# Clinical trials conformity with AURORA COS: a systematic literature review

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## Introduction and objective

- Hereditary angioedema (HAE) is a genetic disorder in which reduced activity of C1INH results in dysregulated production of bradykinin and activation of bradykinin B2 receptor, leading to recurrent and usually painful subcutaneous and submucosal swelling affecting various body parts.[1, 2] Treatment of HAE aims to:
  - Treat all attacks as early as possible via on-demand treatment (ODT);
  - Achieve complete control of the disease and normalise lives of people with HAE via long-term prophylaxis (LTP).[2]
- A systematic literature review (SLR) was conducted with the overarching aim to identify evidence of the clinical efficacy and safety of deucrictibant and comparators, for both the ODT and LTP of HAE attacks.
- The findings of this SLR were then utilised to review conformity of ODT randomised controlled trials (RCTs) to the recently developed Core Outcome Set (COS) for treatment of HAE attacks, an output from Project AURORA.[3]
- The objective of this analysis was to assess conformity of existing phase 3 trials of ODT for HAE with the new AURORA COS (**Table 1**).

**Table 1: AURORA COS in brief (Adapted from Petersen *et al.* 2024)[3]**

| | |
|---|---|
| **COS #1** | Change in overall symptom severity at one predetermined point between 15 minutes and 4 hours after treatment |
| **COS #2** | Time to end of progression |
| **COS #3** | Need for rescue medication during an entire attack |
| **COS #4** | Impairment of daily activities |
| **COS #5** | Treatment satisfaction |

## Methods

- An SLR was performed to identify evidence of clinical efficacy and safety of both ODT and LTP for HAE (PROSPERO: CRD42023470082). Searches conducted in October 2023, included electronic databases, conference proceedings, and key regulatory and HTA websites.
- Screening was performed by two researchers, against a pre-defined PICOS (**Table 2**).

**Table 2: Summary of PICOS (Population, Interventions, Comparators, Outcomes, Study design)**

| Criterion | Inclusion |
|---|---|
| **Population** | HAE type 1 or type 2, participants aged ≥12 years eligible for ODT and/or LTP |
| **Interventions** | **ODT**:<br>• Deucrictibant IR capsule<br>• Ecallantide<br>• Icatibant<br>• pdC1INH<br>• rhC1INH<br>• Sebetralstat<br>**LTP**:<br>• Deucrictibant<br>• Androgens<br>• Anti-fibrinolytics<br>• Berotralstat<br>• Donidalorsen<br>• Garadacimab<br>• Lanadelumab<br>• pdC1INH<br>• rhC1INH<br>• STAR-0215 |
| **Comparators** | Trials with any comparators, including placebo, or trials with no comparator (single arm) |
| **Outcomes** | **Efficacy ODT:** Outcomes related to attack symptoms, use of ODT (re-dosing/rescue)<br>**Efficacy LTP:** Outcomes related to number of attacks/rate of attacks, attack-free status, severity of attacks, use of ODT/rescue<br>**Safety and tolerability:** TEAEs, serious TEAEs, AEs leading to discontinuation/dose reduction, TRAEs, serious TRAEs, deaths<br>**Health related quality of life:** Any generic or disease-specific measure |
| **Study Design** | RCTs, non-RCTs, open-label extensions, non-interventional studies (prospective and retrospective) |
| **Limits** | No language limits. No date limits except for conference proceedings which are included 2021-2023, only. |

*Grey text denotes PICOS criteria related to LTP only.*

## Results

- In total, 34 interventional studies, 25 RCTs and 9 non-RCTs were identified as meeting the PICOS. In the ODT indication, phase 3 RCT evidence was identified for all seven interventions of interest, therefore only phase 3 RCT evidence was taken forward to data synthesis. The characteristics of the eleven phase 3 ODT RCTs are summarised in (**Table 3**).
- Since the conduct of the SLR, the KONFIDENT phase 3 RCT of sebetralstat has reported primary results,[4] and the RAPIDe-3 phase 3 RCT of deucrictibant IR capsule has commenced.[5]
- The trials were designed heterogeneously, with variable treatment strategy (only RAPIDe-3 and KONFIDENT have a crossover design), routes of administration and outcomes.

**Table 3: Characteristics of phase 3 ODT RCTs**

| Intervention | Trial name and ID | | N pts | N attacks | Comparator | Administration | Commenced [a] | Primary outcome |
|---|---|---|---|---|---|---|---|---|
| **Deucrictibant IR capsule** | **RAPIDe-3**[5] | (NCT04618211) | Target 120 | Target 240 | Placebo | Oral; self-admin | Feb 2024 | Time to onset of symptom relief (PGI-C rating of at least "a little better" for 2 consecutive timepoints within 12 hours post-treatment) |
| **Ecallantide** | **EDEMA 3**[6] | (NCT00262080) | 72 | 72 | Placebo | SC; study site | Dec 2005 | TOS at 4 hours post-treatment |
| | **EDEMA 4**[7] | (NCT00457015) | 96 | 96 | Placebo | SC; study site | Apr 2005 | Change in MSCS score at 4 hours post-treatment |
| **Icatibant** | **FAST-1**[8] | (NCT00097695) | 56 | 56 | Placebo | SC; study site | Dec 2004 | Time to clinically significant relief of the index symptom (≥30% decrease in severity, sustained for ≥3 consecutive measurements on the VAS) |
| | **FAST-2**[8] | (NCT00500656) | 74 | 74 | Tranexamic acid | SC/oral; [b] study site | Mar 2005 | Time to clinically significant relief of the index symptom (≥30% decrease in severity, sustained for ≥3 consecutive measurements on the VAS) |
| | **FAST-3**[9] | (NCT00912093) | 93 | 93 | Placebo | SC; study site | Jul 2009 | Subject-assessed time to 50% reduction in symptom severity by VAS-3 (cutaneous/abdominal attacks) |
| **pdC1INH (Berinert®)** | **IMPACT 1**[10] | (NCT00168103) | 126 | 126 | Placebo | IV; study site | Jun 2005 | Time to onset of symptom relief determined by the patient's responses to a standard question posed at intervals to 24 hours after treatment |
| **pdC1INH (Cinryze®)** | **CHANGE A**[11] | (NCT00289211) | 68 | 68 | Placebo | IV; study site | Mar 2005 | Time to unequivocal relief of symptoms at the defining site (first of 3 consecutive reports) |
| **rhC1NH** | **C1 1205-01**[12] | (NCT00225147) | 38 | 38 | Placebo | IV; study site | Jul 2005 | Time to the beginning of relief of symptoms (VAS score at any eligible location had decreased by >20 mm for 2 consecutive VAS recordings) |
| | **C1 1304-01**[12] | (NCT00262301) | 32 | 32 | Placebo | IV; study site | Jun 2004 | Time to the beginning of relief of symptoms (VAS score at any eligible location had decreased by >20 mm for 2 consecutive VAS recordings) |
| **Sebetralstat** | **KONFIDENT**[4] | (NCT05259917) | 110 | 264 | Placebo | Oral; self admin | Feb 2022 | Time to beginning of symptom relief (PGI-C rating of at least "a little better" for 2 consecutive timepoints within 12 hours post-treatment) |

*a = Commencement dates correct to protocols on clinicaltrials.gov (Study Start [Actual]), accessed 1st August 2024. b = double-dummy design due to SC icatibant administration and oral tranexamic acid administration.*

## Heterogeneity amongst outcomes and conformity of phase 3 RCT endpoints to the AURORA COS

- There is considerable heterogeneity amongst the type and definitions of outcomes reported across the RCTs of ODT for HAE, which presents challenges when comparing treatments.[13]
- This heterogeneity in outcomes has been well reported and is hypothesised to be caused at least in part by the difficulty in developing a unique uniform outcome measure that captures the heterogeneity in location, severity, symptoms, and temporal patterns of HAE attacks.[14]
- In addition, outcomes are also largely patient-reported since an objective judgment of HAE attack symptoms such as swelling, pain, discomfort, and subsequent relief by clinicians/investigators is difficult to assert, therefore burden on participants for collection of outcome measurements is high.
- Project AURORA marked a significant step towards harmonising HAE ODT clinical trial outcomes through development of a COS (**Table 1**), recommended for use across ODT studies by a panel of Experts in the management and care of HAE.[3]
- Outcomes reported from the ODT RCTs identified in the SLR were assessed for conformity to the AURORA COS.

### Conformity of phase 3 ODT RCT endpoints to the AURORA COS:

- No completed phase 3 RCT of ODT for HAE attacks conformed with all five COS outcomes (**Table 4**).
- Greatest conformity was observed in change in overall symptom severity at one predetermined timepoint (15min-4hrs post-treatment). Eight of the ten completed RCTs reported outcomes via pre-specified or post-hoc analyses.
- Use of rescue medication (COS #3) was reported in five of ten completed trials.
- No completed phase 3 trial conformed to time to end of progression (COS #2), impairment of daily activities (COS #4), or treatment satisfaction outcomes (COS #5).
- Pre-specified outcomes of KONFIDENT conformed only to COS #1; however post-hoc analyses report use of rescue medication, conforming to COS #3, with the potential for further post-hoc analyses to result in greater conformity.
- Pre-specified outcomes of RAPIDe-3 conform to the full COS.

**Table 4: Conformity to the AURORA COS amongst phase 3 ODT RCTs**

| Intervention | Trial name | COS #1 | COS #2 | COS #3 | COS #4 | COS #5 |
|---|---|---|---|---|---|---|
| **Deucrictibant IR capsule** | RAPIDe-3 | ✓ | ✓ | ✓ | ✓ a | ✓ a |
| **Ecallantide** | EDEMA 3 | ✓ | ✗ | ✓ | ✗ | ✗ |
| | EDEMA 4 | ✓ | ✗ | ✗ | ✗ | ✗ |
| **Icatibant** | FAST-1 | ✓ | ✗ | ✓ | ✗ | ✗ |
| | FAST-2 | ✓ | ✗ | ✓ | ✗ | ✗ |
| | FAST-3 | ✓ | ✗ | ✓ | ✗ | ✗ |
| **pdC1INH (Berinert®)** | IMPACT 1 | ✗ | ✗ | ✗ | ✗ | ✗ |
| **pdC1INH (Cinryze®)** | CHANGE A | ✗ | ✗ | ✗ | ✗ | ✗ |
| **rhC1INH** | C1 1205-01 | ✓ | ✗ | ✗ | ✗ | ✗ |
| | C1 1304-01 | ✓ | ✗ | ✗ | ✗ | ✗ |
| **Sebetralstat** | KONFIDENT b | ✓ | ✗ | ✓ | ✗ | ✗ |

✓ Reported pre-specified outcome ✓ Yet to report pre-specified outcome ✓ Reported post-hoc analysis ✗ Not reported to date

*[a] Assessed via qualitative interviews; [b] Primary publication, reported post-SLR*

## Discussion

- Currently reported HAE ODT RCTs have heterogeneous outcomes and variable conformity to the AURORA COS based on pre-specified outcomes and results of post-hoc analyses presented up until June 2024, making comparability of interventions problematic.
- The design of the RAPIDe-3 RCT of deucrictibant IR capsule was contemporaneous to COS publication and includes five pre-specified conforming outcomes.
- The phase 3 RAPIDe-3 and KONFIDENT RCTs have the potential to fully conform with the COS via pre-specified and post-hoc analyses.
- While consistency is observed between some trials according to the COS conformity, it remains necessary to further advance understanding of the relationship between the different instruments used to define ODT endpoints, which affect the feasibility of incorporating data in indirect treatment comparisons.

## Conclusions

- **ODT study design and outcome definitions are heterogenous, presenting challenges when comparing interventions.**
- **Going forward, inclusion of the AURORA COS in ODT trials is recommended to support future indirect comparisons among interventions by patients, clinicians, and health authorities.**
- **The AURORA COS marks an important step forward in efforts to homogenise the outcome landscape in ODT trials.**
- **Further consensus recommendations on optimal measures and assessment criteria for each outcome of the COS would further support compatibility between interventions and facilitate appropriate statistical methods to perform indirect comparisons in the absence of head-to-head ODT trials.**

**Abbreviations**: AE, adverse event; C1INH, C1 inhibitor; COS, core outcome set; HAE, hereditary angioedema; HTA, Health Technology Assessment; IV, intravenous; IR, immediate release; LTP, long term prophylaxis; MSCS, Mean Symptom Complex Severity; NICE, National Institute for Health and Care Excellence; ODT, on demand treatment; PGI-C, Patient Global Impression of Change; Pts, participants; PICOS, Population, Interventions, Comparators, Outcomes, Study design; RCT, randomised controlled trial; SC, subcutaneous; SLR, systematic literature review; TEAE, treatment emergent adverse event; TOS, Treatment Outcome Score; TRAE, treatment-related adverse event; VAS, visual analog scale.

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**COI**: **R.S.P:** has received speaking fees from Pharvaris and Astria Therapeutics; **G.G:** employee of Pharvaris, holds stocks in Pharvaris; **U.K:** employee of Pharvaris, holds stocks in Pharvaris; **J.M:** employee of Pharvaris, holds stocks in Pharvaris; **C.W:** vendor working under the instruction and funding of Pharvaris; **E.P:** vendor working under the instruction and funding of Pharvaris; **C.C:** vendor working under the instruction and funding of Pharvaris; **D.M.C:** received speaking fees and/or consultancy fees and/or research funding from: Astria, BioCryst, CSL Behring, Intellia, Ionis Pharmaceuticals, KalVista, Pharvaris and Takeda. **J.M:** employee of Pharvaris, holds stocks in Pharvaris.