Deucrictibant vs standard of care in hereditary angioedema: A propensity score-matched analysis

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Rationale

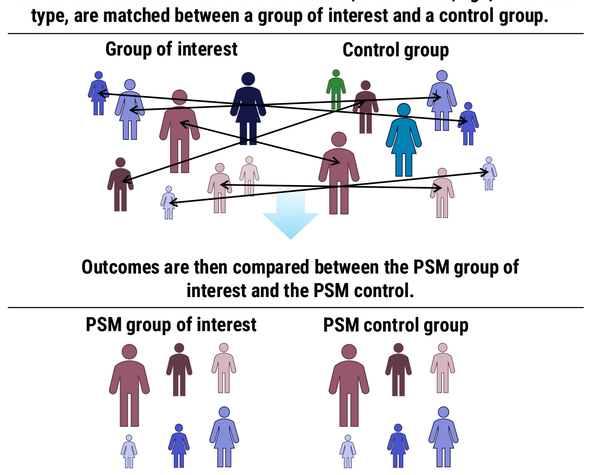
- Current standard-of-care (SOC) on-demand treatment (ODT) options for hereditary angioedema (HAE) attacks are administered by injection, which presents a burden for people with HAE[1-5] and leads to treatment of attacks often being delayed or forgone.[6-10]
- An unmet need exists for oral ODT options 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.
- 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[11] (**Figure 1**) was used to compare clinical outcomes between the cohort from RAPIDe-2,[12] 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.[13]

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.[11]
- Goal is to balance the observed differences between participants in the treatment and potential control groups by matching participant characteristics using propensity scores.[11]
- Patients 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.[11]
- PSM has been used for comparative analyses in other conditions such as multiple sclerosis.[12]



PSM, propensity score matching.

- Data sources (**Table 1**)
  - RAPIDe-2 (NCT05396105) study[12] 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.[11]
    - For further information, please see the poster **Treatment of HAE attacks with oral deucrictibant: RAPIDe-2 extension results** by Maurer et al.
  - Observational mixed-methods study[13] of SOC (e.g., icatibant, C1-inhibitor, etc.) 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.

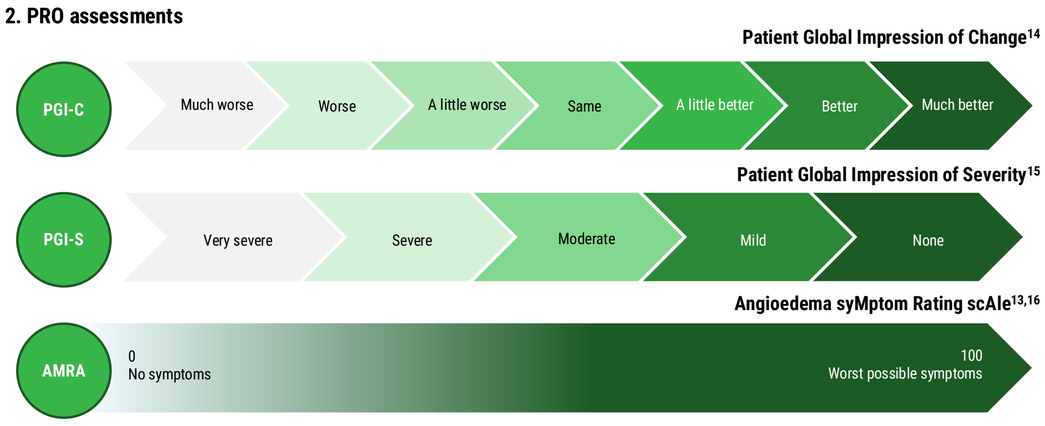
Table 1. Data sources and study parameters for PSM

	RAPIDe-2 study[12]	Mixed-methods study[13]
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, etc.)
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	AMRA, PGI-C, and PGI-S	
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.

- 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**).

Figure 2. PRO assessments



PRO, patient-reported outcome.

- 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**).
- 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, CI 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

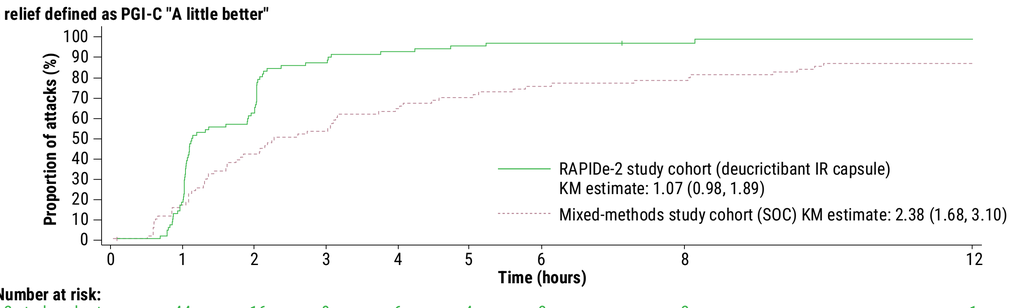
	RAPIDe-2 cohort (deucrictibant IR capsule)	Mixed-methods cohort (SOC)
Participants, n	17	29
Treated attacks per participant, mean (min, max)	15 (1, 42)	3 (1, 9)
Age in years, mean (min, max)	43 (20, 71)	41 (18, 70)
Sex: female, n (%)	11 (64.7)	20 (69.0)
Ethnicity: non-Hispanic, n (%)	13 (76.5)	28 (96.6)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

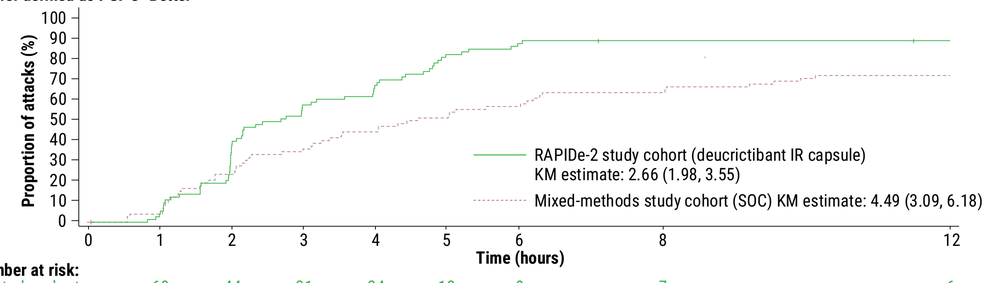
Figure 3. KM estimates for median (95% CI) time to event, PSM base case analysis[a]

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



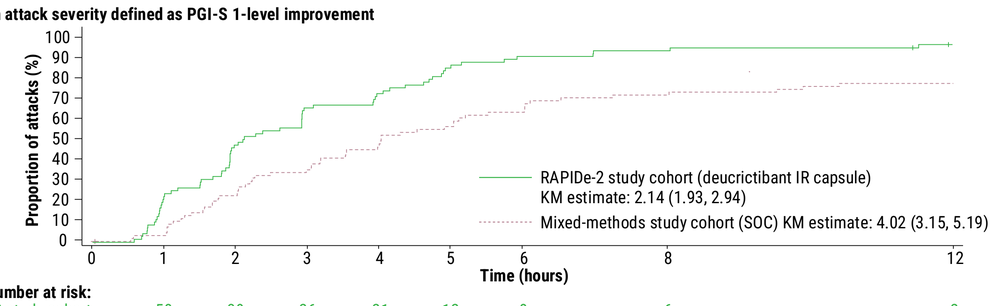
Number at risk:								
RAPIDe-2 study cohort (deucrictibant IR capsule):	44	16	8	6	4	3	2	1
Mixed-methods study cohort (SOC):	59	42	33	25	21	18	16	10

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



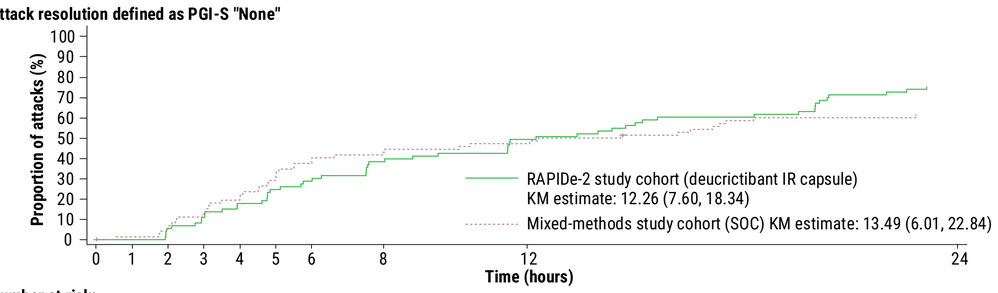
Number at risk:								
RAPIDe-2 study cohort (deucrictibant IR capsule):	69	44	31	24	13	9	7	6
Mixed-methods study cohort (SOC):	69	55	46	40	34	31	26	20

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



Number at risk:								
RAPIDe-2 study cohort (deucrictibant IR capsule):	58	39	26	21	12	8	6	2
Mixed-methods study cohort (SOC):	70	56	47	38	32	27	21	17

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



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; 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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