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

Mark D. Scarupa[1], John Anderson[2], Danny M. Cohn[3], Constance H. Katelaris[4], Marc A. Riedl[5], Maggie Chen[6], Peng Lu[6], Joan Mendivil[7]

[1]Institute for Asthma and Allergy, Chevy Chase, MD, USA; [2]AllerVie Health, Clinical Research Center of Alabama, Birmingham, AL, USA; [3]University of Amsterdam, Amsterdam UMC, Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam, the Netherlands; [4]Campbelltown Hospital and Western Sydney University, Department of Medicine, Sydney, New South Wales, Australia; [5]University of California San Diego, Division of Allergy and Immunology, La Jolla, CA, USA; [6]Pharvaris Inc, Lexington, MA, USA; [7]Pharvaris GmbH, Zug, Switzerland

Key takeaways

This propensity score matching analysis provides 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

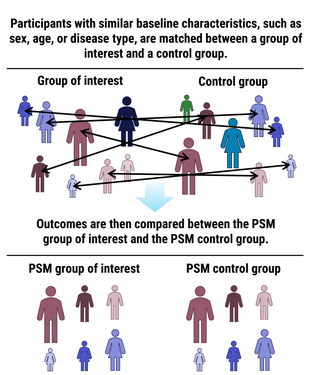
To compare outcomes of a clinical study cohort treating HAE attacks with deucrictibant IR capsule with those of an observational study cohort treating HAE attacks with SOC.

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.

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.
  - Evaluated 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)

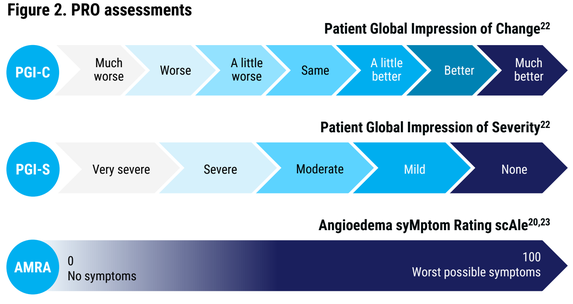
- **PRO assessments:** during an HAE attack, participants in both studies completed 3 PRO assessments (**Figure 2**).
  - Patient Global Impression of Change (PGI-C)
  - Patient Global Impression of Severity (PGI-S)
  - Angioedema syMptom Rating scAle (AMRA)
- In both studies, PRO assessments were completed 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 ≥1-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 at least 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 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. [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 of ≥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	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, hereditary angioedema; IR, immediate-release; SOC, standard of care.

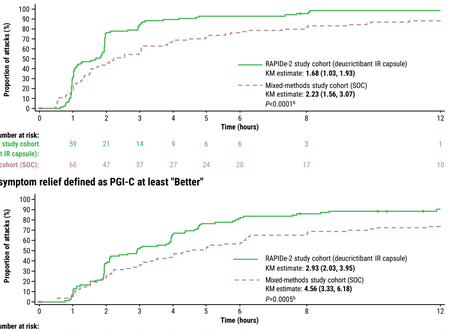
Results

Base case analysis

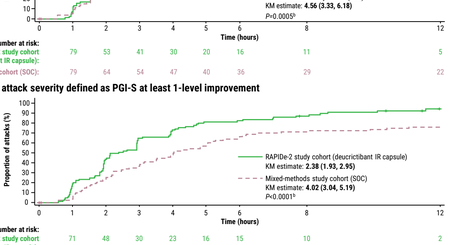
- The base case analysis included 85 attacks.
- The RAPIDe-2 study cohort achieved symptom relief significantly faster than the mixed-methods study cohort, as indicated by the median time to PGI-C "A little better" and "Better" and to ≥1-level improvement in PGI-S (**Figure 3**).
  - The results from 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]

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

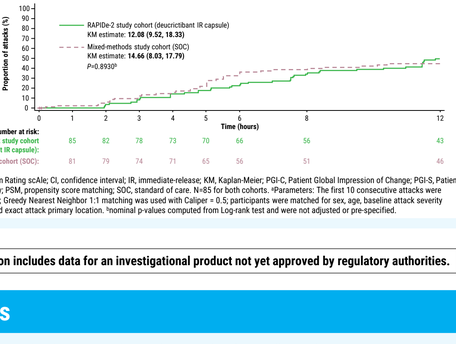


B. Time to substantial symptom relief defined as PGI-C at least "Better"



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

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



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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