# Deucrictibant vs Standard of Care in Hereditary Angioedema: A Propensity Score-Matched Analysis

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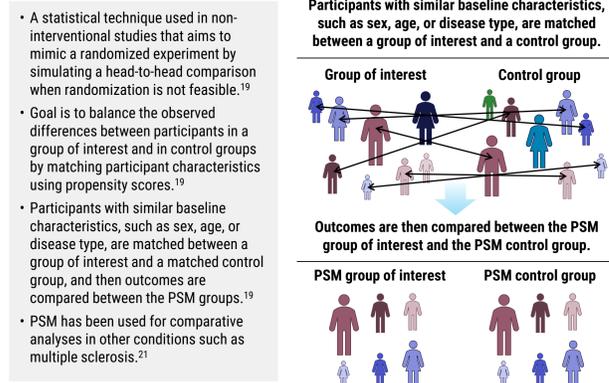
## Rationale

- Current standard-of-care (SOC) on-demand treatment (ODT) options for hereditary angioedema (HAE) attacks are administered by injection,[1-5] which presents a burden for people with HAE and leads to treatment of attacks often being delayed or forgone.[6-10]
- An unmet need exists for oral ODT options that are effective and well tolerated and that may reduce the treatment burden by enabling prompt, discreet administration.[10]
- Deucrictibant is an orally administered, highly potent, specific antagonist of the bradykinin B2 receptor under development for prophylactic and on-demand treatment of HAE attacks.[11-18]
- To date, clinical trials comparing deucrictibant immediate-release (IR) capsule for ODT of HAE attacks with SOC have not been conducted.

## Materials and Methods

- A propensity score matching (PSM) method[19] (**Figure 1**) was used to compare clinical outcomes between the cohort from RAPIDe-2,[13] a clinical study treating HAE attacks with deucrictibant IR capsule, and a cohort from a mixed-methods observational real-world study treating HAE attacks with SOC.[20]

### Figure 1. Overview of PSM



- A statistical technique used in non-interventional studies that aims to mimic a randomized experiment by simulating a head-to-head comparison when randomization is not feasible.[19]
- Goal is to balance the observed differences between participants in a group of interest and in control groups by matching participant characteristics using propensity scores.[19]
- Participants with similar baseline characteristics, such as sex, age, or disease type, are matched between a group of interest and a matched control group, and then outcomes are compared between the PSM groups.[19]
- PSM has been used for comparative analyses in other conditions such as multiple sclerosis.[21]

PSM, propensity score matching.

- Data sources (**Table 1**)
  - RAPIDe-2 (NCT05396105) study[13]* of deucrictibant IR capsule for treatment of HAE attacks.
    - An ongoing Phase 2/3 open-label extension study.
    - Evaluating outcomes of long-term use of deucrictibant IR capsule for treatment of HAE attacks.
    - For further information, please see the oral presentation **Long-Term Safety and Efficacy of Oral Deucrictibant for Prophylactic and On-Demand Treatment of Hereditary Angioedema Attacks: Results of the Ongoing CHAPTER-1 and RAPIDe-2 Extension Trials** by Valerieva A et al at this conference.
- Observational mixed-methods study[20] of SOC (e.g., icatibant, C1 inhibitor) for treatment of HAE attacks.
  - Evaluated patient-reported outcome (PRO) assessments to be used in ODT clinical trials of deucrictibant IR capsule.
  - Clinical outcomes among people with HAE who treated their attacks with SOC were also assessed.
- During an HAE attack, participants in both studies completed 3 PRO assessments: the Patient Global Impression of Change (PGI-C), the Patient Global Impression of Severity (PGI-S), and the Angioedema syMptom Rating scAle (AMRA) (**Figure 2**).
- In both studies, PRO assessments were completed at pre-treatment and every hour up to 4 hours following treatment administration and then at 8, 12, 24, and 48 hours.
- PSM analysis endpoints were time to PGI-C "A little better" or "Better", time to ≥1-level improvement in PGI-S, and time to PGI-S "None" (**Table 1**).
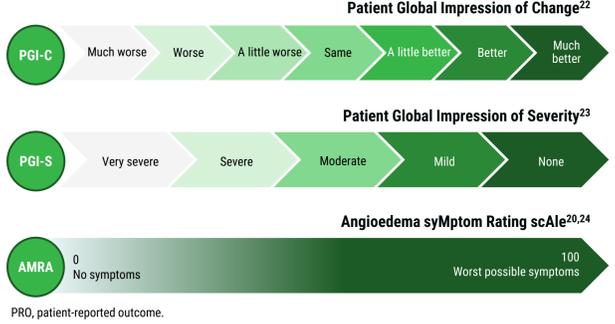
### Table 1. Data sources and study parameters for PSM

| | RAPIDe-2 study[13] | Mixed-methods study[20] |
|---|---|---|
| **Study type** | Clinical study | Observational study |
| **Dates of data collection** | 28 December 2022 to 1 March 2024 | 20 November 2022 to 17 April 2023 |
| **HAE attack treatment** | Deucrictibant IR capsule 10 mg, 20 mg, or 30 mg | Standard of care (e.g., icatibant, C1 inhibitor) |
| **Key inclusion criteria** | Participants ≥18 years of age with HAE type 1 or 2 | Participants ≥16 years of age with HAE type 1 or 2 |
| **Study endpoints/objectives** | **Primary endpoint** • Safety, including TEAEs, clinical laboratory tests, vital signs, and ECG findings. **Secondary endpoints** • **Time to onset of symptom relief:** PGI-C of at least "A little better" for 2 consecutive timepoints post-treatment OR at the last scheduled timepoint (48 hours) provided no rescue medication was used within 12 hours after the last timepoint. • **Time to reduction in attack severity:** PGI-S reduction of ≥1 level from pre-treatment for 2 consecutive timepoints OR at the last scheduled timepoint (48 hours) provided no rescue medication was used within 12 hours after the last timepoint. • **The proportion of attacks achieving symptom resolution:** Post-treatment PGI-S rating of "None".| **Main objectives** • To explore the relationship and correlation between results collected from the PRO assessments. • To generate evidence related to the key symptoms experienced by patients during an HAE attack to support the content validity of the included PRO instruments. • To perform cognitive debriefing of the included PRO instruments to confirm patient understanding and interpretation. • To obtain insight into patient-perceived clinically meaningful change in HAE attack symptoms. |
| **PRO assessments** | PGI-C, PGI-S, and AMRA | |
| **PSM analysis endpoints** | Time to symptom relief and resolution as indicated by the following: PGI-C "A little better" or "Better"  PGI-S ≥1-level improvement  PGI-S "None" | |

AMRA, Angioedema syMptom Rating scAle; ECG, electrocardiogram; HAE, hereditary angioedema; IR, immediate-release; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcome; PSM, propensity score matching; TEAEs, treatment-emergent adverse events.

## Materials and Methods (contd.)

### Figure 2. PRO assessments



**Patient Global Impression of Change[22]**

PGI-C: Much worse — Worse — A little worse — Same — A little better — Better — Much better

**Patient Global Impression of Severity[23]**

PGI-S: Very severe — Severe — Moderate — Mild — None

**Angioedema syMptom Rating scAle[20,24]**

AMRA: 0 No symptoms — 100 Worst possible symptoms

PRO, patient-reported outcome.

- PSM analysis parameters are reported in **Table 2**.
  - Time to administration was not available for all participants in the mixed-methods study and was therefore not included as a parameter for the matching.
  - However, for an attack to qualify for study medication in RAPIDe-2, at least one attack symptom (skin pain, skin swelling, or abdominal pain) had to reach an AMRA score of ≥30.
- Kaplan-Meier estimates were calculated comparing the RAPIDe-2 study cohort treating HAE attacks with deucrictibant IR capsule with the mixed-methods study cohort treating attacks with SOC for each endpoint.

### Table 2. PSM analysis parameters

| | Selected attacks | Matching algorithm | Participant characteristics matched |
|---|---|---|---|
| **Base case** | First 10 consecutive attacks | Greedy Nearest Neighbor 1:1 with Caliper = 0.5 | Sex, age, baseline attack severity,[a] and exact attack primary location |
| **Sensitivity analysis 1** | First 10 consecutive attacks | Greedy Nearest Neighbor 1:1 with Caliper = 0.5 | Sex, age, and baseline attack severity[a] |
| **Sensitivity analysis 2** | Maximum of 10 attacks selected randomly | Greedy Nearest Neighbor 1:1 with Caliper = 0.5 | Sex, age, and baseline attack severity[a] |
| **Sensitivity analysis 3** | First 10 consecutive attacks | Greedy Nearest Neighbor optimal ratio with Caliper = 0.5 | Sex, age, and baseline attack severity[a] |

AMRA, Angioedema syMptom Rating scAle; PSM, propensity score matching. [a]Defined by AMRA score.

## Results

- As of the data cutoff of 1 March 2024, RAPIDe-2 included 17 participants who reported 258 non-laryngeal attacks. All attacks were treated with deucrictibant IR capsule.
  - Safety and efficacy results of RAPIDe-2 will be presented at this conference by Anna Valerieva, MD, PhD, on 8 March 2025.
- The mixed-methods study included 29 participants who reported 97 non-laryngeal attacks from 20 November 2022 to 17 April 2023. All attacks were treated, and the most common medications reported were icatibant (60.2%) and C1 inhibitor concentrate (31.7%; **Table 3**).
- Baseline characteristics were generally similar between cohorts (**Table 4**).

### Table 3. On-demand treatments used for non-laryngeal HAE attacks (N=98[b]) reported by 29 adults in the mixed-methods study

| Treatment | Taken at attack onset n (%)[a] | Taken as additional dose n (%)[a] | Taken as additional new treatment n (%)[a] |
|---|---|---|---|
| **Icatibant** | 59 (60.2) | 8 (8.2) | 0 (0) |
| **Plasma-derived C1 INH** | 22 (22.5) | 0 (0) | 0 (0) |
| **Recombinant C1 INH** | 9 (9.2) | 2 (2.0) | 0 (0) |
| **Other[c]** | 9 (9.2) | 4 (4.1) | 6 (6.1) |

C1 INH, C1 inhibitor; HAE, hereditary angioedema. [a]These percentages are calculated based on the total 98 non-laryngeal attacks represented in this table. [b]Participants could take multiple medications for each attack, either as additional doses (e.g., 2 doses of icatibant) or as additional new treatments (e.g., icatibant and diphenhydramine). [c]Other treatments used included tranexamic acid (n=6), diphenhydramine (n=1), and lanadelumab (n=1), with one not stated.

## Results

### Table 4. Baseline characteristics

| | RAPIDe-2 cohort (deucrictibant IR capsule) | Mixed-methods cohort (SOC) |
|---|---|---|
| **Participants, n** | 17 | 29 |
| **Treated attacks per participant, mean (range)** | 15 (1, 42) | 3 (1, 9) |
| **Age in years, mean (range)** | 43 (20, 71) | 41 (18, 70) |
| **Sex: female, n (%)** | 11 (64.7) | 20 (69.0) |
| **Ethnicity: non-Hispanic, n (%)** | 13 (76.5) | 28 (96.6) |
| **HAE type, n (%)** | | |
| HAE type 1 | 16 (94.1) | 28 (96.6) |
| HAE type 2 | 1 (5.9) | 1 (3.4) |

HAE, hereditary angioedema; IR, immediate-release; SOC, standard of care.

- For the base case (N=73 attacks):
  - The RAPIDe-2 study cohort achieved symptom relief significantly faster than the mixed-methods study cohort, as indicated by the median time to PGI-C "A little better" and "Better" and to ≥1-level improvement in PGI-S (**Figure 3**).
- The results from the sensitivity analyses were consistent with the base case.

### Figure 3. Kaplan-Meier estimates for median (95% CI) time to event, PSM base case analysis[a]



**A. Time to onset of symptom relief defined as PGI-C "A little better"**

RAPIDe-2 study cohort (deucrictibant IR capsule) KM estimate: 1.07 (0.98, 1.89)
Mixed-methods study cohort (SOC) KM estimate: 2.38 (1.68, 3.10)
P<0.0001

Number at risk:
RAPIDe-2 study cohort (deucrictibant IR capsule): 44 16 8 6 4 4 2
Mixed-methods study cohort (SOC): 59 42 33 25 21 18 16 10

**B. Time to onset of symptom relief defined as PGI-C "Better"**

RAPIDe-2 study cohort (deucrictibant IR capsule) KM estimate: 2.66 (1.98, 3.55)
Mixed-methods study cohort (SOC) KM estimate: 4.49 (3.09, 6.18)
P=0.0006

Number at risk:
RAPIDe-2 study cohort (deucrictibant IR capsule): 69 44 31 24 19 9 7 6
Mixed-methods study cohort (SOC): 69 55 46 40 34 5 26 20

**C. Time to reduction in attack severity defined as PGI-S ≥1-level improvement**

RAPIDe-2 study cohort (deucrictibant IR capsule) KM estimate: 2.14 (1.93, 2.94)
Mixed-methods study cohort (SOC) KM estimate: 4.02 (3.15, 5.19)
P<0.0001

Number at risk:
RAPIDe-2 study cohort (deucrictibant IR capsule): 58 39 26 21 8 6 2
Mixed-methods study cohort (SOC): 70 56 47 40 34 7 28 22

**D. Time to complete attack resolution defined as PGI-S "None"**

RAPIDe-2 study cohort (deucrictibant IR capsule) KM estimate: 12.26 (7.60, 18.34)
Mixed-methods study cohort (SOC) KM estimate: 13.49 (6.01, 22.84)
P=0.2225

Number at risk:
RAPIDe-2 study cohort (deucrictibant IR capsule): 73 69 65 60 55 52 45 37 18
Mixed-methods study cohort (SOC): 71 69 63 58 51 45 42 38 27

AMRA, Angioedema syMptom Rating scAle; CI, confidence interval; IR, immediate release; KM, Kaplan-Meier; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PSM, propensity score matching; SOC, standard of care. N=73 for both cohorts. [a]Parameters: The first 10 consecutive attacks were selected for each participant; Greedy Nearest Neighbor 1:1 matching was used with Caliper = 0.5; participants were matched for sex, age, baseline attack severity (defined by AMRA score), and exact attack primary location.

## Conclusion

- This PSM analysis provides evidence that a cohort of participants with HAE in a clinical study treated with deucrictibant IR capsule had more favorable outcomes on PGI-C- and PGI-S-based assessments when compared with a cohort treated with SOC in an observational study.

## References

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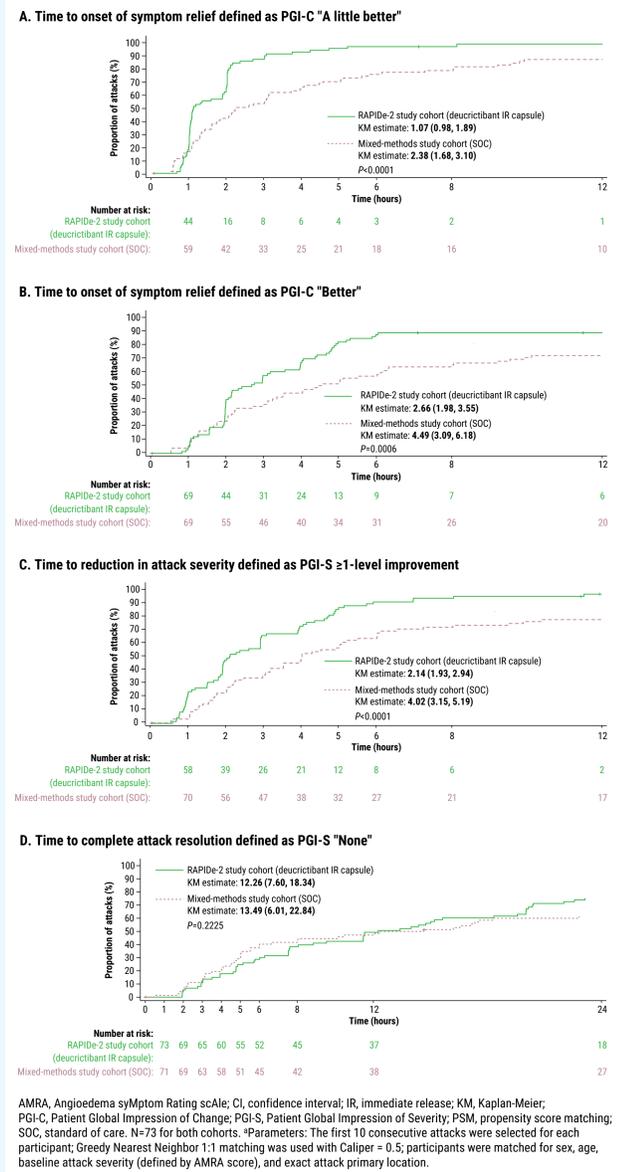This presentation includes data for an investigational product not yet approved by regulatory authorities.

*RAPIDe-2 is a Pharvaris-sponsored clinical trial. ClinicalTrials.gov identifier: NCT05396105.