Propensity Score-Matched Comparison of Outcomes for Deucrictibant vs Standard of Care in People Living with Hereditary Angioedema

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Rationale

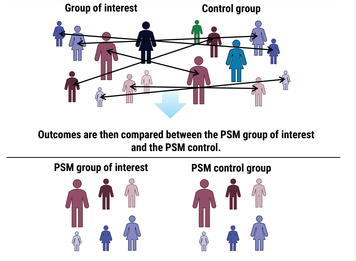
- Current standard-of-care (SOC) on-demand treatment (ODT) options for hereditary angioedema (HAE) attacks are administered by injection,[1-5] which presents a burden for people with HAE and leads to treatment of attacks often being delayed or forgone.[6-10]
- An unmet need exists for oral ODT options 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.[11-15]
- To date, clinical trials comparing deucrictibant immediate-release (IR) capsule for ODT of HAE attacks with SOC have not been conducted.

Methods

- A propensity score matching (PSM) method[16] (**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.[17]

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.[16]
- Goal is to balance the observed differences between participants in the treatment and potential control groups by matching participant characteristics using propensity scores.[16]
- 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.[16]
- PSM has been used for comparative analyses in other conditions such as multiple sclerosis.[18]



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 poster and oral presentation **Long-Term Efficacy and Safety of Oral Deucrictibant, a Bradykinin B2 Receptor Antagonist, in Treatment of Hereditary Angioedema Attacks: Results of the RAPIDe-2 Extension Study** by Maurer et al.
  - Observational mixed-methods study[17] 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**).

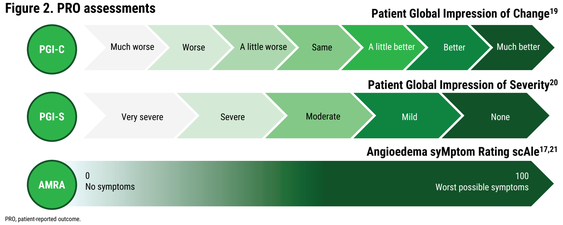
Methods

Table 1. Data sources and study parameters for PSM

	RAPIDe-2 study[13]	Mixed-methods study[17]
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 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; TEAE, treatment-emergent adverse events.

Figure 2. PRO assessments



PRO, patient-reported outcome.

- PSM analysis parameters are reported in **Table 2**.
- 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.
- 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[a] used for non-laryngeal HAE attacks (N=98[b]) reported by 29 adults in the mixed-methods study

Treatment	Taken at attack onset n (%)	Taken as additional dose n (%)	Taken as additional new treatment n (%)
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 onset, 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.

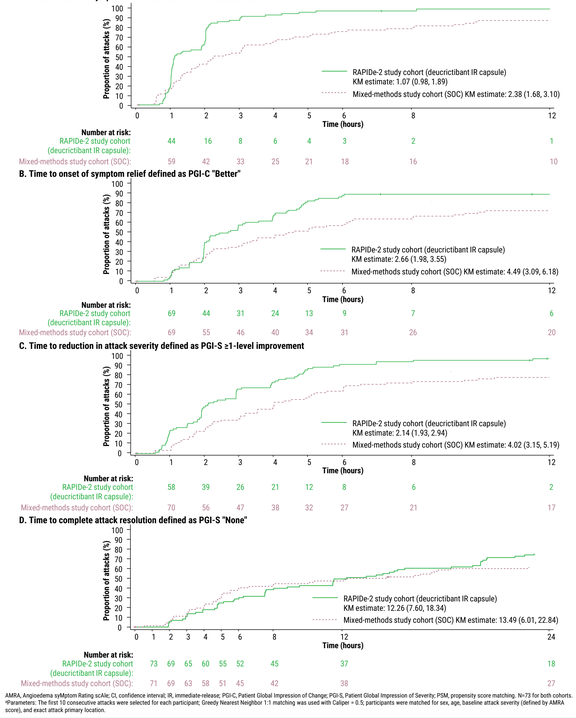
Table 4. Baseline characteristics

	RAPIDe-2 cohort (deucrictibant IR capsule)	Mixed-methods cohort (SOC)
Participants, n	17	29
Treated attacks per participant, mean (min, max)	15 (1, 42)	3 (1, 9)
Age in years, mean (min, max)	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; max, maximum; min, minimum; 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]



AMRA, Angioedema syMptom Rating scAle; CI, confidence interval; IR, immediate-release; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PSM, propensity score matching. 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.

Conclusions

- **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.**

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