PART 1

For public – contains no confidential information

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

Technology appraisal committee C [14 October 2025, ACM1]

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on hereditary angioedema (HAE)

Rare genetic disorder, associated with uncontrolled swellings and inflammation

Figure includes images from ID6394 company submission

Epidemiology

- Rare, affects ~1,041 people in England and Wales. Mean age of onset 8-12 years.

Symptoms and prognosis

- Recurrent and unpredictable attacks of swelling of the skin or submucosal tissues. Severity and frequency of previous attacks do not predict future attacks.
- HAE attacks manifest as painful swellings that occur on any part of the body, but most commonly subcutaneous tissue or mucous membranes. Attacks may be fatal, particularly involving laryngeal swelling.
- HAE does not affect life expectancy with proper treatment and management

Subtypes

- HAE can be categorised into clinically indistinguishable subtypes
- Most cases caused by mutation affecting C1 esterase inhibitor (C1-INH) gene: **Type I** (~85%), **Type II** (~15%). HAE with normal C1-INH uncommon subtype (<1%)
- Eligible NHS population size: ~1,023 people* (Type I and II HAE, ≥12 years and using on demand treatment)

*Estimate from company budget impact assessment submission

Abbreviations: C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema

Clinical and NHS England perspectives

Sebetralstat offers benefits over current on demand treatments

Submissions from the British Society for Immunology*, British Society for Allergy and Clinical Immunology, Royal College of Pathologists, NHS England and clinical experts**

Current treatment options for acute attacks are injectables which can

- delay treatment and deliver poorer outcomes
- be painful, cause anxiety and do not work for all people
- be difficult to carry around and administer

Sebetralstat is the first oral treatment available for acute HAE attacks:

- addresses issues with injectable therapies. Earlier administration is associated with better outcomes and aligns to international guidelines
- adolescents and adults who are unable to self-administer injections would particularly benefit from an oral treatment which is less invasive
- well tolerated in trials with no expected significant AEs

Benefits not captured in QALY: remove injection barriers, greater usability, reduced A&E reliance, lower anxiety, caregiver benefits, patient preference, addresses the broader physical, psychological, and social aspects of HAE

*Clinical Immunology Professional Network, **Immunology and Allergy Clinical Reference Group

"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"

"main aim of treatment for HAE is to achieve complete control of the disease and the normalisation of patients' lives… preventing or minimising attacks so … patients can live safely, fully, and without restrictions"

NICE

Abbreviations: AE, adverse events; A&E, accident and emergency; HAE, hereditary angioedema; QALY, quality-adjusted life year

Patient perspectives

Attacks are debilitating. Unmet need for oral, on demand medication

Experience of HAE attack: Hereditary Angioedema UK and patient experts

- Excruciating pain with swelling of subcutaneous tissues anywhere in body – uncomfortable and unsightly, can be fatal (e.g. laryngeal swelling)
- Debilitating with rapid onset over a few hours. Attacks usually last between 24-72 hours, post recovery time of 48-72 hours

Expected advantages of oral on demand treatment (sebetralstat)

- Addresses unmet need: prophylactic treatments are not always suitable and prescribing is based on frequency of attack and not severity (as per NHS commissioning guidance)
- Current on demand treatments are given by injection. Many people are needle-phobic. Injectables need continual refrigeration and impact daily life
- Sebetralstat is oral, easily carried around and works fast. Can reduce anxiety and workload of managing HAE for both patients and carers

"There is a need for... an [oral] on demand medication for patients who…have a relatively small number of attacks, but also to be able to treat a breakthrough attack"

"The introduction of an oral [option] for an acute attack will improve the lives of HAE patients enormously. They will be able to avoid the inconvenience of administering a subcutaneous injection…speed of administration being crucial and taking an oral preparation will get around this."

NICE

Abbreviations: HAE, hereditary angioedema

Equality considerations

Access to current treatments may be limited by ethical and religious beliefs

Potential equality issue raised		Related considerations
Age	Current treatments are available to all ages. If sebetralstat is approved in the current age group, it should be made available to all ages once appropriate studies have been conducted	• NICE committee makes recommendations within a technology's marketing authorisation • Sebetralstat is indicated for use in people aged 12 years and older
Religion	Religious groups may refuse to accept C1-INH comparators • Cinryze and Berinert are derived from human plasma • Ruconest is derived from animal DNA	• Icatibant is an existing alternative to C1-INHs, which is not from human or animal products
HAE subtype	Sebetralstat should be available to people with all subtypes of HAE	• Trial evidence covers only HAE subtypes I and II

How should these equality issues be considered?

Abbreviations: C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema

Treatment pathway

* See appendix - full treatment algorithm

On demand HAE treatment pathway based on NHS clinical commissioning algorithm

People (all ages) with HAE-C1-INH (Types I and II) with clinically significant attack that requires admission/injected treatment on clinical and risk assessment

Decision informed by:
- Clinical judgement
- Clinical effectiveness
- Contraindications
- Place of care
- Patient choice
- Need for rescue pack
- Ability of patient/carer to use required administration technique

Consider first

Icatibant (subcutaneous injection)**

C1-esterase inhibitor (C1-INH) (intravenous injection):
- Berinert
- Cinryze
- Ruconest

≥ 12 years old

Sebetralstat (oral treatment)

**NHSE estimate - [redacted] of people have icatibant

Usually administered in hospital setting or self-administration at home*
*selected patients - high-risk profile, poor attack control or live far from an emergency department that carries on demand treatment

Pre-procedure prophylaxis: Eligible for C1-INHs before having dental, medical, obstetric or surgical procedures

- **Is the treatment pathway reflective of clinical practice?**
- **How are treatment decisions made on the appropriate treatment option?**
- **Are outcomes expected to be different for alternative treatment options?**

Abbreviations: C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; NHSE, NHS England

Sebetralstat (Ekterly, KalVista)

Information about sebetralstat

Marketing authorisation (MA)	• Sebetralstat is indicated for the treatment of HAE attacks in adults and adolescents aged 12 years and older • MHRA MA granted 15 July 2025 • Currently being offered as part of EAMS (approved in March 2025) in selected immunology centres
Mechanism of action	• Oral plasma kallikrein inhibitor → lowers bradykinin levels which reduces swelling and pain associated with HAE attacks
Administration	• Recommended dose of sebetralstat is a 1 x 300 mg tablet to be taken at the earliest sign of a HAE attack. An additional dose may be taken if needed
Price	• List price is £12,000 per pack of 6 tablets (£2,000 per 300mg tablet) • Company has a confidential commercial arrangement [simple discount patient access • scheme (PAS)]

SmPC on sebetralstat use in children <12 years of age:

- Safety and efficacy of sebetralstat in children <12 years has not been established → no data available

Abbreviations: EAMS, Early Access to Medicines Scheme; HAE, hereditary angioedema; MHRA, Medicines and Healthcare products Regulatory Agency; SmPC, Summary of Product Characteristics

Key issues

Issue	ICER impact
• Uncertainty whether HAE-nC1-INH subtype is included in decision problem	Unknown
• Lack of adjustment in the MAIC analysis	None (not modelled)
• Definition of comparators	Large
○ Proportion having treatments in the model	Large
○ Lack of comparative clinical data	Unknown
○ Model results are counterintuitive for some scenario analyses	Unknown

EAG has identified 3 secondary key issues which may have an impact on decision making depending on how comparators are defined or if a plausible scenario results in the ICER being close to threshold used for decision-making

Abbreviations: HAE-nC1-INH, hereditary angioedema with normal C1-esterase inhibitor; ICER; incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparisons

Unknown ICER impact

Key issues: Uncertainty whether HAE-nC1-INH subtype is included in decision problem

Company have not presented evidence for sebetralstat in people with HAE-nC1-INH

Background and company response to clarification

*See appendix – decision problem

- Population in final scope*: people 12 years and over with HAE having an acute attack (in line with MA)
- Company clarification response: HAE-nC1-INH subtype has not been considered
  - subtype is very rare (UK prevalence 1:3,000,000)
  - focus of clinical programme for sebetralstat has been on HAE Types I and II (better understood and to ensure homogenous study population within trials) → reflects evidence presented in submission

EAG comments

- Company submission appears to exclude third subtype of HAE (HAE-nC1-INH) from decision problem
- Although population for subtype likely to be very small, the uncertainty as to whether it is included in the decision problem and lack of evidence on this population, implies it is a key issue

- **Are there any concerns to consider if sebetralstat is only available in HAE Types I and II?**

Abbreviations: C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; HAE-nC1-INH, hereditary angioedema with normal C1-esterase inhibitor; ICER, incremental cost-effectiveness ratio; MA, marketing authorisation; SoC; standard of care

Note: slide has been updated post committee meeting to remove a factual inaccuracy

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

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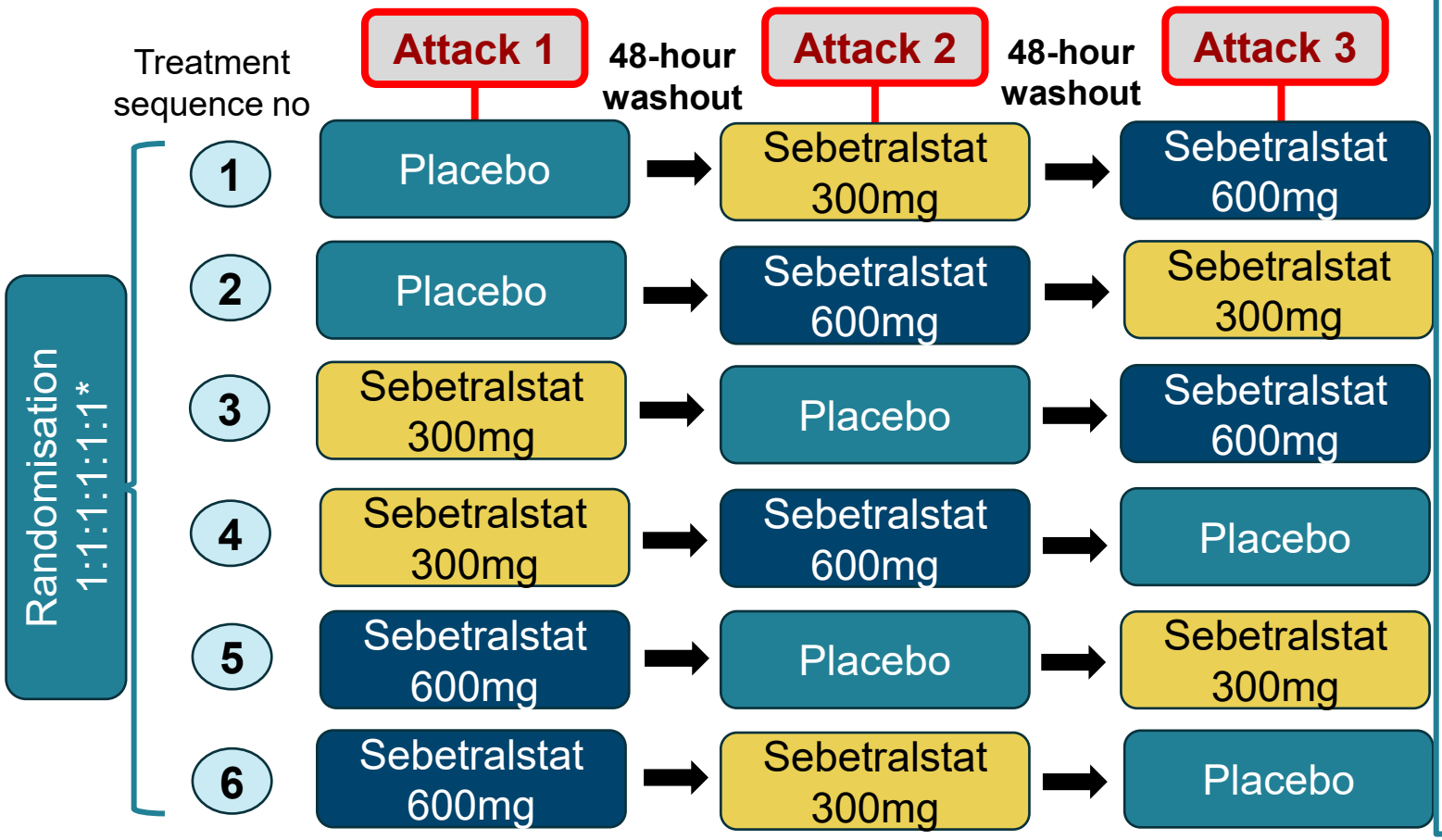
Key clinical trial - KONFIDENT

Phase 3 double-blind, randomised, 3-way crossover trial



- **Population**: people aged ≥12 years with HAE Type I or II (≥2 attacks within previous 3 months), n=8 UK
- **Intervention and comparator:** participants (n=136) assigned to 1 of 6 treatment sequences to take:
  - sebetralstat (300 mg or 600 mg) or placebo as early as possible after onset of attack
  - optional second dose** (matching initial dose) if needed
- **Key outcomes:** time to the beginning of symptom relief (primary outcome), time to reduction in attack severity, time to attack resolution, AEs

EAG: washout period sufficient to reduce contamination by previous treatment (sebetralstat half life ~ 3 hours)
KONFIDENT is at low risk of bias

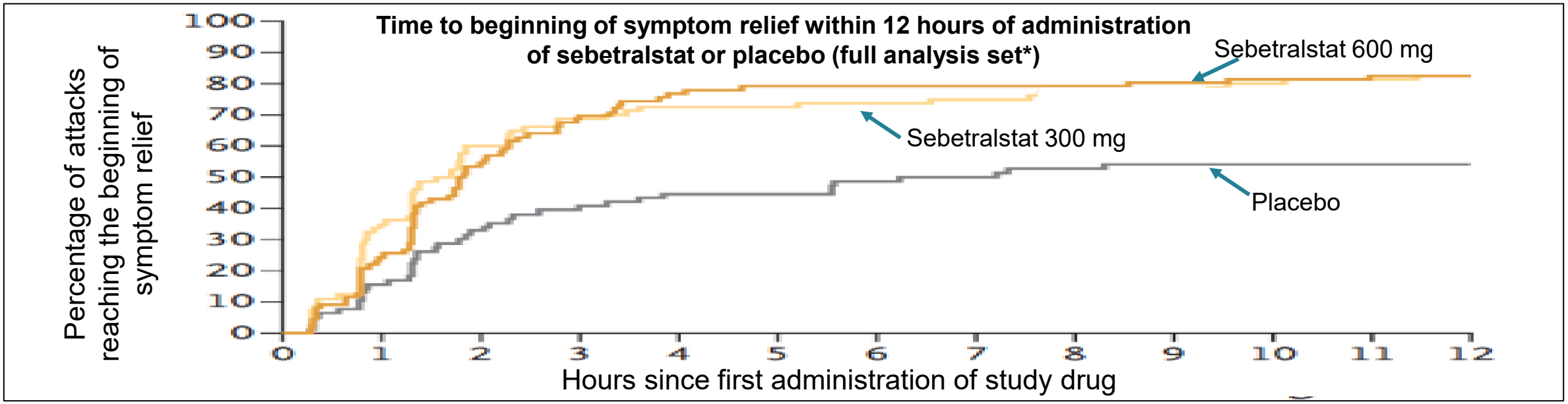
Participants could continue to use conventional on demand treatment for HAE attacks and long-term prophylactic treatment (allowed in protocol) if on stable dose/regimen 3 months before and during trial. *Randomisation was stratified on use of long-term prophylaxis at enrolment. ** Taken ≥3 hours after first dose

Abbreviations: AEs, adverse events; HAE, hereditary angioedema

KONFIDENT – primary endpoint

see appendix for other key results

Time to the beginning of symptom relief was significantly shorter with sebetralstat than placebo



Defined as a rating of at least "A Little Better" on the PGI-C scale** for 2 or more consecutive time points

	Sebetralstat 300 mg (Number of attacks = 87)	Placebo (Number of attacks = 84)
Events (symptom relief)	66 (75.9%)	41 (48.8%)
Censored	21 (24.1%)	43 (51.2%)
Censored at hour 0†	7 (8.0%)	8 (9.5%)
Adjusted P value vs placebo	<0.001	
Median time in hours (IQR)	1.61 (0.78 to 7.04)	6.72 (1.34 to >12)

Note: recommended dose of sebetralstat in SmPC is 300mg

*N=110 received at least 1 dose of double-blind treatment **Patient Global Impression of Change includes 7-point scale → ratings range from "much better" to "much worse" †Underivable end point because of missing data → analyses assumed data was missing at random

Abbreviations: IQR, interquartile range; PGI-C, Patient Global Impression of Change; SmPC, Summary of Product Characteristics

Indirect treatment comparison (ITC)

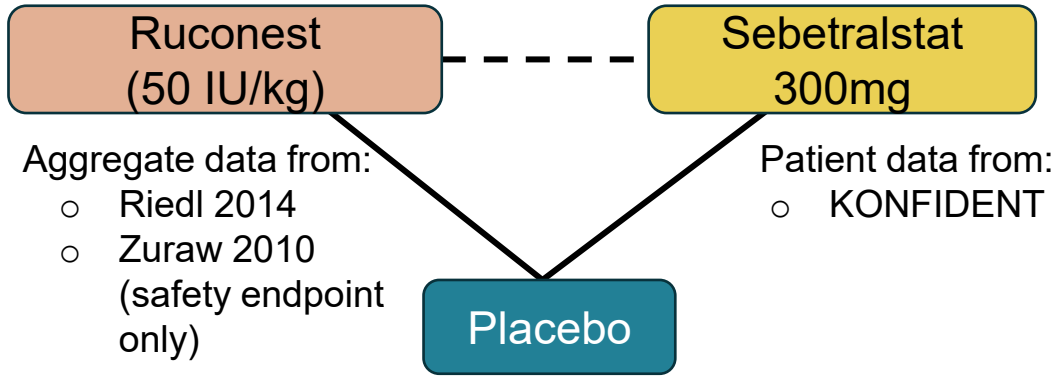
see appendix – ITC results

No direct evidence comparing sebetralstat to icatibant or C1-1NHs (as on demand HAE treatments):

- Company provided results from published ITC (Li et al 2025) to show the method-of-administration comparability between an oral on demand treatment (sebetralstat) and an intravenous on demand treatment (Ruconest)
- NMAs compared time to beginning of symptom relief and TRAEs (safety outcome)
  - no significant differences between treatments (using fixed or random effects models) → see table below
- MAICs were also performed as differences in baseline attack severity and demographics may have affected time to beginning of symptom relief → see next slide
- NHS England commissioning policy states - little reliable head-to-head comparison of clinical efficacy of the different acute treatment options. Scottish Medicines Consortium assessment of icatibant assumed equivalent effectiveness for icatibant and Berinert

Time to beginning of symptom relief	HR (95% CrI)
Fixed effects NMA, stratified for region	0.96 (0.42 to 2.15)
Fixed effects NMA, stratified for sex	1.19 (0.58 to 2.45)
Random effects NMA, stratified for region	0.95 (0.21 to 4.30)
Random effects, NMA, stratified for sex	1.19 (0.30 to 4.81)

HR >1 favour sebetralstat 300 mg



Company comments

- ITCs of on demand treatments difficult because of heterogeneity in trial designs and endpoint definitions
- Key efficacy outcome in model is **time to attack resolution** → unable to conduct ITC for this outcome

Abbreviations: C1-INH, C1-esterase inhibitor; CrI, credible interval; HAE, hereditary angioedema; HR, hazard ratio; MAIC, matching-adjusted indirect comparisons; NMA, network meta-analysis; TRAEs, treatment-related adverse events

No ICER impact (MAIC not included in model)

Key issues: Lack of adjustment in the MAIC analysis (1)

Uncertainty whether MAICs for time to onset of symptom relief adjust for key prognostic variables

Background on MAICs

- Performed for time to beginning of symptom relief → MAIC results not included in the model
- KONFIDENT population (n=171) was matched to Riedl 2014 population (n=75):

Stratification	Time to beginning of symptom relief (sebetralstat vs Ruconest)	HR (95% CI)
For region	Matching for attack severity (ESS=62)	1.27 (0.48 to 3.35)
For region	Matching for attack severity + age, sex and race (ESS=58)	1.24 (0.46 to 3.31)
For sex	Matching for attack severity (ESS=62)	1.59 (0.65 to 3.92)
For sex	Matching for attack severity + age, sex and race, (ESS=58)	1.56 (0.63 to 3.88)

- **MAICs estimate no difference between treatments in either scenario**

HR >1 favour sebetralstat 300 mg

Company response to clarification

- No evidence suggesting potential treatment effect modifiers for HAE on demand therapies
- Assessed list of potential prognostic factors from ITC of HAE prophylactic treatments - *see appendix

EAG comments

- Several important prognostic variables (HAE Type, comorbidity and baseline attack frequency) not adjusted for in MAIC analysis due to unavailability of data. May compromise validity of results

- **Can clinical equivalence be assumed for all treatments around time to attack resolution?**

Abbreviations: CI, confidence interval; ESS, effective sample size; HAE, hereditary angioedema; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparisons

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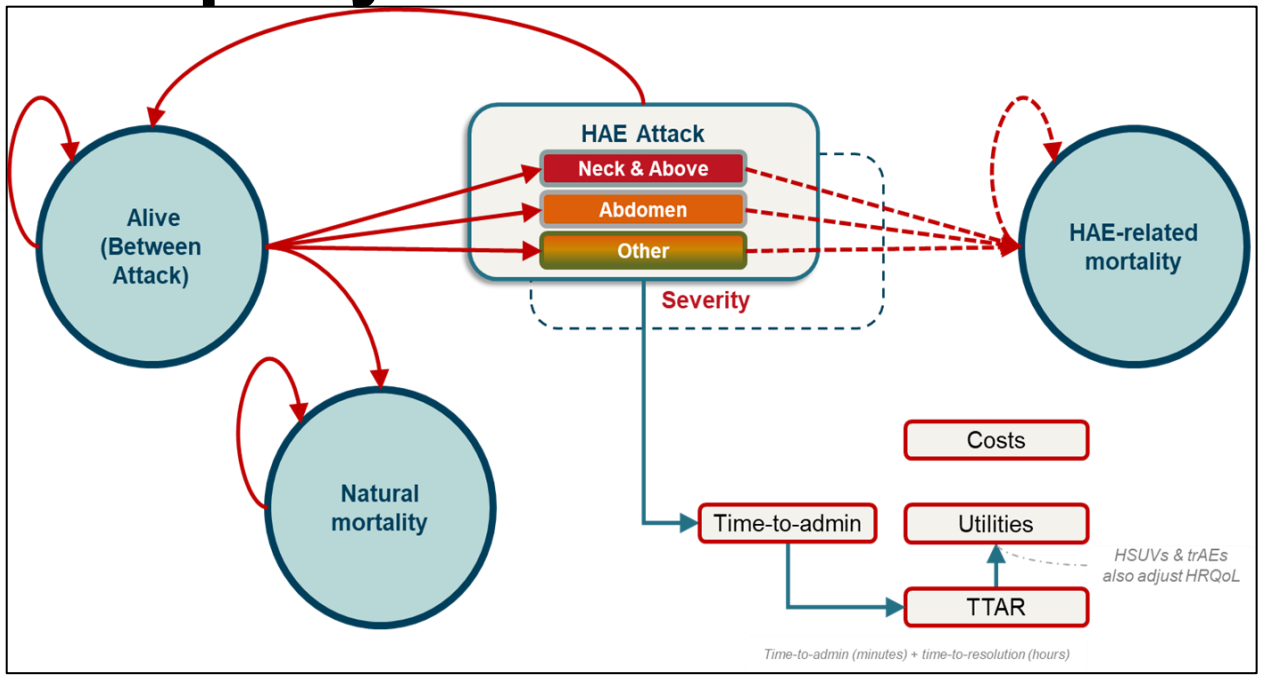
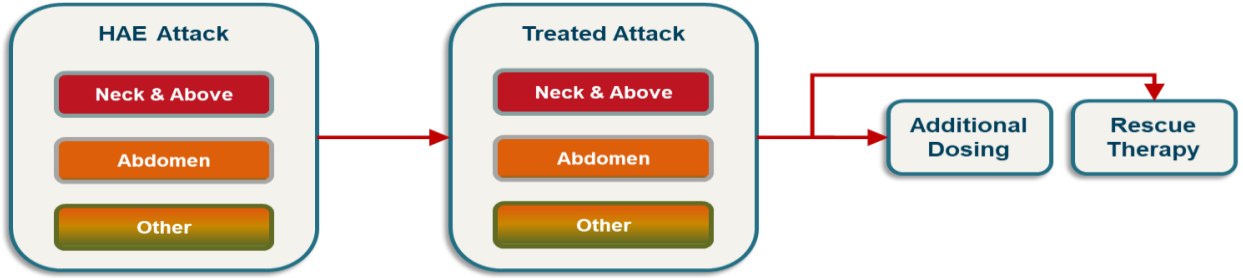
Company's model overview





Cohort state-transition model

- 2 health states in base case: alive and dead (natural mortality)
- Attacks are modelled as acute transient events within the alive health state
  - constant cycle-level risk over time
- All attacks are treated initially with on demand treatments: sebetralstat or SoC basket (icatibant, Berinert, Cinryze and Ruconest)
  - % additional doses and rescue therapy are fixed per cycle and treatment-specific
- 3 attack locations used to estimate impact of HAE attacks on HRQoL*
- 14.71 annual attack rate based on expected attack rate of on demand only (17.78, Longhurst et al 2018) and LTP + on demand (11, Mendivil et al 2023)
- Time horizon: lifetime
- 21-day cycle + half-cycle correction

* Neck and above have largest impact

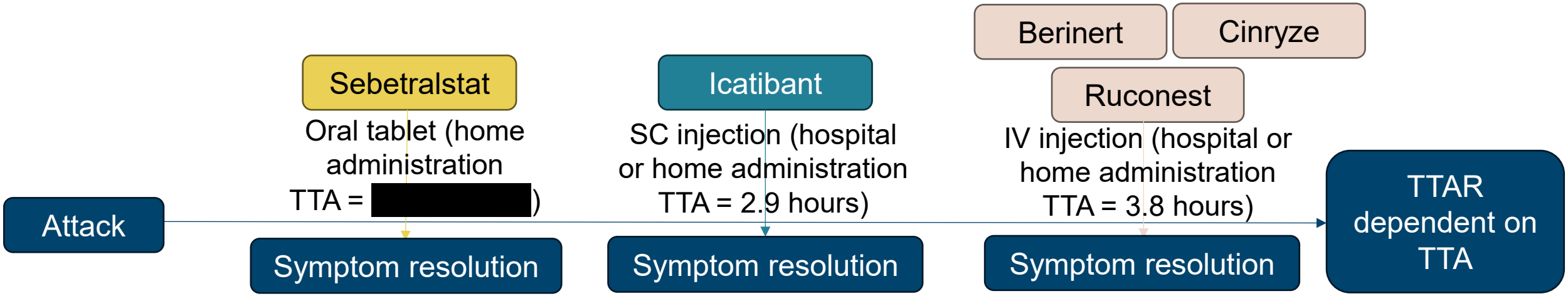
Disutility of attack (by location) is adjusted by expected TTAR = key efficacy outcome in model

Abbreviations: HAE, hereditary angioedema; HRQoL, health-related quality of life; LTP, long term prophylaxis; SoC, standard of care; TTA, time to treatment administration; TTAR, time to attack resolution

Modelled data sources

No comparative TTAR evidence. Company consider that earlier on demand administration is associated with a shorter total attack duration → model includes statistical sub-model (Cox model) to estimate TTAR from TTA

- Company Cox model estimated treatment effects (TTA and attack location used as predictors for TTAR)
  - included set of covariates: treatment sequence, attack number, severity and location and TTA
- Sebetralstat TTA sourced from KONFIDENT OLE 600mg, mean TTA [redacted]
- Icatibant UK average TTA ~2.9 hours (Longhurst et al 2018)
- IV–administered treatments average TTA ~3.8 hours (Christiansen et al 2024)
- Treatment sequence, attack number, baseline severity, and attack location data based on KONFIDENT



Equal efficacy for symptom resolution assumed

Are the TTA values used reflective of clinical practice?

Abbreviations: IV, intravenous; OLE, open label extension; SC, subcutaneous; TTA, time to administration; TTAR, time to attack resolution

Secondary key issue: Lack of comparative clinical data

(*see appendix – HAE attack inputs)

Clinical evidence is a post-hoc analysis, EAG prefer analyses comparing TTAR between treatments

Background – no direct or indirect evidence for time to attack resolution (TTAR)

- Difficult to conduct ITCs (for HAE on demand treatments) due to heterogeneity of trial criteria and endpoints
- Company Cox model estimated treatment effects (TTA and attack location used as predictors for TTAR)
  - included set of covariates: treatment sequence, attack number, severity and location and TTA

EAG comments

- Well-conducted ITCs preferred to post-hoc analyses → requested ITC results (Li et al 2025) to inform model
- Cox model is retrospective, non-comparative and not pre-specified → potentially increasing risk of bias
- Cox regression should be re-estimated using TTA and attack location only → consistent with model inputs
- Company should conduct/identify additional studies to incorporate comparative clinical data in the model
  - if comparative evidence on TTAR is identified, impact on model results is not expected to be large
- Company model likely overestimates benefit of sebetralstat as it projects first-dose TTA differences onto TTAR, does not account for reduced effectiveness when additional doses or rescue therapy are required

Company response to clarification and factual accuracy check of EAG report

- ITC (Li et al 2025) cannot inform model as outcomes do not correspond to key clinical inputs in the model
- Difficulty of producing reliable ITCs was acknowledged by NICE during Early Scientific Advice

Is the company's regression analysis appropriate for estimating treatment effects?

Abbreviations: HAE, hereditary angioedema; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; TTA, time to treatment administration; TTAR; time to attack resolution

Summary of key model assumptions/inputs

Input	Assumption and evidence source
Population	• People ≥12 years with Type I or II HAE ○ cohort split: 45% LTP + on demand treatment, 55% on demand treatment only
Modelled treatments	Sebetralstat (intervention) vs SoC basket (comparator)
Treatment effectiveness and extrapolation (TTAR = modelled efficacy outcome)	• Attack inputs: TTA (KONFIDENT-S OLE for sebetralstat, literature for comparator treatments) and distribution of attack locations (KONFIDENT). • Attack resolution: post-hoc Cox proportional hazards model estimates the HRs to adjust TTAR for each treatment based on TTA and attack location • Mortality applied using general population life tables*
Adverse events (AEs)	• Annual rate of hospitalisation dependent on self administered (5.8%) or administered by HCP (12.5%), from TA606 (Lanadelumab) • Treatment-related side effects: injection site reactions, painful burning or stinging with injections (% from literature, disutility from DCE study – see next slide)
Costs and resource use	• Drug costs (including rescue therapy, HCP administration). No health state costs. • AEs: Hospitalisation only, TRAEs assumed to resolve without additional costs** • Drug wastage assumed for IV weight-based treatments by rounding to 0.2-vial increments. EAG explore full vial wastage and no wastage scenarios

*Adjusted by cycle, age and gender **No consistent Grade 3 or higher TRAEs were identified across on demand treatments

Is the company's approach to estimating drug wastage appropriate?

Abbreviations: DCE, discrete choice experiment; HAE, hereditary angioedema; HCP, healthcare professional; HR, hazard ratios; IV, intravenous; LTP, long-term prophylaxis; OLE, open-label extension; SoC, standard of care; TRAEs; treatment related adverse event; TTA, time to treatment administration; TTAR, time to attack resolution

Utilities

see appendix – utilities used in company base-case analysis

HRQoL data was not collected in KONFIDENT. Company base case includes:

- Disutility of acute HAE attacks by body location (informed by time trade-off analysis* by Lo et al 2022)
  - disutilities scaled by attack duration, cycle length and adjusted by treatment-specific TTAR
- UK general population utility values** applied for baseline health states across all treatments
  - disutilities were used for route of treatment administration and side effects (informed by discrete choice experiment commissioned by company†)
  - no disutility difference between SC and oral treatment administration in company base case
- No consistent Grade 3+ TRAEs observed for any on demand treatment → AE disutility not applied

EAG comments

- May be limitations related to modelled utilities, but changes in quality-of-life inputs are unlikely to significantly increase the ICER
- Recognise oral administration may offer benefit over SC, provide scenario with utility difference applied

*Vignette study included 15 patients, 5 caregivers and 1 clinician to develop health state descriptions which were then valued by 100 members of public through TTO tasks ** Adjusted over time using age- and gender-specific norms †Analyses were conducted separately for patients with HAE (used in base case) and members of public

Abbreviations: AE, adverse event; HAE, hereditary angioedema; HRQoL; health-related quality of life; ICER, incremental cost-effectiveness ratio; SC, subcutaneous; TRAEs; treatment related adverse event; TTAR, time to attack resolution

Large ICER impact

Key issues: Definition of comparators (1)

*NICE TA1051 and TA1054

Company define comparator as basket of treatments, EAG prefer fully incremental analysis

Background and company response to clarification

- Company have defined SoC (icatibant and C1-INHs) as a basket of treatments as it considers this better reflects NHS clinical practice (HAE treatment is individualised) and approach has been used in previous NICE TAs* (not related to HAE)
- Company refer to NICE HTE manual which states: "*In exceptional circumstances, 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*" (section 4.2.17)
- Company consider that while on demand treatments can differ in mechanism of action, they are functionally substitutable and differences in efficacy largely driven by time to treatment administration (TTA)

EAG comments (1)

- Class of treatments are those with the same or similar mechanism of action (as defined in NICE glossary)
- Icatibant (bradykinin B2 receptor antagonist) and C1-INHs do not have the same mechanism of action
- Company have not provided evidence to support clinical equivalence
  - submission shows that icatibant has shorter time to attack resolution (TTAR) than any of the other C1-INHs because of its faster time to administration → TTAR = only driver of differential efficacy in model
- Assuming that HAE treatments are functionally substitutable does not align with clinical practice → people would remain on icatibant and only receive other options in exceptional circumstances (as rescue therapy)

Abbreviations: C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; HTE, health technology evaluation; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care; TA, technology appraisal; TTA, time to treatment administration; TTAR; time to attack resolution

Large ICER impact

Key issues: Definition of comparators (2)

EAG comments (2)

- NICE TAs mentioned by company are not valid precedents for using basket of treatments in this appraisal
- Definition of comparator as a basket of treatments is not appropriate, results should be presented in a fully incremental analysis → significantly increases ICER (more costly comparator treatments are dominated)
  - all other uncertainties and key issues become irrelevant for decision making purposes
  - EAG has identified 3 secondary key issues which may have an impact on decision making if committee consider SoC basket is appropriate or plausible scenarios are presented that result in ICER close to threshold used for decision making

Company response to factual accuracy check of EAG report

- If all treatments had equal TTA in the model, expected TTAR of each treatment would be equivalent across locations or severity → TTA = only driver of differential efficacy in model

- **Can icatibant and C1-INHs be assumed to be clinically equivalent?**
- **Is the company's approach to model SoC as a basket of treatments appropriate?**

Abbreviations: C1-INH, C1-esterase inhibitor; ICER; incremental cost-effectiveness ratio; SoC, standard of care; TA, technology appraisal; TTA, time to treatment administration; TTAR; time to attack resolution

Large ICER impact

Secondary key issue: Proportion having treatments (1)

EAG consider that additional data on key cost parameters is needed to reduce uncertainty

Background

- Comparators are defined as a basket of treatments with percentages determined by market share
  - market shares are derived from a study commissioned by the company
- Model allows for additional dosing (same on demand treatment) and rescue treatment (alternative on demand treatment) → treated as independent events (due to limited data on their conditional relationship)
  - it is assumed that sebetralstat will not be used a rescue therapy

Market share of comparators (rescue treatment usage assumed equivalent to market share)

Comparator	Market share in company model	Current NHSE estimate	EAG scenario
Berinert (IV)	[redacted]	[redacted]	[redacted]
Cinryze (IV)	[redacted]	[redacted]	[redacted]
Ruconest (IV)	[redacted]	[redacted]	[redacted]
Icatibant (SC)	[redacted]	[redacted]	[redacted]

EAG scenario substantially increases ICER

Company proportion having additional dosing and rescue therapy in model

Parameter	Sebetralstat	Icatibant	Ruconest	Berinert	Cinryze
Additional dosing (% per attack)	22.25*	8.91†	18.18†	1.11†	18.18**
Rescue therapy (% per attack)	5.25*	12.70†	7.32†	7.32**	7.32**

NHSE: additional dosing should be 1.11% for Cinryze and Berinert

- EAG base case for proportion of rescue therapy with icatibant = 9.78% from Aberer 2017

- **What proportion of people have each treatment in clinical practice?**
- **Are additional dosing and rescue treatment reflective of clinical practice?**

*KONFIDENT-S OLE sebetralstat 600mg (interim analysis) **assumed equivalent to Ruconest, †sourced from literature

Abbreviations: ICER; incremental cost-effectiveness ratio; IV, intravenous; NHSE: NHS England; OLE, open-label extension; SC, subcutaneous; SoC, standard of care

Large ICER impact

Secondary key issue: Proportion having treatments (2)

EAG comments

- CE results vs SoC basket are extremely sensitive to small changes on key cost parameters
- Market share for comparators: sebetralstat more cost-effective when increasing % IV options in SoC basket
- Proportion requiring additional dosing and rescue therapy:
  - expect additional dosing reduces need for rescue therapy → company base case, additional doses and rescue therapy independent, may overestimate rescue therapy use and costs with higher additional dosing
  - unclear if sebetralstat additional dosing rates will increase or decrease over time in clinical practice
  - EAG presented scenarios 1) 0% rescue therapy for all treatments → moderate increase in the ICER 2) 0% additional dosing for all treatments → large decrease in the ICER

Company response to factual accuracy check of EAG report

- Additional dosing for sebetralstat will likely decrease over time to similar rates for icatibant and C1-INHs

Abbreviations: C1-INH, C1-esterase inhibitor; CE, cost-effectiveness; ICER; incremental cost-effectiveness ratio; IV, intravenous; LTP, long-term prophylaxis; SoC, standard of care

Unknown ICER impact

Secondary key issue: Model results are counterintuitive for some scenario analyses

EAG consider model needs further investigation to determine cause for counter-intuitive results

Background

- Company submission states that internal, face, and external validation of model was undertaken

EAG comments

- Model produces counterintuitive results that do not align with health economic expectations
  - Increasing disease burden worsens the ICER for sebetralstat vs SoC in the following scenarios:
    - reducing proportion of people having LTP therapies (base case: 45% LTP + on demand treatment)
    - increasing annual attack rate (base case:14.7 per year)
- EAG conducted additional analyses to explore this outcome by simplifying cost assumptions
  - incremental costs rise faster than QALYs as disease burden rises → increases ICER
  - underlying structural/computational cause could not be identified within available time
  - consider that further investigation is needed to strengthen confidence in model outcomes

Company response to clarification

- On impact of changing % LTP on cost-effectiveness results: the total average cost per attack is inflated by the proportion of patients using additional doses and rescue therapy

Is the company's model appropriate for decision making?

Abbreviations: ICER, incremental cost-effectiveness ratio; LTP, long term prophylaxis; SoC, standard of care; QALYs, quality-adjusted life years

Differences in company and EAG base case assumptions

Assumption	Company base case (post clarification)	EAG base case
Price of icatibant	BNF (list price £837*)	eMIT (£172.32* - in line with NICE process for the preferred order of prices for modelled treatments)
Life tables (for mortality)	Based on data from 2021-2023	Based on data from 2016-2018 (before COVID-19)
Proportion of rescue medication in people using icatibant	12.70% (Longhurst et al 2018)	9.78% (weighted average of the reported rates from LTP + on demand and on demand only groups from Aberer et al 2017**)
HCP time for icatibant administration	1 hour	20 minutes (in line with clinical expert opinion)
Definition of comparator	SoC basket of treatments	Fully incremental analysis

EAG preferred assumptions using eMIT price for icatibant and a full incremental analysis have a significant impact on the ICER

*Most recent price at the time of submission

**To align with approach used in company base case for % additional dosing in people using icatibant

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; HCP, healthcare professional; ICER, incremental cost-effectiveness ratio; LTP, long term prophylaxis; SoC, standard of care

Cost-effectiveness results (1)

As confidential discounts are available for treatments in the pathway, ICERs will be presented in Part 2 slides

ICER ranges (including confidential discounts) presented below to aid transparency

Company and EAG agree that no additional QALY weighting for severity should be applied

- Company base case results:
  - Sebetralstat vs SoC basket → ICER significantly above £30,000/QALY gained
- EAG base case results:
  - Sebetralstat vs icatibant (fully incremental analysis results in other comparators being dominated) → ICER significantly higher than company base case results

Note: model is highly sensitive to price of sebetralstat and comparator treatments

Impact of EAG scenarios applied to company base case presented on next slide (include eMIT price for icatibant and confidential comparator prices)

No additional scenarios using EAG base case presented in Part 2

Abbreviations: eMIT, electronic market information tool; ICER, incremental cost-effectiveness ratio; SoC, standard of care; QALY, quality-adjusted life year

Cost-effectiveness results (2)

EAG scenarios using company base case presented in Part 2:	Impact on ICER
Proportion having rescue therapy on icatibant: 9.78% (from 12.70%)	**Small ↑**
Proportion having rescue therapy on sebetralstat: 8.10% (from 5.25%)	**Small ↑**
Proportion having additional dosing on sebetralstat: 24.10% (from 22.25%)	**Small ↑**
Assuming 5% usage of sebetralstat as rescue therapy	**Small ↓**
HCP assisted administration time for icatibant: 10 or 20 minutes (from 1 hour)	**Small ↑**
HCP assisted administration time for IV treatments: 30 minutes (from 1 hour)	**Small ↑**
No wastage for IV treatments (from 0.2 increments)	**Small ↑**
Proportion having LTP + on demand treatment : a) 50% or b) 70% (from 45%)	**a) Small ↓ b) Moderate ↓**
TTA for icatibant treatment: a) 3 hours or b) 0.8 hours (from 2.9 hours)	**a) Small ↓ b) Moderate ↑**
No rescue therapy (all treatments)	**Moderate ↑**
TTA for IV treatment: a) 5 hours or b) 1 hour (from 3.8 hours)	**a) Moderate ↓ b) Large ↑**
Treatment-related utility values from the general population	**Large ↓**
Annual attack rate: a) 11.0 or b) 5.49 (from 14.71)	**a) Large ↓ b) Very large ↓**
No additional dosing (all treatments)	**Very large ↓**
Alternative market share data for comparators in SoC basket	**Very large ↑**
Full vial wastage for IV treatments (from 0.2 increments)	**Very large ↓**

Abbreviations: HCP, healthcare professional; ICER, incremental cost-effectiveness ratio; IV, intravenous; LTP, long term prophylaxis; SoC, standard of care; TTA, time to treatment administration

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

NICE National Institute for Health and Care Excellence

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Company submission does not include managed access proposal for sebetralstat

- KONFIDENT-S OLE is ongoing (recruitment is complete)

Abbreviations: OLE, open-label extension

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Key issues

Key issue	ICER impact	Slide(s)
• Uncertainty whether HAE-nC1-INH subtype is included in decision problem	Unknown	10
• Lack of adjustment in the MAIC analysis	None, not modelled	15
• Definition of comparators	Large	22-23
○ Proportion having treatments in the model	Large	24-25
○ Lack of comparative clinical data	Unknown	19
○ Model results are counterintuitive for some scenario analyses	Unknown	26

Abbreviations: HAE-nC1-INH, hereditary angioedema with normal C1-esterase inhibitor; ICER; incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparisons

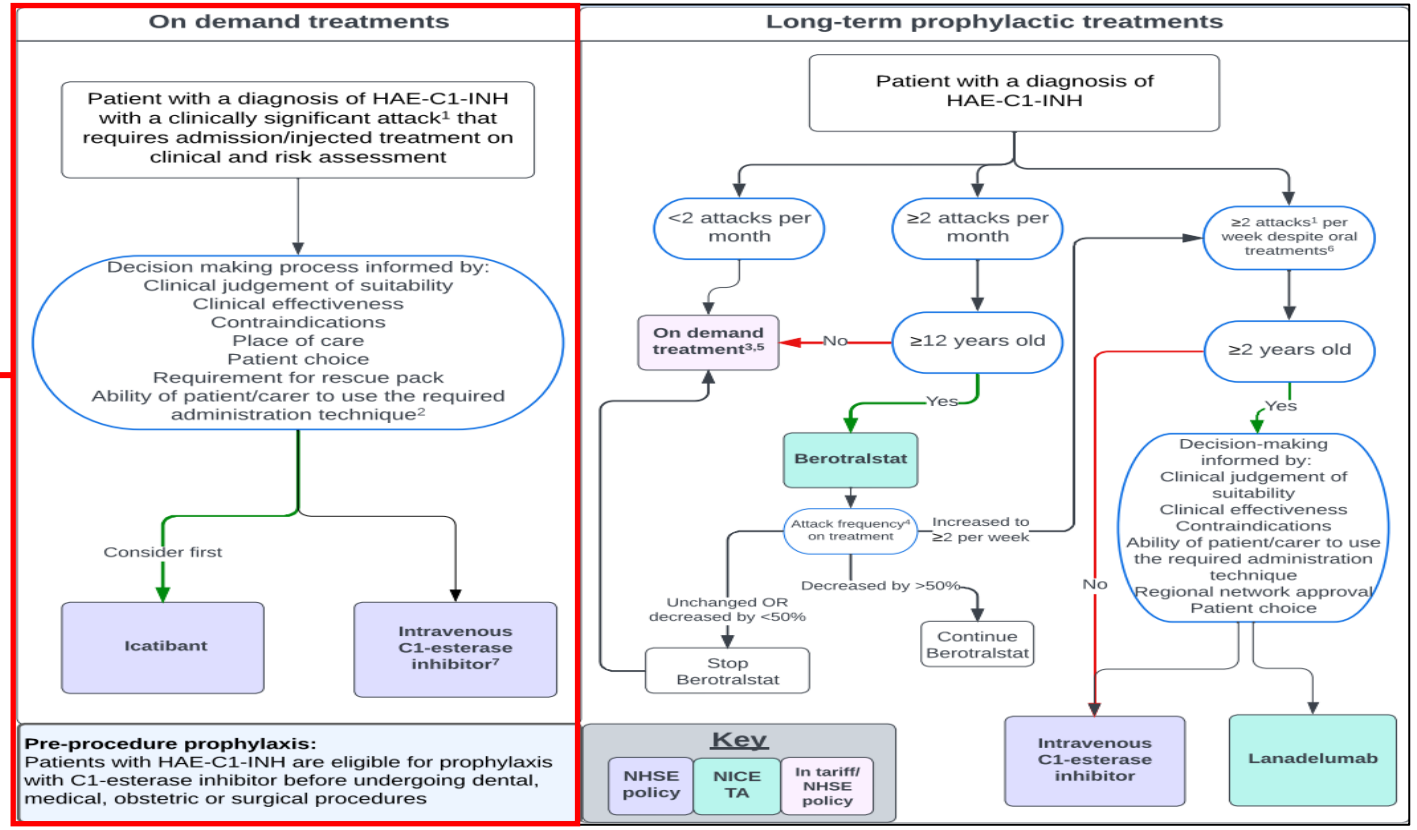
Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over [ID6284]

Supplementary appendix

NICE National Institute for Health and Care Excellence

NHSE clinical commissioning algorithm for HAE secondary to C1-esterase inhibitor deficiency

Treatment of acute attacks relevant to this appraisal



* Link back to slide on treatment pathway

Source: hereditary-amd-acquired-angioedema-algorithms.pdf

[1] The lanadelumab TA refers to clinically significant attacks as defined by i) potentially life threatening because it affects the head or neck or ii) causes pain or disability such that the patient cannot continue their normal activities. Frequency should be calculated over a period of at least 56 days.
[2] This includes securing venous access for C1-esterase inhibitors, and ability to reconstitute doses from multiple vials.
[3] Some adult patients are treated with androgens as oral prophylactic treatment. However, evidence is limited and accessing treatment is difficult so this is not recommended as first line for patients newly starting on prophylaxis. Where existing patients are established on androgen therapy, this may continue if considered clinically appropriate; if established patients do cease treatment with androgen therapy then review the need for any prophylaxis. An individualised assessment to withdrawal of androgens and commencing new prophylaxis should be taken. If a historical attack frequency is documented, it can be used as the basis for selecting other prophylaxis treatment options.
[4] Berotralstat should be stopped if, after 3 months of treatment, attack frequency has not reduced by at least 50% compared to baseline.
[5] Some patients, including children under 12, are treated with tranexamic acid however evidence is limited.
[6] Patients who are unable to tolerate oral medications are also eligible for lanadelumab/intravenous C1-esterase inhibitor.
[7] In appropriate cases and where available, licensed recombinant products should be considered in preference to plasma-derived products in the treatment of acute attacks.

Abbreviations: HAE; hereditary angioedema; C1-INH, C1-esterase inhibitor; NHSE, NHS England; TA, technology appraisal

Decision problem (1)

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	People 12 years and over with HAE having an acute attack	Same as scope	Population addressed in company submission is aligned with final scope but • evidence is only presented for Type I or II HAE • unclear if third subtype (HAE-nC1-INH) is included in decision problem
Intervention	Sebetralstat	Same as scope	Dose for sebetralstat is 300 mg to 600 mg as required, as opposed to 300 mg or 600 mg in key trials • incorporated as a dose of 300 mg in CEA, with an additional dose as required

* Link back to slide on key issue

Abbreviations: CEA, cost-effectiveness analysis; HAE, hereditary angioedema; HAE-nC1-INH, hereditary angioedema with normal C1-esterase inhibitor

Decision problem (2)

	Final scope	Company	EAG comments
Comparators	Established clinical management for the treatment of acute attacks which may include: • C1-esterase inhibitors (Cinryze, Berinert and Ruconest) • icatibant	Same as scope • implemented as a basket of comparators (SoC) with percentages determined by market share in CEA	Sebetralstat should be compared separately with each comparator in a full incremental analysis
Outcomes	• Severity of attacks • Duration of attacks • Time to beginning of symptom relief • Reduction in symptoms of attacks • Mortality • Use of rescue medication • Frequency and duration of hospitalisation • Adverse effects of treatment • HRQoL (patients and carers)	Same as scope	No comments

* Link back to slide on key issue

Abbreviations: CEA, cost-effectiveness analysis; HRQoL, health-related quality of life; SoC, standard of care

Other clinical trial evidence presented in company submission

KONFIDENT-S OLE trial

- **Design:** ongoing multicentre open-label (assessing long-term safety and efficacy of sebetralstat)
- **Population:** people ≥12 years with HAE Type I or II (n=≤150 enrolled):
  - roll-over participants from KONFIDENT
  - non-rollover participants [phase 2 study (see below) and people who are sebetralstat naive]
- **Intervention**: sebetralstat 600 mg
  - dose switched to 300 mg in January 2025 (KONFIDENT results indicated dose equivalence)
- **Treatment period:** 0-24 months
- **Location:** 23 countries, n=8 UK (n=7 still ongoing)
- **Interim analysis data cut** (September 2024): ([redacted] attacks treated with sebetralstat)
  - safety profile and effectiveness* of sebetralstat appears consistent with results from KONFIDENT

- Company also presented evidence from a phase 2 trial comparing sebetralstat (600mg) vs placebo in adults with HAE Type I or II (part 1: open-label, part 2: randomised, double-blind, 2 period cross-over)
  - trial not included in model as phase 3 data is available from KONFIDENT

*times to beginning of symptom relief, reduction in attack severity and attack resolution

Abbreviations: HAE, hereditary angioedema; OLE, open-label extension

KONFIDENT other key results (1)

Key secondary outcome: time to reduction in the severity of attack within 12 hours of administration of sebetralstat or placebo* (full analysis set)**

	Sebetralstat 300 mg (Number of attacks = 87)	Placebo (Number of attacks = 84)
Events (reduction in severity)	44 (50.6%)	26 (31.0%)
Censored	43 (49.4%)	58 (69.0%)
Censored at hour 0 due to underivable end point†	6 (6.9%)	7 (8.3)
Adjusted P value compared with placebo	0.004	
Median time in hours (IQR)	9.27 (1.53 to >12)	>12 (6.23 to >12)

*Defined as an improved rating from baseline in Patient Global Impression of Severity scale (PGI-S) for 2 or more consecutive time point. 5-point PGI-S scale ratings range from “none” to “very severe”

**N=110 received at least 1 dose of double-blind treatment

†Underivable end point because of missing data → analyses assumed data was missing at random

Link back to slide on primary endpoint results

Abbreviations: IQR, interquartile range; PGI-S, Patient Global Impression of Severity

KONFIDENT other key results (2)

Key secondary outcome: time to attack resolution within 24 hours of administration of sebetralstat or placebo* (full analysis set)**

	Sebetralstat 300 mg (Number of attacks = 87)	Placebo (Number of attacks = 84)
Events (attack resolution)	37 (42.5%)	23 (27.4%)
Censored	50 (57.5%)	61 (72.6%)
Censored at hour 0 due to underivable end point†	3 (3.4%)	3 (3.6%)
Adjusted P value compared with placebo	0.002	
Median time in hours (IQR)	>24 (8.58 to >24)	>24 (22.78 to >24)

*Defined as a Patient Global Impression of Severity scale (PGI-S) rating of "none". 5-point PGI-S scale ratings range from "none" to "very severe"

**N=110 received at least 1 dose of double-blind treatment

†Underivable end point because of missing data → analyses assumed data was missing at random

Adverse events

- Safety profile for sebetralstat (both doses) was similar to placebo, with no on-treatment serious adverse events or deaths reported in the trial

* Link back to slide on primary endpoint results

NICE

Abbreviations: IQR, interquartile range; PGI-S, Patient Global Impression of Severity

ITC results (1) - NMA: time to beginning of symptom relief

Time to beginning of symptom relief as per (A) fixed effects and (B) random effects (sensitivity analysis) models

(A)	Model	Comparison	Stratification	PGI-C/TEQ-based time to symptom relief	HR (95% CrI)
	FE NMA	Sebetralstat 300 mg vs rhC1INH 50 IU/kg	MA for region		0.96 (0.42 to 2.15)
			MA for sex		1.19 (0.58 to 2.45)

(B)	Model	Comparison	Stratification	PGI-C/TEQ-based time to symptom relief	HR (95% CrI)
	RE NMA	Sebetralstat 300 mg vs rhC1INH 50 IU/kg	MA for region		0.95 (0.21 to 4.30)
			MA for sex		1.19 (0.30 to 4.81)

Fixed-effects model was considered appropriate as the main analysis

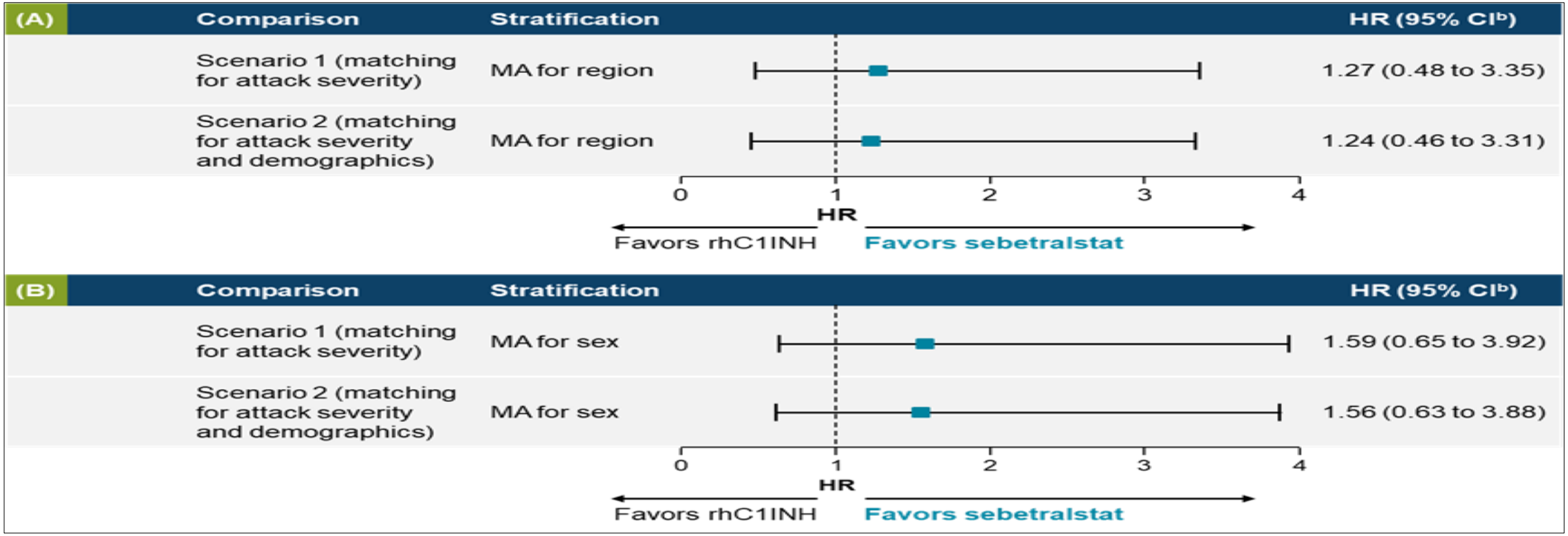
* Link back to slide on ITC

NICE

Abbreviations: CrI, credible interval; FE, fixed effects; HR, hazard ratio; ITC, indirect treatment comparison; MA, meta-analysis; NMA, network meta-analysis; PGI-C, Patient Global Impression of Change; RE, random effects; rhC1-INH, recombinant human C1 esterase inhibitor; TEQ, treatment effect questionnaire

ITC results (2) - MAICs: time to beginning of symptom relief

Time to beginning of symptom relief matched for baseline attack severity only (scenario 1) and baseline attack severity, age, sex and race (scenario 2) stratified by A) region and B) sex



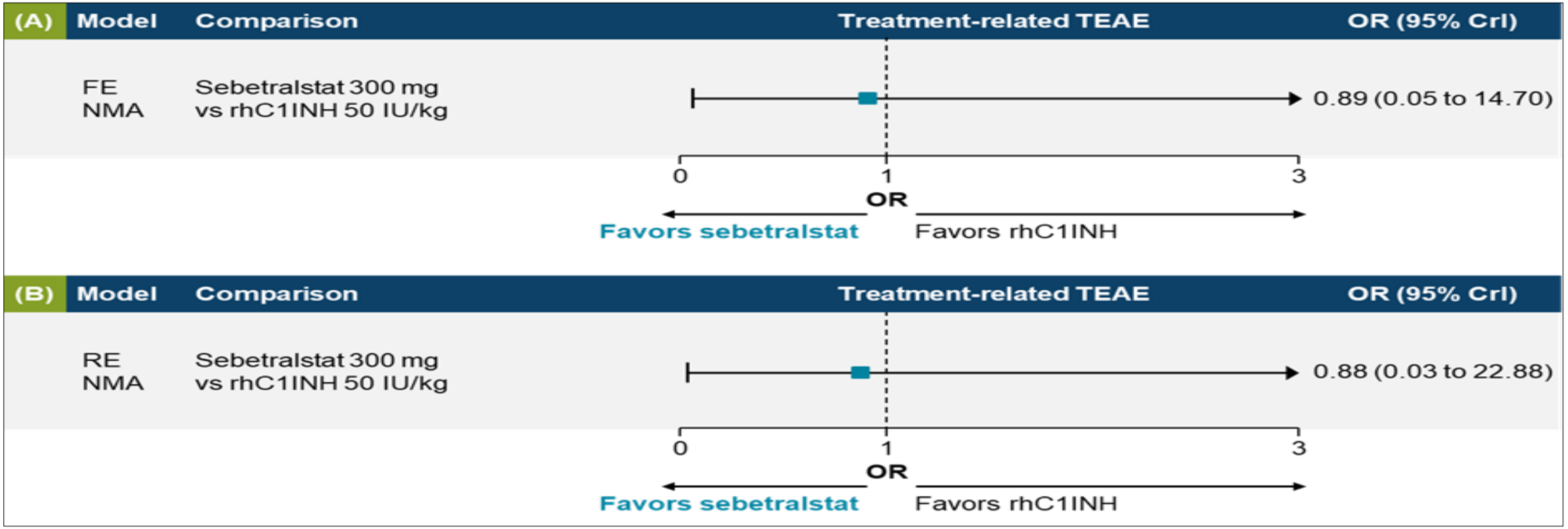
Baseline attack severity = maximum of 3 baseline overall severity VAS scores

* Link back to slide on ITC

Abbreviations: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; MA, meta-analysis; MAIC, matching-adjusted indirect comparison; rhC1-INH, recombinant human C1 esterase inhibitor

ITC results (3) - NMA: treatment-related adverse events

Treatment-related adverse events per (A) fixed effects and (B) random effects (sensitivity analysis) models



Fixed-effects model was considered appropriate as the main analysis

* Link back to main slide on ITC

NICE

Abbreviations: CrI, credible interval; FE, fixed effects; ITC; indirect treatment comparison; OR, odds ratio; NMA, network meta-analysis; RE, random effects; rhC1-INH, recombinant human C1 esterase inhibitor; TRAE; treatment-related adverse event

No ICER impact (MAIC not included in model)

Key issues: Lack of adjustment in the MAIC analysis

Company response to clarification:

- Assessed list of potential prognostic factors from ITC of HAE prophylactic treatments (Watt et at 2024) and data availability in KONFIDENT

Potential prognostic factors, confounders and/or treatment effect modifiers	Watt et al (2024)	Available in KONFIDENT	Used for matching in MAICs
Disease severity	x	x	x
Demographics (age, sex, race only)	x	x	x
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, alcohol consumption	x		

* Link back to main slide on key issue

Abbreviations: HAE, hereditary angioedema; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparisons

Attack related inputs used in economic model

HAE attack-related input parameters used in the economic model

Parameter definition	Mean value
Duration of HAE attack (hours)	96
TTA sebetralstat (minutes)	[redacted]
TTA icatibant SC (minutes)	174
TTA ruconest IV (minutes)	228
TTA berinert IV (minutes)	228
TTA cinryze IV (minutes)	228
Attack location – neck and above (%)	13.74
Attack location – abdominal (%)	40.08
Attack location – other (%)	46.18
Attack severity – severe (%)	16.47
Attack severity – moderate (%)	41.18
Attack severity – mild (%)	42.35

- EAG scenarios using lower and upper bounds for TTA:
  - SC treatment = 48 minutes and 120 minutes
  - IV treatment = 60 minutes and 300 minutes

Base case adjusted TTAR (hours) by treatment and attack location (company calculation)

	Neck and Above	Abdominal	Other
Sebetralstat	[redacted]	[redacted]	[redacted]
Icatibant	[redacted]	[redacted]	[redacted]
Ruconest, Berinert and Cinryze	[redacted]	[redacted]	[redacted]

* Link back to secondary key issue

Abbreviations: HAE, hereditary angioedema; IV; intravenous; SC, subcutaneous; TTA, time to treatment administration; TTAR; time to attack resolution

Utilities used in company 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

* Link back to main slide on Utilities

Abbreviations: CI, confidence interval; HCP, healthcare professional; SE, standard error