 5.12. The analyses included in the confidential appendix are the following:

- Company's base-case (after clarification)
- EAG's base-case
- EAG's exploratory analyses using company's base-case as in Table 5.8.

Table 5.12: Summary of treatments with a discounted price used in the model

Drug	Form	Dose per unit/strength	Pack size	Price used in CS (£)	Source	Discounted price (£)	Source for discounted price
Sebetralstat	Tablet	300 mg	1,800 mg	12,000	Company	[redacted] (per pack)	New PAS price
Icatibant	Pre-filled syringe	30 mg/3 ml	30 mg	837	BNF	172.32	eMIT
Ruconest	Powder	50 IU/kg	2100 IU	750	BNF	CiC	MPSC
Berinert	Powder	20 IU/kg	500 IU	670	BNF	CiC	MPSC
Cinryze	Powder	1000 IU	500 IU	668	BNF	CiC	MPSC

Compiled by the EAG from prices supplied by NICE.
BNF = British National Formulary; CiC = commercial in confidence; CS = company submission; eMIT = electronic Market Information Tool; IU = international units; kg = kilogram; mg = milligram; ml = millilitre; MPSC = medicines procurement supply chain; PAS = Patient Access Scheme

5.5 Conclusions of the CE Section

The CS, Appendices E, F and G and response to clarification[6, 8, 10] provided sufficient detail for the EAG to appraise the literature searches conducted to identify relevant studies on CE, HRQoL and cost/HCRU in HAE. Searches were conducted February/March 2024 and updated in November 2024. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of

databases and conference proceedings were searched. Overall, the EAG has no major concerns about the literature searches conducted.

The CE-specific key issues highlighted by the EAG throughout this report are summarised in Table 5.11. Of these, the EAG identified the definition of the comparator technology as a basket of available treatments as the main key issue associated with the CE analyses. The EAG's view is that defining the comparator as a basket of treatments is not justified in this case, since there is no similar mechanism of action and no clinical equivalence between C1-INHs (berinert, ruconest and cinryze) and BR2 antagonists (icatibant). Thus, a fully incremental analysis should be conducted, where all C1-INHs may be grouped together (even though this would make no difference since they would be dominated). When such an analysis is performed, all other uncertainties and key issues become irrelevant for decision making purposes, as their impact is much smaller than when performing a fully incremental analysis.

In case the AC considers that SoC can be defined as a basket of treatments, or in case plausible scenarios are presented that result in ICERs closer to the thresholds used by NICE for decision making, the EAG also identified the following (secondary) key issues:

1) Under the assumption that the definition of the comparator as a basket of treatments is appropriate, the model results are extremely sensitive to changes in some key cost input parameters.
2) Lack of comparative data to determine clinical effectiveness.
3) The model results are counterintuitive for some scenario analyses.

The first secondary key issue relates to the model results being extremely sensitive to changes in some key parameters. These include the proportion of patients requiring additional treatment doses or rescue medication, the market shares of the comparators (when icatibant's share is increased to 75%), and comparator prices (when the price of icatibant is based on the eMIT price). This is a relevant issue, because small changes in any of these parameters can result in sebetralstat dominance or an ICER well above the common CE thresholds used by NICE for decision making.

The second secondary key issue relates to the lack of comparative data, a methodological limitation that the company attempted to address by conducting a post-hoc analysis using TTA and attack location as predictors for TTAR. In terms of evidence hierarchy, well-conducted ITCs usually rank higher and are preferred for estimating relative treatment effects (i.e., differences in TTAR between different treatment options). However, should comparative evidence on TTARs be identified, the impact on the model results is not expected to be major.

The third secondary key issue concerns counterintuitive model behaviour. Despite the company's validation efforts, the model produces results that are not aligned with clinical or economic expectations. These effects persist even when simplifying cost assumptions as per the company's justification. Although the EAG explored this issue further, underlying structural or computational cause could not be fully identified due to time constraints. Further investigation is needed to strengthen confidence in the results.

Based on all these concerns, the EAG defined a new preferred base-case by:

1. Using the most recent eMIT public price for icatibant (£172.32).[1]
2. Selecting life tables (before COVID-19) based on data from 2016-2018.
3. Setting the proportion of rescue medication in patients using icatibant at 9.78% as in Aberer et al (2017).[2]

4. Assuming 20 minutes of HCP-time for SC assisted administration, in line with experts consulted by the EAG.[3]
5. Using a fully incremental analysis, as explained in Section 4.2.4 of this report.

The results of the EAG's base-case analysis indicated that, in a fully incremental analysis, all IV options, ruconest, berinert, and cinryze are dominated by the SC option icatibant, which is thus the only relevant comparator. The estimated ICER was £[redacted] per QALY gained, which is well above the common thresholds used by NICE. The PSA results comparing sebetralstat against icatibant only are in line with the deterministic results, with all PSA outcomes in the North-East quadrant of the CE-plane, and a CEAC plot indicating that for all the thresholds included in the economic model, the estimated probability that sebetralstat is a cost-effective alternative to icatibant was [redacted]%. The EAG did not conduct any additional scenario analyses using the EAG's preferred assumptions, because, seeing the magnitude of the EAG's base-case ICER, no plausible scenario would result in an ICER within the range of those typically accepted by NICE.

In conclusion, for the current assessment, it is crucial to determine whether the definition of the comparator as a basket of treatment options is appropriate or not. Under a fully incremental analysis, where the only relevant comparator is icatibant, none of the uncertainties identified by the EAG have impact on decision-making.

6. References

[1] Gov.uk. Drugs and pharmaceutical electronic market information tool (eMIT): eMIT national database [Internet]. 2025 [accessed 23.7.25]. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit

[2] Aberer W, Maurer M, Bouillet L, Zanichelli A, Caballero T, Longhurst HJ, et al. Breakthrough attacks in patients with hereditary angioedema receiving long-term prophylaxis are responsive to icatibant: findings from the Icatibant Outcome Survey. Allergy Asthma Clin Immunol 2017; 13:31

[3] National Institute for Health and Care Excellence. *Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over [ID6284]: Questions to experts: responses combined*. London: NICE, 2025. 17p.

[4] KalVista. *Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over [ID6284]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Cost effectiveness model v2.0 [14.7.25]*: KalVista, 2025

[5] National Institute for Health and Care Excellence. *Sebetralstat for treating acute attacks of hereditary angioedema in people 12 years and over: final scope [Internet]*. London: NICE, 2025 [accessed 28.5.25]. 3p.

[6] KalVista. *Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over [ID6284]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B - Company evidence submission*: KalVista, 2025. 180p.

[7] National Institute for Health and Care Excellence. *Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over [ID6284]: Clarification questions*. London: NICE, 2025. 19p.

[8] National Institute for Health and Care Excellence. *Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over [ID6284]: Response to request for clarification from the EAG*. London: NICE, 2025. 76p.

[9] McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline statement. J Clin Epidemiol 2016; 75:40-6

[10] KalVista. *Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over [ID6284]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Appendices [updated version sent 8.7.25]*: KalVista, 2025. 281p.

[11] Aygören-Pürsün E, Zanichelli A, Cohn DM, Cancian M, Hakl R, Kinaciyan T, et al. An investigational oral plasma kallikrein inhibitor for on-demand treatment of hereditary angioedema: a two-part, randomised, double-blind, placebo-controlled, crossover Phase 2 trial. Lancet 2023; 401(10375):458-469

[12] KalVista Pharmaceuticals Ltd. An open-label extension trial to evaluate the long-term safety of KVD900 for on-demand treatment of angioedema attacks in adolescent and adult patients with hereditary angioedema (HAE). NCT05505916. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2024 [accessed 28.10.24]. Available from: https://www.clinicaltrials.gov/study/NCT05505916?term=NCT05505916&rank=1

[13] KalVista. *A randomized, double-blind, placebo-controlled, phase 3, three-way crossover trial to evaluate the efficacy and safety of two dose levels of KVD900, an oral plasma kallikrein inhibitor, for on-demand treatment of angioedema attacks in adolescent and adult patients with hereditary angioedema type I or II [Protocol for KONFIDENT]*: KalVista, 2023

[14] KalVista. *HCP validation and clinician survey. Summary report [in press] [Data on File]*, 2024

[15] Li HH, Aygören-Pürsün E, Magerl M, Craig TJ, Manning ME, Hummel N, et al. Indirect treatment comparison of oral sebetralstat and intravenous recombinant human C1 esterase inhibitor for on-demand treatment of hereditary angioedema attacks. Allergy Asthma Clin Immunol 2025; 21(1):10

[16] Wang A, Li H, Magerl M, Craig TJ, Manning M, Hummel N, et al. Indirect treatment comparison of oral sebetralstat and intravenous RHC1-INH as on-demand treatments for hereditary angioedema. Ann Allergy Asthma Immunol 2024; 133(Suppl):S28-S29

[17] Riedl MA, Bernstein JA, Li H, Reshef A, Lumry W, Moldovan D, et al. Recombinant human C1-esterase inhibitor relieves symptoms of hereditary angioedema attacks: phase 3, randomized, placebo-controlled trial. Ann Allergy Asthma Immunol 2014; 112(2):163-169.e1

[18] Li HH, Magerl M, Craig T, Manning ME, Hummel N, Wang A, et al. R083. Indirect treatment comparison of oral sebetralstat and intravenous rhC1-INH as on-demand treatments for hereditary angioedema [Poster]. *American Academy of Allergy, Asthma & Immunology 2024*. Boston, USA, 2024.

[19] Lo SH, Lloyd A, Elkhalifa S, Sisic Z, van Nooten FE. Time trade-off utilities for hereditary angioedema health and caregiver states. Pharmacoecon Open 2022; 6(2):231-239

[20] KalVista. *Hereditary angioedema (HAE) utilities [Data on file]*, 2025

[21] PBAC. *Icatibant public summary document. November 2016 PBAC meeting*: PBAC, 2016. 7p. Available from: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2010-07/Icatibant_FIRAZYR_Shire.pdf

[22] Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygoren-Pursun E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema - the 2021 revision and update. Allergy 2022; 77(7):1961-1990

[23] Bygum A, Busse P, Caballero T, Maurer M. Disease severity, activity, impact, and control and how to assess them in patients with hereditary angioedema. Front Med (Lausanne) 2017; 4:212

[24] Guan X, Sheng Y, Liu S, He M, Chen T, Zhi Y. Epidemiology, economic, and humanistic burden of hereditary angioedema: a systematic review. Orphanet J Rare Dis 2024; 19(1):256

[25] Savarese L, Mormile I, Bova M, Petraroli A, Maiello A, Spadaro G, et al. Psychology and hereditary angioedema: a systematic review. Allergy Asthma Proc 2021; 42(1):e1-e7

[26] National Institute for Health and Care Excellence. *Berotralstat for preventing acute attacks of hereditary angioedema [ID1624] [Public observer slides - redacted]*. London: NICE, 2021. 1-30p. Available from: https://www.nice.org.uk/guidance/ta738/documents/1

[27] Christiansen S, O'Connor M, Craig T, Radojicic C, Wedner HJ, Danese S, et al. On-demand treatment of hereditary angioedema attacks: patient-reported utilization, barriers, and outcomes. Ann Allergy Asthma Immunol 2025; 134(5):570-579

[28] National Institute for Health and Care Excellence. *Single Technology Appraisal. Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]. Draft guidance committee papers*. London: NICE, 2021. 1-501p. Available from: https://www.nice.org.uk/guidance/ta738/documents/committee-papers

[29] KalVista. *A randomized, double-blind, placebo-controlled, phase 3, three-way crossover trial to evaluate the efficacy and safety of two dose levels of KVD900, an oral plasma kallikrein inhibitor, for on-demand treatment of angioedema attacks in adolescent and adult patients with hereditary angioedema type I or II (KONFIDENT) [KONFIDENT CSR report] [Data on file]*: KalVista, 2024

[30] KalVista. *Interim clinical trial report: an open-label extension trial to evaluate the long-term safety of KVD900, an oral plasma kallikrein inhibitor, for on-demand treatment of angioedema attacks in adolescent and adult patients with hereditary angioedema Type I or II (KONFIDENT-S) [KONFIDENT-S OLE interim CSR report - 14 Sept 2024 data cut off date]*: KalVista, 2024

[31] KalVista. *Post-hoc statistical analysis: association between time to administration and time to attack resolution [Data on file]*, 2025

[32] Bork K, Bernstein JA, Machnig T, Craig TJ. Efficacy of different medical therapies for the treatment of acute laryngeal attacks of hereditary angioedema due to C1-esterase inhibitor deficiency. J Emerg Med 2016; 50(4):567-80.e1

[33] Betschel S, Badiou J, Binkley K, Borici-Mazi R, Hébert J, Kanani A, et al. The International/Canadian hereditary angioedema guideline. Allergy Asthma Clin Immunol 2019; 15:72

[34] Busse PJ, Christiansen SC, Riedl MA, Banerji A, Bernstein JA, Castaldo AJ, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. J Allergy Clin Immunol Pract 2021; 9(1):132-150.e3

[35] Cohn DM, Aygören-Pürsün E, Bernstein JA, Farkas H, Lumry WR, Maurer M, et al. Evaluation of patient-reported outcome measures for on-demand treatment of hereditary angioedema attacks and design of KONFIDENT, a phase 3 trial of sebetralstat. Clin Transl Allergy 2023; 13(9):e12288

[36] Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. *Network meta-analysis for decision-making*: Wiley, 2018.

[37] Decision Support Unit. *NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE*: University of Sheffield, 2016 Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list

[38] National Institute for Health and Care Excellence. *Lanadelumab for preventing recurrent attacks of hereditary angioedema [TA606]*. London: NICE, 2019. 1-24p. Available from: https://www.nice.org.uk/guidance/ta606/resources/lanadelumab-for-preventing-recurrent-attacks-of-hereditary-angioedema-pdf-82608899683525

[39] Office for National Statistics. National life tables – life expectancy in the UK: 2021 to 2023 [Internet]. 2025. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2021to2023additionaldata

[40] NHS England. *Health Survey for England 2022, Part 2: Data tables: HSE 2022: Adult health tables*: NHS England, 2022 Available from: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2022-part-2/health-survey-for-england-hse-2022-part-2-data-tables

[41] Yong PFK, Coulter T, El-Shanawany T, Garcez T, Hackett S, Jain R, et al. A national survey of hereditary angioedema and acquired C1 inhibitor deficiency in the United Kingdom. J Allergy Clin Immunol Pract 2023; 11(8):2476-2483

[42] Longhurst HJ, Dempster J, Lorenzo L, Buckland M, Grigoriadou S, Symons C, et al. Real-world outcomes in hereditary angioedema: first experience from the Icatibant Outcome Survey in the United Kingdom. Allergy Asthma Clin Immunol 2018; 14:28

[43] Mendivil J, DerSarkissian M, Banerji A, Diwakar L, Katelaris CH, Keith PK, et al. A multicenter chart review of patient characteristics, treatment, and outcomes in hereditary angioedema: unmet need for more effective long-term prophylaxis. Allergy Asthma Clin Immunol 2023; 19(1):48

[44] National Institute for Health and Care Excellence. *NICE health technology evaluations: the manual. NICE process and methods [PMG36] [Internet]*. London: National Institute for Health and Care Excellence, 2023 [accessed 10.1.24]. 200p. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741

[45] National Institute for Health and Care Excellence. Glossary [Internet]. [accessed 23.7.25]. Available from: https://www.nice.org.uk/glossary

[46] National Institute for Health and Care Excellence. *Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]: Committee Papers [Internet]*. London: NICE, 2024 [accessed 23.7.25]. 143p. Available from: https://www.nice.org.uk/guidance/ta1051/documents/committee-papers

[47] National Institute for Health and Care Excellence. *Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over (review of TA839) [ID6377]: Committee Papers [Internet]*. London: NICE, 2024 [accessed 23.7.25]. 501p. Available from: https://www.nice.org.uk/guidance/ta1054/documents/committee-papers

[48] National Institute for Health and Care Excellence. *Ruxolitinib for treating acute graft versus host disease refractory to corticosteroids in people aged 12 and over [TA1054]: Final draft guidance [Internet]*. London: NICE, 2025 [accessed 23.7.25]. 23p. Available from: https://www.nice.org.uk/guidance/ta1054/documents/674

[49] National Institute for Health and Care Excellence. *Relugolix for treating hormone-sensitive prostate cancer [ID6187]: Committee Papers [Internet]*. London: NICE, 2024 [accessed 23.7.25]. 499p. Available from: https://www.nice.org.uk/guidance/ta1054/documents/674

[50] Christiansen SC, O'Connor M, Ulloa J, Danese S. Delayed on-demand treatment of hereditary angioedema attacks: patient perceptions and associated barriers [Poster]. Allergy Asthma Clin Immunol 2024; 153(2 Suppl 1)

[51] Andrasi N, Veszeli N, Holdonner A, Temesszentandrási G, Kohalmi KV, Varga L, et al. Evaluation of the efficacy and safety of home treatment with the recombinant human C1-inhibitor in hereditary angioedema resulting from C1-inhibitor deficiency. Int Immunopharmacol 2020; 80:106216

[52] Craig TJ, Rojavin MA, Machnig T, Keinecke HO, Bernstein JA. Effect of time to treatment on response to C1 esterase inhibitor concentrate for hereditary angioedema attacks. Ann Allergy Asthma Immunol 2013; 111(3):211-5

[53] Maurer M, Aberer W, Bouillet L, Caballero T, Fabien V, Kanny G, et al. Hereditary angioedema attacks resolve faster and are shorter after early icatibant treatment. PLoS One 2013; 8(2):e53773

[54] Zuraw B, Cicardi M, Levy RJ, Nuijens JH, Relan A, Visscher S, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. J Allergy Clin Immunol 2010; 126(4):821-827.e14

[55] Craig TJ, Bewtra AK, Bahna SL, Hurewitz D, Schneider LC, Levy RJ, et al. C1 esterase inhibitor concentrate in 1085 hereditary angioedema attacks - final results of the I.M.P.A.C.T.2 study. Allergy 2011; 66(12):1604-11

[56] Scottish Medicines Consortium. *Icatibant acetate, 30mg, solution for injection in pre-filled syringe (Firazyr®). SMC No. (476/08)*. Glasgow: SMC, 2012. 10p. Available from: https://scottishmedicines.org.uk/media/1808/icatibant_firazyr_resubmission_final_february_2012_amended_060312_for_website.pdf

[57] Collett D. *Modelling survival data in medical research*: CRC Press, 2023.

[58] Riedl MA, Hurewitz DS, Levy R, Busse PJ, Fitts D, Kalfus I. Nanofiltered C1 esterase inhibitor (human) for the treatment of acute attacks of hereditary angioedema: an open-label trial. Ann Allergy Asthma Immunol 2012; 108(1):49-53

[59] Zanichelli A, Azin GM, Cristina F, Vacchini R, Caballero T. Safety, effectiveness, and impact on quality of life of self-administration with plasma-derived nanofiltered C1 inhibitor (Berinert) in patients with hereditary angioedema: the SABHA study. Orphanet J Rare Dis 2018; 13(1):51

[60] Cicardi M, Banerji A, Bracho F, Malbrán A, Rosenkranz B, Riedl M, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med 2010; 363(6):532-41

[61] Riedl MA, Li HH, Cicardi M, Harper JR, Relan A. Recombinant human C1 esterase inhibitor for acute hereditary angioedema attacks with upper airway involvement. Allergy Asthma Proc 2017; 38(6):462-466

[62] Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, Boysen HB, et al. Estimation of EuroQol 5-Dimensions health status utility values in hereditary angioedema. Patient Prefer Adherence 2016; 10:1699-707

[63] Matza LS, Stewart KD, Lloyd AJ, Rowen D, Brazier J. Vignette-based utilities: usefulness, limitations, and methodological recommendations. Value Health 2021; 24:812-821

[64] Ara R, Brazier J. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010; 24:812-821

[65] Hernández Alava M, Pudney S, Wailoo A. *NICE DSU Report: Estimating EQ-5D by age and sex for the UK [Internet]*. Sheffield: Decision Support Unit, ScHARR, 2022 [accessed 13.3.24]. 23p. Available from: https://www.sheffield.ac.uk/media/34059/download?attachment

[66] IQVIA. *HAE UK monthly IQVIA [Data on file]*, 2025 Available from: https://kar.kent.ac.uk/109563/1/The%20unit%20costs%20of%20health%20and%20social%20care%202024%20%28for%20publication%29_Final.pdf

[67] Jones K, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, et al. *Unit Costs of Health and Social Care. Table 9.2.1 Nurse, Band 6, Cost per working hour*, 2022 Available from: https://kar.kent.ac.uk/109563/1/The%20unit%20costs%20of%20health%20and%20social%20care%202024%20%28for%20publication%29_Final.pdf.

[68] BNF. Icatibant 30mg/3ml solution for injection pre-filled syringes [Internet]. 2024 [accessed 5.11.24]. Available from: https://bnf.nice.org.uk/drugs/icatibant/medicinal-forms/

[69] KalVista. *Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over [ID6284]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Cost effectiveness model*: KalVista, 2025

[70] KalVista. *Sebetralstat conceptual model KoL validation [Data on file]*, 2024

[71] Vemer P, Corro Ramos I, van Voorn GA, Al MJ, Feenstra TL. AdViSHE: a validation-assessment tool of health-economic models for decision makers and model users. Pharmacoeconomics 2016; 34(4):349-61

[72] Kaltenthaler E, Carroll C, Hill-McManus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. Health Technol Assess 2016; 20(26):1-48

[73] Grimm SE, Pouwels X, Ramaekers BLT, Wijnen B, Knies S, Grutters J, et al. Development and Validation of the TRansparent Uncertainty ASsessmenT (TRUST) Tool for assessing uncertainties in health economic decision models. Pharmacoeconomics 2020; 38(2):205-216

Single Technology Appraisal

Sebetralstat for treating acute attacks of hereditary angioedema in people 12 years and over [ID6284]

EAG report – factual accuracy check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 8 August 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr>
<td>There is multiple references to an old base-case [redacted] ICER) which is not reflective of the new PAS price and new resulting ICER of [redacted] using the final PAS price of [redacted] per pill.</td>
<td>We propose any mention of the £[redacted] ICER and old PAS price in the CS base-case results are updated to the below results:
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td colspan="6">CS base-case</td></tr>
<tr><td>Sebetralstat</td><td>[redacted]</td><td>18.35</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>SoC</td><td>[redacted]</td><td>18.24</td><td>[redacted]</td><td>0.1112</td><td>[redacted]</td></tr>
</table>
Specifically, these changes should be made in:

Table 1.8 “Individual impact of EAG’s preferred assumptions and EAG base-case deterministic”. Page 15. CS base-case results. Updated as above

Page 89. Table 4.8. The treatment acquisition cost of sebetralstat should be amended from [redacted] to [redacted]

Table 5.1 “Company base-case deterministic CE results (sebetralstat 300 mg versus SoC, discounted)”. Page 93. Table should be updated as below:
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incr. Costs (£)</th><th>Incr. LYG</th><th>Incr. QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>Sebetralstat</td><td>[redacted]</td><td>22.01</td><td>18.35</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>SoC</td><td>[redacted]</td><td>22.01</td><td>18.24</td><td>[redacted]</td><td>0.00</td><td>0.1112</td><td>[redacted]</td></tr>
</table>
Note: page 93 also mentions “The ICER was [redacted] per QALY gained, which is above the common CE thresholds used by NICE for decision-making.” Given the updated PAS and</td>
<td>This change is important to accurately reflect the final CS base case ICER of £[redacted].

There are several base-case ICER changes throughout the document, reflecting the previous PAS and updated PAS price. This can be unclear to the reader and thus should be updated consistently to ensure clarity.</td>
<td>Not a factual inaccuracy.

The final CS base case ICER was £[redacted]. The updated PAS price, together with other changes, led to the company’s base-case ICER (after clarification), as described in Section 5.1.3 of the EAG report.</td>
</tr>
</table>

resulting ICER, this is not correct and should be updated to reflect the change in ICER to [redacted]

Table 5.5 *"Company scenario analysis results (sebetralstat 300 mg versus SoC, discounted)".* **Page 98**. Scenario 0. Base-case *rows should be updated as below:*

Scenario number	Scenario description	Base-case assumption	Incr. costs (£)	Incr. QALYs	ICER
0. Base-case	N/A	N/A	[redacted]	0.1112	[redacted]

Table 5.10 *"Cumulative impact of EAG's preferred assumptions (deterministic)".* ***Page 108****. CS base-case rows should be updated as below:*

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
CS base-case					
Sebetralstat	[redacted]	18.35	-	-	-
SoC	[redacted]	18.24	[redacted]	0.1112	[redacted]

.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 19, section 2.2 Intervention EAG comment. The EAG comment reads “The EAG notes that the intervention is 300 mg to 600 mg as required, as opposed to 300 mg or 600 mg, as in the key trials (see Section 3). This means that the assumption of 300 mg in the cost-effectiveness analysis (CEA) (see Section 4) is an underestimate of the dose and therefore the cost.” *Please note that* sebetralstat dosing is either 300 mg OR 600 mg with a second tablet (should that be needed) as per the SmPC guidance: “The recommended dose of Ekterly is 300 mg administered at the earliest recognition of an attack. An additional dose may be taken if needed.” Furthermore, the model does not underestimate costs of the dosing as any costs of the second dose (600 mg) are captured in the additional dosing rates.	We suggest the EAG comment is removed as it is inaccurate.	To provide clarity on dosing and model costs	Amended.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 24, Table 3.2 KONFIDENT quality appraisal. Row 3, column 2 of Table 3.2 states "Yes. As described in Section 2.3 disease characteristics were well balanced between treatment groups at baseline." It is not clear what section 2.3 refers to.	The text in the table should read: "*Yes. As described in Section 2.3 of the company submission disease characteristics were well balanced between treatment groups at baseline*."	To clarify Section 2.3 relates to the company submission and not the EAG report	Corrected.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 27, 3.2.1 study retrieval. 3,792 studies were removed after duplicates not 3,793	After duplicates records were removed, 3,792 title and abstracts were screened	Typographical error	Corrected.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 37, 3.2.2.3 Summary of KONFIDENT-S OLE trial. Incorrect figure number is referenced	"...the KONFIDENT trial (rollover) or de novo (see Figure 3.4)."	Incorrect figure number is referenced	Corrected.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 37, Section 3.2.2 Trial summaries states "Those receiving long-term prophylaxis (LTP) must be on a stable dose and regimen for ≥3 months immediately before and during the trial" for KONIFDENT-S OLE however this changed in January 2025	"Originally, those receiving long-term prophylaxis (LTP) must be on a stable dose and regimen for ≥3 months immediately before and during the trial, however from January 2025 this was amended to allow patients to start, stop, or change long-term prophylactic treatment at the discretion of the PI during the trial"	To reflect KONFIDENT-S OLE protocol changes	Amended.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 37, 3.2.2.3 Summary of KONFIDENT-S OLE trial grammatical error	"The CS also emphasises the following information of importance 'Please note that from January 2025 the dose in KONFIDENT-S changed from 600 mg to 300 mg. The study was designed with the original 600 mg dose before results from the Phase 3 KONFIDENT study were available. Since then, the 300 mg and 600 mg have been demonstrated to be dose equivalent, so the open-label study changed to 300 mg dosing from 2025'	Grammatical error	Not a factual inaccuracy.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 39, Table 3.6 last row "Oral sebetralstat 600 mg". it is worth adding clarity of the	Suggest amendment to include a note: "Oral sebetralstat 600 mg – note this changed to 300 mg in January 2025."	For accuracy to reflect the change in KONFIDENT-S dosing protocol from January 2025.	Amended.

dose change in KONFIDENT-S.			

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 43 Section 3.2.3.2 heading is incorrect	The correct heading should be 3.2.3.2 KONFIDENT-S OLE	Incorrect study heading	Corrected.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 43, section 3.2.3.2 incorrect study referenced	"The KONFIDENT-S OLE study utilised both de novo and rollover patients"	Wrong study referenced	Corrected.

Issue 11.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 44, incorrect data presented	Additionally, there was [redacted] undefined 'other' ethnicity versus [redacted] in the non-rollover group	Incorrect data presented	Corrected.

Issue 12.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 45, 3.2.5.1 KONFIDENT Phase 3 trial primary endpoint description is missing detail	"This was to be based on a difference in survival distribution of the time to beginning of symptom relief defined by the PGI-C as at least "a little better" for 2 time points in a row within 12 hours of the first IMP administration"	Grammatical error and missing detail for the primary endpoint	Corrected.

Issue 13.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 45, 3.2.5.1 KONFIDENT Phase 3 trial inaccuracy in patient numbers. The protocol included the word "approximately" ahead of the 114 patient number.	Addition of the word "approximately" for accuracy and alignment with the protocol so that it reads: "Approximately one hundred and fourteen patients were to be randomised to ensure approximately 84...."	Accuracy	Amended.

Issue 14.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 45, Section 3.2.5.1 KONFIDENT Phase 3 trial - primary endpoint description is missing detail	".... the primary endpoint of time to beginning of symptom relief of the HAE attack defined by PGI-C as at least "a little better" for 2 time points in a row within 12 hours of the first IMP administration"	Missing detail for the primary endpoint	Corrected.

Issue 15.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 46 Section 3.2.5.1 KONFIDENT phase 3 trial – grammatical error	Gehan score transformation tests were used to analyse efficacy endpoints.	Grammatical error	Corrected.

Issue 16.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 49 Section 3.2.7.2 Primary efficacy results – incorrect section referenced	"Section 2.6 of the CS included...."	Incorrect section referenced	Corrected.

Issue 17.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 49 Section 3.2.7.2 Primary efficacy results – need to clarify results presented are from the KONFIDENT trial	"Section 2.6 of the CS included the following statements from the KONFIDENT trial results..."	Accuracy	Not a factual inaccuracy.

Issue 18.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 50, Table 3.9 KONIFDENT Phase 3 –	Data in row "Adjusted P value compared with placebo" "6.72 (1.34-	Accuracy	Corrected.

primary endpoint results have data on the wrong line of the table.	>12)" should sit on the row below titled "Median (IQR)" in column "Placebo (N=84)" and there should be no data in the place where "6.72 (1.34->12)" data is currently presented.		

Issue 19.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 52, Figure heading 3.6 references the wrong study phase	Figure 3.6 KONFIDENT Phase 3 key secondary endpoint results: reduction in severity of attack	Accuracy	Corrected.

Issue 20.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 52, Figure 3.7 source references the wrong figure in the CS	Source: Based on Figure 6 of the CS	Accuracy	Corrected.

Issue 21.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 55, Table 3.11. Grammatical error “Number of patients events” in the heading	“Number of patient events[a]”	Grammatical error	Corrected.

Issue 22.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 56, Table 3.11. Incorrect source table referenced from the CS	“Source: Based on Table 11 of the CS”	Accuracy	Corrected.

Issue 23.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 63, 3.4.1 Time to beginning of symptom relief references the incorrect	“....see Figure 3.9 [A]) or sex (HR, 1.19; 95% CrI, 0.58–2.45; Figure 3.9 [B]).”	Accuracy	Corrected.

figure (Figure 3.7 instead of Figure 3.9)			

Issue 24.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 63, 3.4.2 Time to beginning of symptom relief references the incorrect figure (Figure 3.8 instead of Figure 3.10)	"....see Figure 3.10 [A]).... the results did not materially change (region: HR, 1.24 [95% CI, 0.46–3.31]; sex: HR, 1.56 [95% CI, 0.63–3.88]; Figure 3.10 [B])."	Accuracy	Corrected.

Issue 25.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 69 Section 4.1.1 Searches performed for the CE section. Incorrectly states dates of CE searches.	"The CE searches were conducted in February 2024 and the HRQoL searches were conducted in March 2024. Both sets of searches were updated in November 2024." Following correction during NICE Clarification, this should be changed to "Both the CE searches and HRQoL searches	Accuracy of literature search dates	Corrected

	were conducted in March 2024 and updated in November 2024”		

Issue 26.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 70, Section 4.1.3 Findings of the CE review. Incorrect CE original search date	Following correction during NICE Clarification this should now be corrected to state: “The original searches were conducted on 15 March 2024...”	Accuracy of literature search dates	Corrected

Issue 27.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 75, Section 4.2.4 Interventions and comparators EAG comment that “In addition, the company have not presented evidence to support clinical equivalence. On the	To state that we provide evidence that icatibant is more effective than C1-INHs is potentially misleading, especially if stated without further context. Based on our justification, we propose the following amendment: "… the evidence provided by the company shows that the faster the	Accuracy, to ensure clear interpretation of statistical model and original CS assumptions. We consider the EAG's statement to be potentially	The EAG does not completely agree with the company’s justification. The sentence has been amended as follows: “In addition, the company have not presented

contrary, the evidence provided by the company in the CS shows that icatibant (BR2 antagonist) is more effective than any of the C1-INHs in terms of time to attack resolution (see e.g., Table 4.4 of this report)..." which is incorrect	TTA of any treatment, the shorter the TTAR across locations or severity."	misleading and carry a high risk of misinterpretation. While we do not provide statistical evidence to support clinical equivalence, it is an assumption in the absence of reliable direct or indirect comparative data for decision making. Nevertheless, based on a review of literature and feedback from clinical experts, time to administration (TTA) was identified as a key point of value for OD HAE treatments. The assumption that the TTA of OD treatment modifies the time to attack resolution (TTAR) of an acute HAE attack is well-supported by literature, clinicians, and WAO guidelines. Due to the pathophysiology of acute HAE attacks, once swelling is established, no existing OD treatment can rapidly reverse existing tissue oedema. Thus, the earlier an OD treatment is administered - regardless of MoA - the quicker the swelling	evidence to support clinical equivalence. The evidence provided by the company in the CS shows that icatibant (BR2 antagonist) has shorter time to attack resolution than any of the C1-INHs (see e.g., Table 4.4 of this report), due to its faster time to administration, which is the only driver of differential efficacy in the regression model included in the present economic analyses.”

		is halted. In other words, current contemporary OD treatments only halt progression, while the body gradually reabsorbs existing oedema fluid caused by an acute HAE attack. We would like to highlight that we provided a large body of supporting evidence in the original CS. Following the above, the only driver of differential efficacy in the regression model is TTA. Thus, if all treatments had equal TTA in the economic model, the expected TTAR of each treatment would be equivalent, across locations or severity. To reiterate, the economic model does not assume any intrinsic or independent differences in efficacy between treatments. Rather, observed differences in efficacy are assumed to be driven primarily by the timing of TTA.	

Issue 28.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 79 Section 4.2.5.2, the report includes narrative from the point of view of the company saying "Additionally, we apply a MD" when this was the company not the EAG.	Change "we" to "the company" "Additionally, the company applied a MD to TTA..." And also in the below: "The company provide the following example..."	Accuracy, clarity	Amended. The EAG changed "We apply a MD" into "The company applied a MD", and "We provide the following example" into "The company provided the following example".

Issue 29.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 80, Section 4.2.4.2 Attack resolution EAG comments on evidence hierarchy for ITCs lack context	We propose the following amendment to this statement, to ensure that the reasons for not including an ITC in the economic model are clear: "In terms of evidence hierarchy, well-conducted ITCs usually rank higher	Clarification and to provide context on the challenges of conducting ITCs of acute treatments in this indication. To also ensure clarity on why KalVista did not submit an economic model using an ITC	Amended as suggested by the company.

	than company-conducted post-hoc analyses and should be preferred for estimating relative treatment effects (i.e., differences in TTAR between different treatment options). However, the company noted difficulties in conducting ITCs due to heterogeneity of trial criteria and endpoints. The precariousness of ITCs within the context of the current HAE OD evidence landscape was also highlighted by NICE experts during Early Scientific Advice."	for comparative evidence in the original CS. To add further support, the difficulty of producing reliable ITCs was acknowledged by NICE during Early Scientific Advice, with NICE stating that: "NICE has concerns that the considerable heterogeneity identified may mean the trials in the network are too dissimilar to allow a valid comparison of outcomes in a standard ITC, even when utilising techniques to control for heterogeneity such as matching adjusted indirect comparisons."	

Issue 30.

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 82, Table 4.5 Other treatment-related input parameters used in the	Source: Based on Table 30 of the CS	Accuracy	Amended.

economic model. Incorrect source table from CS.			

Issue 31.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 83, "EAG considers it reasonable to expect higher rates of additional dosing with oral treatments compared to SC/IV OD which may not be appropriately captured in a trial setting." In fact, it is likely significantly overestimated.	We propose the following amendment: "… EAG considers it reasonable to expect higher rates of additional dosing with oral treatments compared to SC/IV OD. Conversely, the real-world additional dosing rate may also be lower than the rate observed the trial setting. Lower additional dosing rates in the real-world are likely due to factors including no placebo arm and the opportunity to treat multiple attacks and therefore build trust with new OD treatment use.	Accuracy. The statement by the EAG is highly uncertain and could be misinterpreted by the reader. The additional dosing rate of sebetralstat will most likely continue to decrease, plateauing at rates at least similar to those observed for icatibant and C1-INHs. Generally, OD treatments have been observed to have decreasing additional dosing rates over time, especially once patients are accustomed to the new treatment in the real-world setting. This trend, of declining additional dosing	Not a factual inaccuracy. The EAG consulted clinical experts who supported this statement. However, to incorporate the company's point, the following sentence was added to the EAG report: "However, this assumption remains uncertain: it cannot be ruled out that, conversely, rates of additional dosing with oral OD treatments may be lower (over time) in the real world, especially

		rates over time, has been observed in the OLE data for sebetralstat.	once patients become accustomed to the new treatment, compared to trial settings.”

Issue 32.

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 89, Table 4.8 Drug acquisition costs, administration costs, recuse therapy costs, and AE costs. Incorrect sebetralstat acquisition cost per pack	Please note that during NICE Clarification, the price was amended to [redacted] per pack not [redacted] *Note the final PAS price is [redacted]	Accuracy of price	Not a factual inaccuracy. The values in Table 4.8 reflect the information originally submitted. Further changes made after clarification are described in Section 5.1.3. A note has been added to Table 4.8 to clarify this.

Issue 33.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 99, Section 5.1.3 Updated company's CE results. Incorrect price stated.	Should read "...changed from [redacted] per pill in the original CS..."	Accuracy	Amended

Issue 34.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 99, Section 5.1.3 Updated company's CE results. Minor wording change to reflect change from Longhurst et al to Aberer et al source. EAG state "The proportion of patients using icatibant additional dosing was amended erroneous interpretation from Aberer et al 2017.[2] This was 12.7% in	We propose the following amendment: "The proportion of icatibant patients requiring additional dosing was based on an erroneous interpretation of data from Longhurst et al. The original CS inputted an additional dosing value of 12.7%. However, this has now been amended to a value 8.91%, sourced from Aberer et al 2017.[2]"	Clarity of error and original data source	Amended

the original CS and 8.91% now."			

Issue 35.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 100 Section 5.2.1 Model validation and face validity check. Typographical error.	“The model’s conceptual structure was reviewed by four clinicians to ensure clinical relevance for HAE patients using OD treatment”	Clarification for on-demand treatment	Amended