Long-Term Efficacy and Safety of Oral Bradykinin B2 Receptor Antagonist Deucrictibant in Treatment of Hereditary Angioedema Attacks: RAPIDe-2 Extension Study Results

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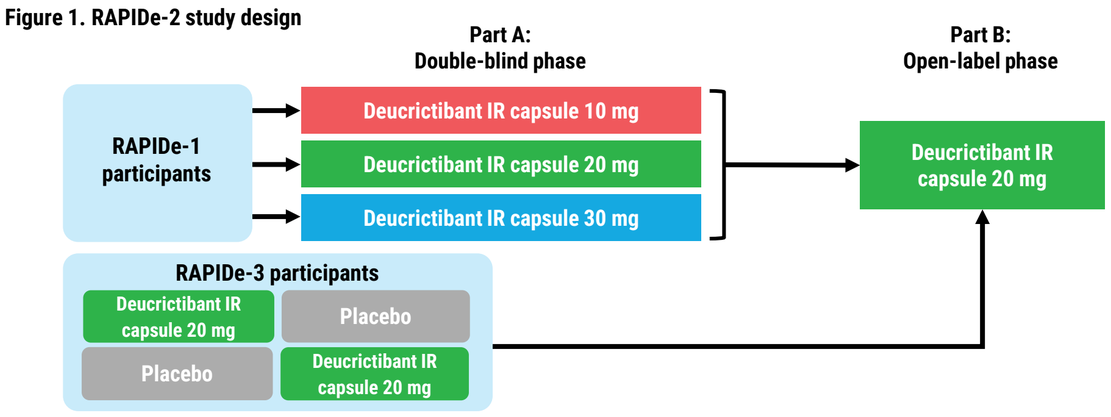
Rationale

- International guidelines recommend that hereditary angioedema (HAE) attacks are treated as early as possible.[1-3]
- The burden associated with parenteral administration of currently approved on-demand medications[4-8] often leads to treatment of HAE attacks being delayed or forgone.[9-13]
- An unmet need exists for on-demand oral therapies that are effective and well tolerated and may reduce the treatment burden, thus enabling prompt administration.[13]
- Deucrictibant is a selective, orally-administered bradykinin B2 receptor antagonist under development for prophylactic and on-demand treatment of HAE attacks.[14-19]
- In the RAPIDe-1 Phase 2 trial (NCT04618211)[14] deucrictibant immediate-release (IR) capsule reduced the time to onset of symptom relief and to resolution of HAE attacks vs placebo and was well tolerated.[15]

Methods

- RAPIDe-2 (NCT05396105)[16†] is an ongoing, two-part Phase 2/3 extension study evaluating long-term safety and efficacy of orally-administered deucrictibant IR capsule for the treatment of HAE attacks.
- Part A enrolls adult (≥18 years) participants who completed RAPIDe-1. 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 non-laryngeal attacks (≥1 symptom with Visual Analogue Scale score ≥30), and laryngeal attacks presenting without breathing difficulties (**Figure 1**).
- During Part A, no long-term HAE prophylaxis treatment is allowed. Recent use of long-term HAE prophylaxis treatment with C1-INH, oral kallikrein inhibitors, attenuated androgens, or anti-fibrinolytics is allowed provided a 2-week washout period prior to enrollment is observed. Use of lanadelumab is not allowed within 12 weeks of enrollment.

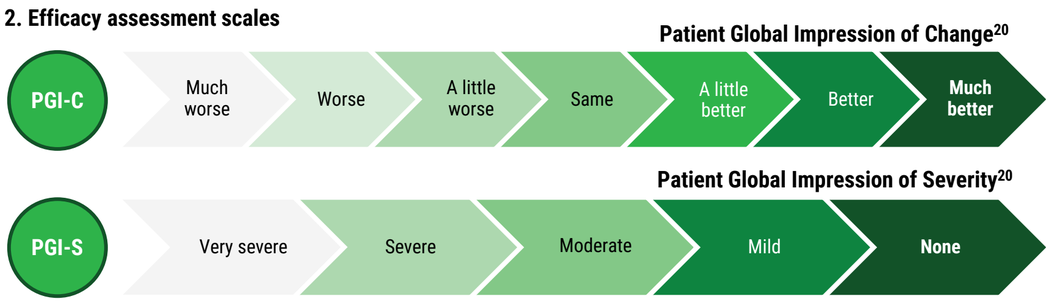
Figure 1. RAPIDe-2 study design



IR, immediate-release.

- The primary endpoint assesses safety, including treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, and electrocardiogram (ECG) findings.
- Patient-reported outcome (PRO) tools are used to assess efficacy (**Figure 2**), with data collection pre-specified at pre-treatment, every hour up to 6 hours, and then at 8, 12, 24, and 48 hours, from administration of deucrictibant IR capsule.
- Key efficacy endpoints (**Figure 2**) include:
  - Time to onset of symptom relief, defined as Patient Global Impression of Change (PGI-C) rating of at least "a little better" for 2 consecutive timepoints by 12 hours post-treatment.
  - Time to substantial symptom relief, defined as PGI-C rating of at least "better" for 2 consecutive timepoints by 12 hours post-treatment.
  - Time to reduction in attack severity, defined as achieving ≥1-level reduction in the Patient Global Impression of Severity (PGI-S) from pre-treatment for 2 consecutive timepoints by 12 hours post-treatment.
  - Proportion of attacks achieving complete attack resolution, defined as achieving PGI-S rating of "none" at 24 hours post-treatment.

Figure 2. Efficacy assessment scales



Results

- Data from the RAPIDe-2 Part A combined-dose group at the date of cutoff are reported here.
- A total of 265 attacks from 17 participants were included in the modified intention-to-treat efficacy analysis set at data cutoff (1 March 2024), defined as all participants who had ≥1 attack treated with deucrictibant IR capsule and non-missing PGI-C results from ≥1 post-treatment timepoint.
- A total of 337 attacks from 19 participants were included in the safety analysis set at data cutoff (10 June 2024), defined as all participants who received any dose of deucrictibant IR capsule in the study.
  - 7 of 337 attacks were laryngeal.
- Baseline characteristics were consistent with the RAPIDe-1 Phase 2 trial (**Table 1**).

Table 1. Baseline characteristics

	Deucrictibant IR capsule (combined dose group)
Number of attacks treated[a]	337
Number of participants[a]	19
Age in years, mean (SD)	42.7 (17.6)
Sex: Male/female, n (%)	7 (36.8) / 12 (63.2)
Race: White/other	18 / 1
BMI, mean (SD)	27.0 (3.8)
Years since HAE diagnosis, mean (SD)	21.7 (15.2)
HAE type, n (%)	
HAE-1	17 (89.5)
HAE-2	2 (10.5)

BMI, body mass index; HAE, hereditary angioedema; IR, immediate-release; SD, standard deviation. [a]Number by the cutoff date (10 June 2024).

Safety

- Deucrictibant IR capsule was well tolerated across all doses, with no treatment-related TEAEs (**Table 2**).
- No treatment-related serious or severe TEAEs, no treatment-related TEAEs in laboratory parameters, vital signs, or ECG findings, and no TEAEs leading to treatment discontinuation, study withdrawal, or death were reported.

Table 2. TEAEs within 5 days after administration of study drug

Adverse events	Deucrictibant IR capsule (combined dose group)
Number of attacks treated[a]	337
Number of participants[a]	19
Attacks with any TEAE, n (%)	13 (3.9)
Treatment-related TEAEs, n	0
Serious TEAEs, n	1[b]
Treatment-related serious TEAEs, n	0
TEAEs leading to study drug discontinuation, study withdrawal, or death, n	0

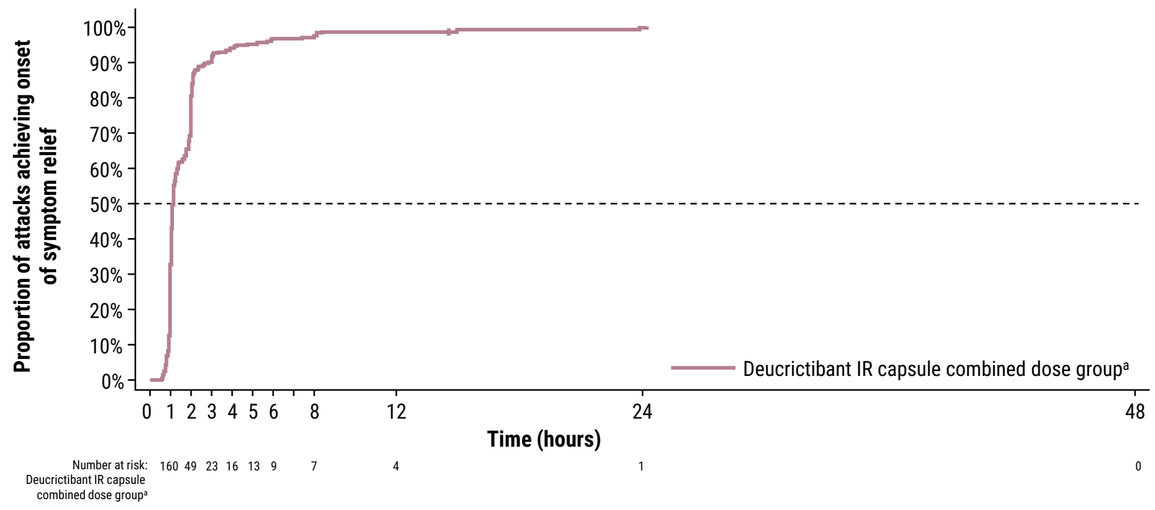
IR, immediate-release; TEAE, treatment-emergent adverse event (defined as adverse event occurring during time window from first study drug administration). [a]Number in the safety analysis set at data cutoff (10 June 2024). [b]Tooth caries unrelated to treatment.

Results

Efficacy

- The median time to onset of symptom relief was 1.1 hours (95% CI, 1.0, 1.2) (**Figure 3, Table 3**).
- 98.5% (261/265) of attacks achieved onset of symptom relief by 12 hours (**Figures 3 and 4**).

Figure 3. Kaplan-Meier plot of time to onset of symptom relief



IR, immediate-release. [a]Includes 10 mg, 20 mg, and 30 mg dose groups.

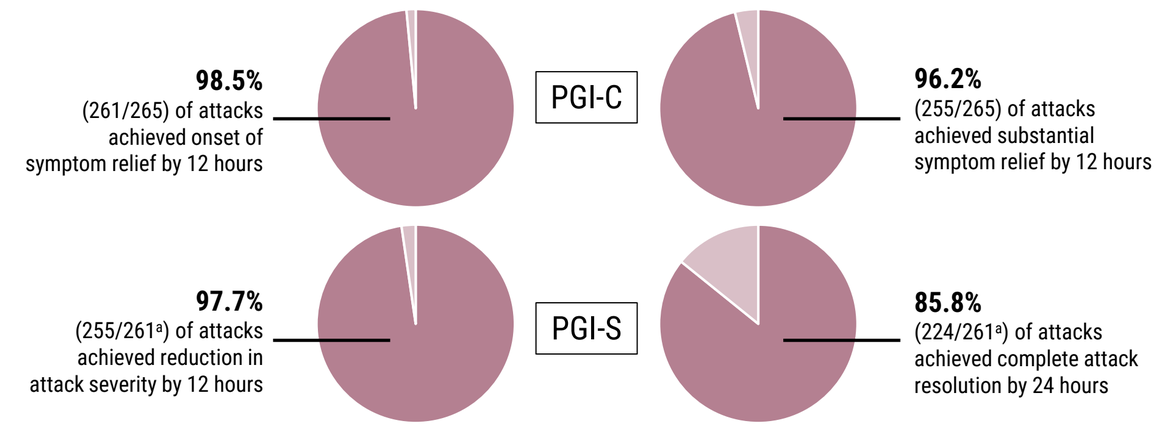
Table 3. Median time to achieving key efficacy endpoints

	Deucrictibant IR capsule (combined dose group)
Number of attacks treated[a]	265
Number of participants with treated attacks[a]	17
Median time to onset of symptom relief using PGI-C, hours (95% CI)	1.1 (1.0, 1.2)
Median time to substantial symptom relief using PGI-C, hours (95% CI)	2.7 (2.1, 2.9)
Median time to reduction in attack severity using PGI-S,[b] hours (95% CI)	2.6 (2.0, 2.9)
Median time to complete attack resolution using PGI-S,[b] hours (95% CI)	11.5 (11.0, 13.0)

IR, immediate-release; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity. [a]Number in the modified intention-to-treat efficacy analysis set at data cutoff (01 March 2024). [b]261 attacks have non-missing pre-treatment PGI-S.

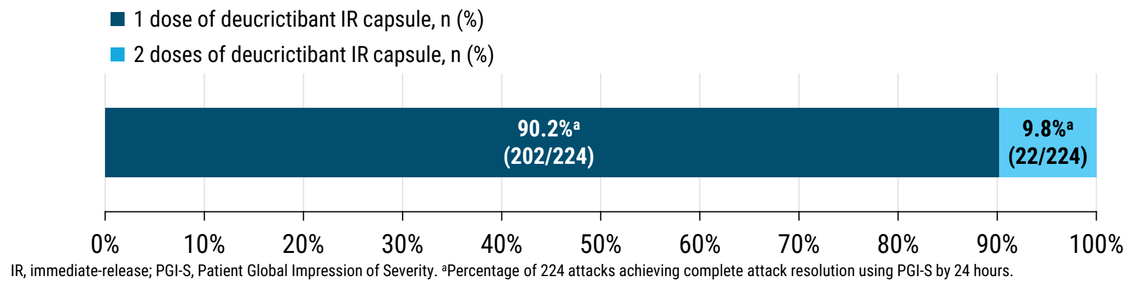
- 85.8% (224/261) of attacks achieved complete attack resolution by 24 hours (**Figure 4**).
  - 90.2% (202/224) of attacks achieved this milestone with a single dose of deucrictibant IR capsule (**Figure 5**).

Figure 4. Proportion of attacks achieving key efficacy endpoints



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

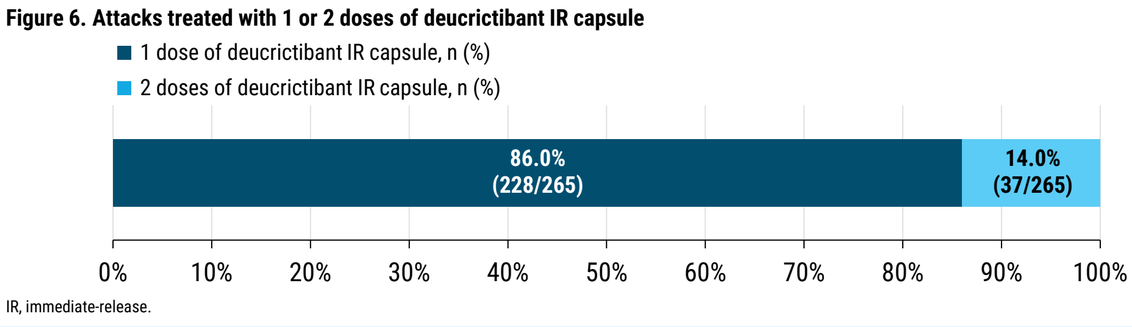
Figure 5. Attacks treated with 1 or 2 doses of deucrictibant IR capsule prior to achieving complete attack resolution



IR, immediate-release; PGI-S, Patient Global Impression of Severity. [a]Percentage of 224 attacks achieving complete attack resolution using PGI-S by 24 hours.

- A total of 86.0% (228/265) of all attacks were treated with a single dose of deucrictibant IR capsule (**Figure 6**).

Figure 6. Attacks treated with 1 or 2 doses of deucrictibant IR capsule



IR, immediate-release.

Conclusions

- **In the current analysis of the ongoing RAPIDe-2 Phase 2/3 extension study, deucrictibant IR capsule was well tolerated for all studied doses with no safety signals observed.**
- **Efficacy analysis showed:**
  - **1.1 hours median time to onset of symptom relief using PGI-C – 98.5% of attacks by 12 hours.**
  - **2.7 hours median time to substantial symptom relief using PGI-C –96.2% of attacks by 12 hours.**
  - **2.6 hours median time to reduction in attack severity using PGI-S – 97.7% of attacks by 12 hours.**
  - **11.5 hours median time to complete attack resolution using PGI-S – 85.8% of attacks by 24 hours.**
  - **86.0% of attacks were treated with a single dose of deucrictibant IR capsule.**
- **Results from the ongoing RAPIDe-2 extension are consistent with the Phase 2 RAPIDe-1 study and provide evidence on the long-term safety and efficacy of deucrictibant IR capsule for repeat treatment of HAE attacks.**

References

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

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Acknowledgments: Medical writing services were provided by Scott Salsman, PhD of Two Labs Pharma Services.

***Our distinguished colleague and friend, Prof. Marcus Maurer, sadly passed away during the finalization of this poster. †RAPIDe-2 is a Pharvaris-sponsored clinical trial. ClinicalTrials.gov identifier: NCT05396105.**