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

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Key takeaways

This propensity score matching analysis provided evidence that a cohort of participants with hereditary angioedema (HAE) in a clinical study treated with deucrictibant immediate-release (IR) capsule had more favorable outcomes on Patient Global Impression of Change (PGI-C) and Severity (PGI-S)-based assessments compared with a cohort treated with standard of care in a mixed-methods, real-world, observational study.

Cohort treated with deucrictibant in a clinical study vs. Cohort treated with standard of care in a mixed methods observational study

- **1.68 hours vs 2.23 hours** — median time to onset of symptom relief as measured with PGI-C
- **2.93 hours vs 4.56 hours** — median time to substantial symptom relief as measured with PGI-C
- **2.38 hours vs 4.02 hours** — median time to reduction in attack severity as measured with PGI-S

PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.

Background

- **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]
- **Unmet need:** oral ODT options that are effective and well tolerated and that may reduce the treatment burden by enabling prompt, discreet administration.[10]
- **Deucrictibant:** an orally administered, highly potent, specific antagonist of the bradykinin B2 receptor under development for prophylactic and ODT of HAE attacks.[11-18]
- **Knowledge gap:** to date, clinical trials comparing deucrictibant immediate-release (IR) capsule for ODT of HAE attacks with SOC have not been conducted.

Objective

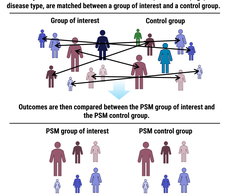
To compare outcomes of a clinical study cohort treating HAE attacks with deucrictibant IR capsule with those of an observational study cohort treating HAE attacks with SOC.

Methods

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

Methods

Data sources (Table 1)

- **RAPIDe-2 (NCT05396105)[13]*:** an ongoing, two-part, Phase 2/3 open-label extension study of deucrictibant IR capsule for treatment of HAE attacks.
  - Evaluates outcomes of long-term use of deucrictibant IR capsule for treatment of repeat HAE attacks.
- **Mixed-methods study[20]:** an observational study of SOC for treatment of HAE attacks.
  - Patient-reported outcome (PRO) assessments used in ODT clinical trials of deucrictibant IR capsule were evaluated.
  - Clinical outcomes among people with HAE who treated their attacks with SOC were assessed.

Assessments and endpoints (Table 1)

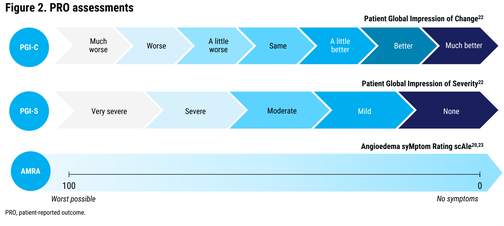
- **PRO assessments:** during an HAE attack, participants in both studies completed 3 PRO assessments (**Figure 2**).
  - Patient Global Impression of Change (PGI-C)
  - Patient Global Impression of Severity (PGI-S)
  - Angioedema syMptom Rating scAle (AMRA)
- In both studies, PRO assessments were completed 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:** time to PGI-C "A little better" or "Better", time to at least one-level improvement in PGI-S, and time to PGI-S "None".

Table 1. Data sources and study parameters for PSM

	RAPIDe-2 clinical study[13]	Mixed-methods observational study[20]
Study type	**Clinical study**	**Observational study**
Dates of data collection	**28 December 2022 to 18 December 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.[a] • **Time to substantial symptom relief:** PGI-C of at least "Better" for 2 consecutive timepoints post-treatment.[a] • **Time to reduction in attack severity**: PGI-S improvement of ≥1 level from pre-treatment for 2 consecutive timepoints.[a] • **The proportion of attacks achieving complete attack 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 onset of symptom relief defined as PGI-C at least "A little better"** **Time to substantial symptom relief defined as PGI-C at least "Better"** **Time to reduction in attack severity defined as PGI-S at least 1-level improvement** **Time to complete attack resolution defined as 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; TEAE, treatment-emergent adverse event. [a]Or at the last scheduled timepoint (48 hours) provided no rescue medication was used within 12 hours after the last timepoint.

Figure 2. PRO assessments



PRO, patient-reported outcome.

Methods

PSM analysis parameters (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 ≥30.
- **Kaplan-Meier estimates:** were calculated for each endpoint by comparing the RAPIDe-2 study cohort treating HAE attacks with deucrictibant IR capsule with the mixed-methods study cohort treating attacks with SOC.

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

Participants

- Final RAPIDe-2 Part A data included 18 participants who reported 438 non-laryngeal attacks. All attacks were treated with deucrictibant IR capsule.
- 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 SOC 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[a]) reported by 29 adults in the mixed-methods study

Treatment	Taken at attack onset n (%)[b]	Taken as additional dose n (%)[b]	Taken as additional new treatment n (%)[b]
Icatibant	59 (60.2)	8 (8.2)	0 (0)
Plasma-derived C1INH	22 (22.5)	0 (0)	0 (0)
Recombinant C1INH	9 (9.2)	2 (2.0)	0 (0)
Other[c]	9 (9.2)	4 (4.1)	6 (6.1)

C1INH, C1 inhibitor; HAE, hereditary angioedema. [a]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). [b]These percentages are calculated based on the total 98 non-laryngeal attacks represented in this table. [c]Other treatments used included tranexamic acid (n=6), diphenhydramine (n=1), and lanadelumab (n=1), with one not stated.

Table 4. Baseline characteristics

	RAPIDe-2 cohort (deucrictibant IR capsule)	Mixed-methods cohort (SOC)
Participants, n	18[a]	29
Treated attacks per participant, mean (range)	24.3 (3, 78)	3.3 (1, 9)
Age in years, mean (range)	43.3 (22, 73)	41 (18, 70)
Sex: female, n (%)	12 (66.7)	20 (69.0)
Ethnicity: non-Hispanic, n (%)	14 (77.8)	28 (96.6)
HAE type, n (%)		
HAE type 1	16 (88.9)	28 (96.6)
HAE type 2	2 (11.1)	0 (0)
HAE with normal C1INH	0 (0)	1 (3.4)

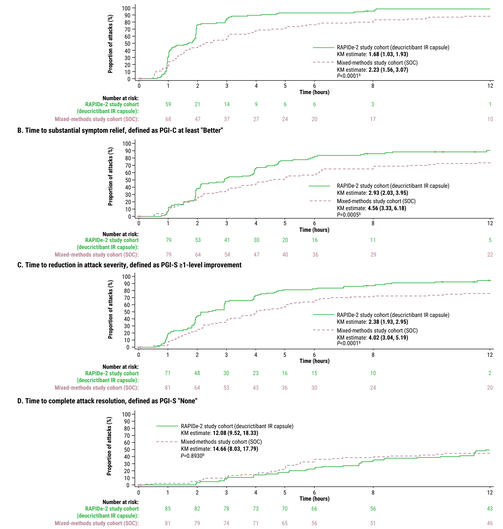
HAE, hereditary angioedema; IR, immediate-release; SOC, standard of care. [a]One participant from RAPIDe-2 Part A lacked matched attacks for analysis in the propensity score matched sample and was therefore excluded from the tables.

Results

Base case analysis

- The base case analysis included 85 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 at least one-level improvement in PGI-S (**Figure 3**).
  - The results from the sensitivity analyses were consistent with the base case (not shown).

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



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=85 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. [b]Nominal P-values computed from Log-rank test and were not adjusted or pre-specified.

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

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