Long-Term Safety and Efficacy of Oral Deucrictibant for Treatment of Hereditary Angioedema Attacks: Results of the RAPIDe-2 Extension Study

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Key takeaways

The ongoing Phase 2/3 RAPIDe-2 extension study provides evidence on the long-term safety and efficacy of deucrictibant immediate-release (IR) capsule for on-demand treatment of repeat hereditary angioedema (HAE) attacks.

Safety

- Deucrictibant was well tolerated with no safety signals

Efficacy

- **1.1 Hours** — Median time to onset of symptom relief
- **98.5%** of attacks treated with deucrictibant IR capsule did not use rescue medication
- Similar times to onset of symptom relief for upper airway attacks and other attacks

IR, immediate release.

Background

- **Hereditary angioedema (HAE):** a bradykinin-mediated condition with painful swelling attacks affecting multiple locations in the body.[1]
- **Current landscape:** guidelines recommend HAE attacks are treated as early as possible.[2-4] Parenteral administration often leads to on-demand treatment of HAE attacks being delayed or forgone.[5-14]
- **Oral deucrictibant:** a selective, bradykinin B2 receptor antagonist under development for both prophylactic and on-demand treatment of HAE attacks.[15-22]

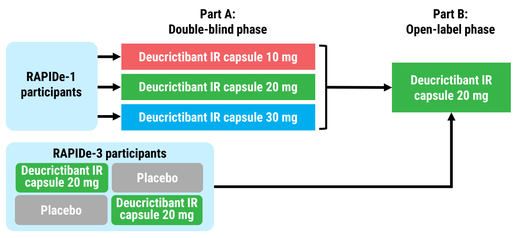
Objective

Evaluate the long-term safety and efficacy of deucrictibant IR capsule for on-demand treatment of repeat HAE attacks in the RAPIDe-2 extension study.

Methods

- **RAPIDe-2 (NCT05396105)*:** a two-part, double-blind Phase 2/3 extension study.[17]
- **Part A eligible participants:** adults who completed RAPIDe-1 (NCT04618211).[15]
- **Part A:** participants continue self-administering the same double-blinded dose of deucrictibant IR capsule (10 mg, 20 mg, or 30 mg) received in RAPIDe-1 to treat qualifying qualifying attacks including non-severe laryngeal attacks presenting without breathing difficulties.
- **Part A prophylaxis:** no long-term HAE prophylaxis treatment is allowed. Recent use of long-term HAE prophylaxis treatment prior to screening is allowed provided a pre-specified washout period is observed.

Figure 1. RAPIDe-2 study design



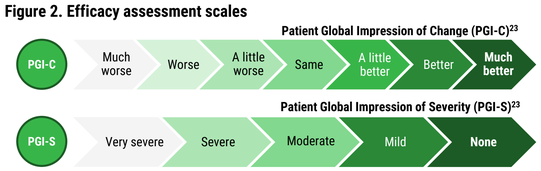
IR, immediate-release.

Methods

Primary endpoint: safety including treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs (including blood pressure), and electrocardiogram findings.

Secondary endpoints: efficacy endpoints using patient-reported outcome tools.

Figure 2. Efficacy assessment scales



- Data collection pre-specified at pre-treatment, hourly for 6 hours, and at 8, 12, 24, and 48 hours post-treatment.

Table 1. Efficacy endpoints

Key efficacy endpoints	Defined as
Time to	
Onset of symptom relief	By 12 hours, PGI-C rating of at least "a little better" for 2 consecutive timepoints[a]
Reduction in attack severity	By 12 hours, ≥1-level reduction in the PGI-S from pre-treatment for 2 consecutive timepoints[a]
Substantial symptom relief	By 12 hours, PGI-C rating of at least "better" for 2 consecutive timepoints[a]
Proportion of attacks achieving	
Complete attack resolution	By 24 hours, PGI-S rating of "none"[b]

Data collection pre-specified at pre-treatment, hourly for 6 hours, and at 8, 12, 24, and 48 hours post-treatment. PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity. [a]If rescue medication used within 14.5 hours post-treatment, time to event was censored at 14.5 hours regardless of whether event occurred within 12 hours post-treatment. [b]Rescue medication use within 33.5 hours post-treatment was regarded as not achieving complete attack resolution at 24 hours.

Post hoc analyses: safety and efficacy for on-demand treatment of upper airway attacks, including laryngeal attacks without breathing difficulties.

- Upper airway attacks confirmed by investigators as per protocol definition: swelling of the lips/tongue or any sensation of lump in the throat, difficulty swallowing, or voice change.
- Difficulty swallowing and voice change were assessed using the 5-symptom composite Angioedema syMptom Rating scAle (AMRA-5).

Results

Data

- Data snapshot from RAPIDe-2 Part A. Combined dose-blinded group data shown.

Safety analysis

- Participants who received ≥1 dose of deucrictibant IR capsule in the study at data cutoff (10 June 2024).
- 337 attacks from 19 participants.

Table 2. TEAEs within 5 days of study drug administration

Adverse events	Deucrictibant IR capsule (Combined dose group)
Attacks with any TEAE, n (%)	13 (3.9)
Treatment-related TEAEs, n	0
Serious TEAEs, n	1[a]
Treatment-related serious TEAEs, n	0
TEAEs leading to study drug discontinuation, study withdrawal, or death, n	0

IR, immediate-release; TEAE, treatment-emergent adverse event (defined as adverse event occurring during time window from first study drug administration). [a]Tooth caries unrelated to treatment.

Results

Efficacy analysis

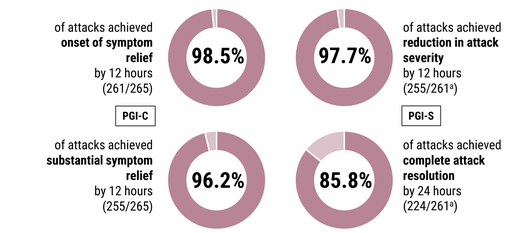
- Modified intention-to-treat analysis set: participants who treated ≥1 attack with deucrictibant IR capsule and non-missing PGI-C results from ≥1 post-treatment timepoint at data cutoff (01 March 2024).
- 265 attacks from 17 participants.

Figure 3. Median time to achieving key efficacy endpoints

Median time to (95% CIs)	Onset of symptom relief	Reduction in attack severity	Substantial symptom relief	Complete attack resolution
	1.1 hours (1.0, 1.1)[a]	2.6 hours (2.0, 2.9)[a,b]	2.7 hours (2.1, 2.9)[a]	11.5 hours (11.0, 13.0)[a,b]

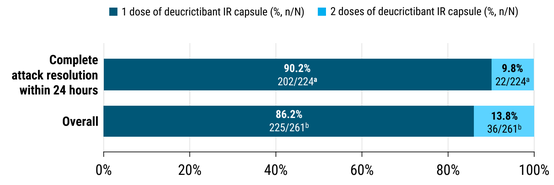
CI, confidence interval; PGI-S, Patient Global Impression of Severity. [a]Analysis included participants in the modified intention-to-treat efficacy analysis set at data cutoff (01 March 2024); 265 attacks from 17 participants. [b]261 attacks have non-missing pre-treatment PGI-S. [c]Within-participant correlation was not accounted for in all Kaplan-Meier estimates.

Figure 4. Majority of attacks achieved key efficacy endpoints within timeframe



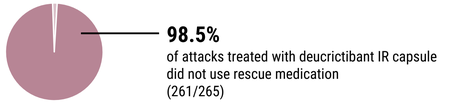
PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity. [a]261 attacks had non-missing pre-treatment PGI-S.

Figure 5. Over 90% of attacks achieving complete attack resolution within 24 hours were treated with a single dose of deucrictibant



IR, immediate-release; PGI-S, Patient Global Impression of Severity. [a]Number of 224 attacks achieving complete attack resolution, defined as PGI-S score of 'none' by 24 hours. [b]Number of attacks that were not treated with rescue medication. Rescue medication was used for four attacks: three after 1 dose of deucrictibant and one after 2 doses of deucrictibant.

Figure 6. 98.5% of attacks treated with deucrictibant did not use rescue medication



IR, immediate-release.

Upper airways attack analysis

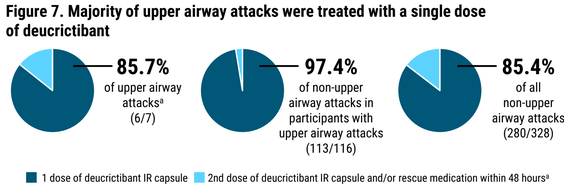
- 337 attacks at data cutoff (31 May 2024), of which 7 were upper airway, including laryngeal, attacks.
  - Difficulty in swallowing and/or voice change were reported as symptom manifestations of 3 attacks before treatment.

Table 3. Similar times to symptom relief for upper airway and other attacks

	Upper airway attacks	Non-upper airway attacks in participants with upper airway attacks	Total non-upper airway attacks
Number of participants	5	5	19
Total number of attacks treated[a]	7	116	328
Time to onset of symptom relief[b,c]			
Number of attacks[d]	7	112	318
Median hours (95% CI)	**0.9** (0.5, 2.0)	**1.0** (1.0, 1.1)	**1.1** (1.0, 1.1)
Time to reduction in attack severity[c,e]			
Number of attacks[f]	6	111	312
Median hours (95% CI)	**3.0** (0.9, NE)	**2.0** (2.0, 2.7)	**2.7** (2.1, 2.9)

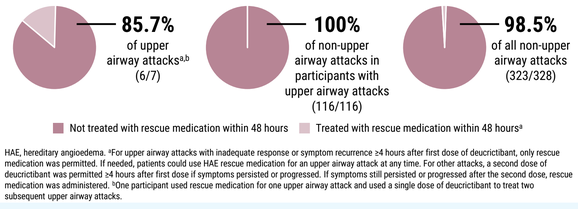
CI, confidence interval; NE, not estimable (insufficient data to calculate reliable estimate); PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity. [a]337 attacks treated by 19 participants at data cutoff (31 May 2024). [b]PGI-C rating of at least "a little better" for 2 consecutive timepoints by 12 hours post-treatment. [c]Within-participant correlation not accounted for in all Kaplan-Meier estimates. [d]Evaluable attacks include deucrictibant-treated attacks with ≥1 post-treatment PGI-C assessment. [e]≥1-level reduction in PGI-S from pre-treatment for 2 consecutive timepoints by 12 hours. [f]Evaluable attacks included deucrictibant-treated attacks with a pre- and ≥1 post-treatment PGI-S assessment.

Figure 7. Majority of upper airway attacks were treated with a single dose of deucrictibant



HAE, hereditary angioedema; IR, immediate-release. [a]For upper airway attacks with inadequate response or symptom recurrence ≥4 hours after first dose of deucrictibant, only rescue medication was permitted. If needed, patients could use HAE rescue medication for an upper airway attack at any time. For other attacks, a second dose of deucrictibant was permitted ≥4 hours after first dose if symptoms persisted or progressed. If symptoms still persisted or progressed after the second dose of deucrictibant, rescue medication was administered.

Figure 8. Majority of upper airway and other attacks did not use rescue medication by 48 hours post-treatment



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