Design of RAPIDe-3 Phase 3 Trial: Efficacy and Safety of the Oral Bradykinin B2 Receptor Antagonist Deucrictibant Immediate-Release Capsule in Treatment of Hereditary Angioedema Attacks

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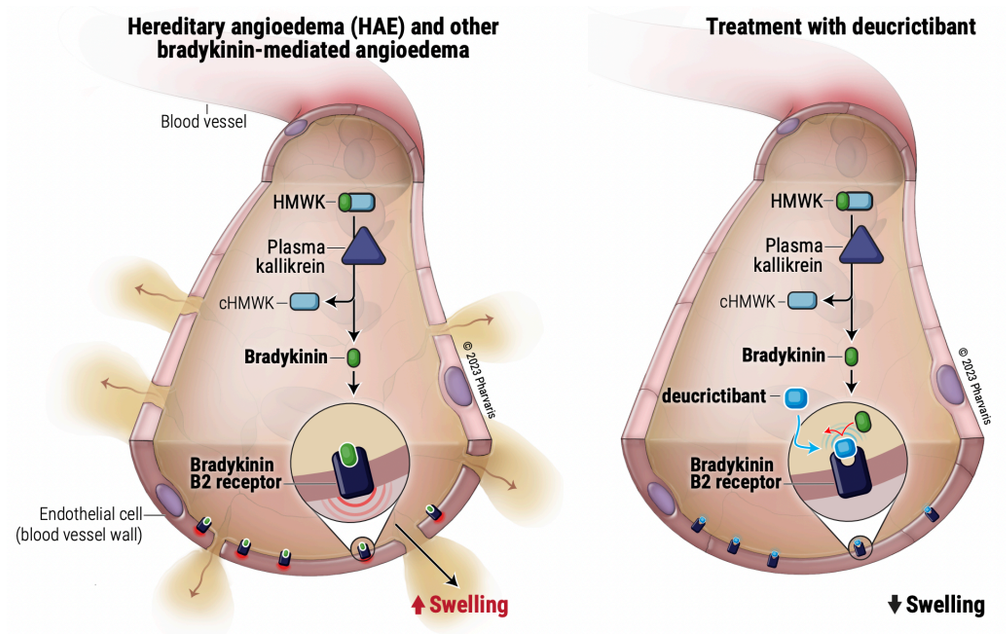
Rationale

- Hereditary angioedema (HAE) attacks are caused by excess bradykinin activating bradykinin B2 receptors (**Figure 1**).[1]
- Burden associated with parenteral administration of approved on-demand treatments (ODTs)[2-6] leads to treatment of many HAE attacks being delayed or forgone.[6-10] An unmet need exists for oral ODTs that are effective and well tolerated, which may reduce the treatment burden and allow for prompt treatment administration.[6-10]
- Deucrictibant is an orally administered, highly potent, specific antagonist of the bradykinin B2 receptor (**Figure 1**) under development for on-demand and prophylactic treatment of HAE attacks.[11-13]
- In the RAPIDe-1 Phase 2 trial, deucrictibant immediate-release (IR) capsule treatment resulted in rapid onset of action, symptom relief, and resolution of HAE attacks, in addition to a substantial reduction in use of rescue medication, and was well tolerated at all dose levels.[11]

Figure 1. Deucrictibant mechanism of action

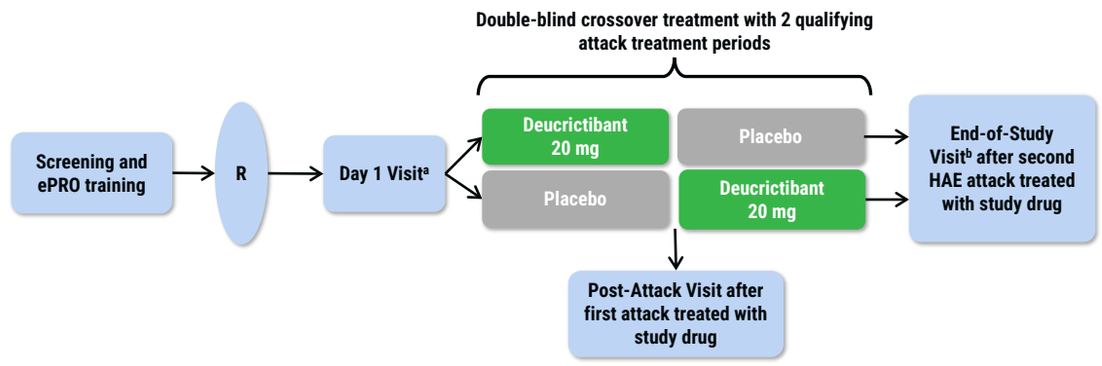


cHMWK, cleaved HMWK; HMWK, high-molecular-weight kininogen.

Methods

- **RAPIDe-3*** is a planned Phase 3 randomized, double-blind, placebo-controlled, crossover trial of oral deucrictibant IR capsule for the ODT of HAE attacks (**Figure 2**).
  - **Primary objective**: to evaluate the efficacy of deucrictibant IR capsule as an ODT compared with placebo on the onset of symptom relief during HAE attacks.
  - **Secondary objectives**: to evaluate the efficacy of deucrictibant as an ODT compared with placebo on symptom relief and resolution of HAE attacks; to evaluate the safety and tolerability of deucrictibant compared with placebo; to assess the pharmacokinetics of deucrictibant in adolescent participants (≥12 to <18 years) in a non-attack state.
  - **Exploratory objective**: to evaluate participants' health-related quality of life (HRQoL).

Figure 2. Study design



ePRO, electronic patient-reported outcome; HAE, hereditary angioedema; R, randomization. [a]Adolescent participants receive a non-attack dose for pharmacokinetic sampling at Day 1 Visit prior to R. [b]Data from the End-of-Study Visit may be used to qualify the participant for an open-label extension study with deucrictibant.

- Eligible participants will be aged ≥12 to ≤75 years old, have been diagnosed with HAE type 1 or 2 (HAE-1/2), and have a history of ≥2 HAE attacks in the last 3 months before screening (**Table 1**).

Table 1. Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• Aged ≥12 to ≤75 years • Diagnosed with HAE-1/2 • History of ≥2 HAE attacks in the last 3 months before screening • Experience using standard-of-care treatment to manage HAE attacks • Participants using long-term prophylactic HAE treatment must be on a stable dose ≥6 months before and during the study	• Pregnancy or breast-feeding • Any comorbidity that would interfere with the participant's safety or ability to participate in the study • Use of attenuated androgens for short-term prophylaxis ≤30 days prior to randomization • Received prior HAE ODT with deucrictibant • Participation in any other investigational drug study

HAE, hereditary angioedema; ODT, on-demand treatment.

Methods (continued)

- The study will include a proportion of participants on long-term prophylactic treatment for HAE.
- Randomization will be stratified according to age (≥12 to <18 years, ≥18 years) and use of long-term HAE prophylaxis (Yes/No).
- During the treatment phase, participants will self-administer double-blinded study drug (deucrictibant IR capsule 20 mg or placebo, in a crossover fashion) to treat 2 qualifying attacks (**Figure 2**).
- For qualified non-laryngeal attacks, a second dose of study drug is permitted ≥4 hours post-first dose if symptoms are persisting or progressing. If symptoms persist or progress at ≥1 hour post-second dose, HAE on-demand rescue medication can be administered.
- After participants self-administer study drug, they will have an on-site or remote Post-Attack Visit (first attack: ≥48 hours to ≤10 days) or on-site End-of-Study Visit (second attack: 10 ± 5 days) for evaluation of treatment-emergent adverse events (TEAEs) and concomitant medication use.

Results (Anticipated Outcomes)

- Approximately 120 participants will be enrolled globally.
- The primary efficacy endpoint is patient-reported time to onset of symptom relief following treatment (**Table 2**).

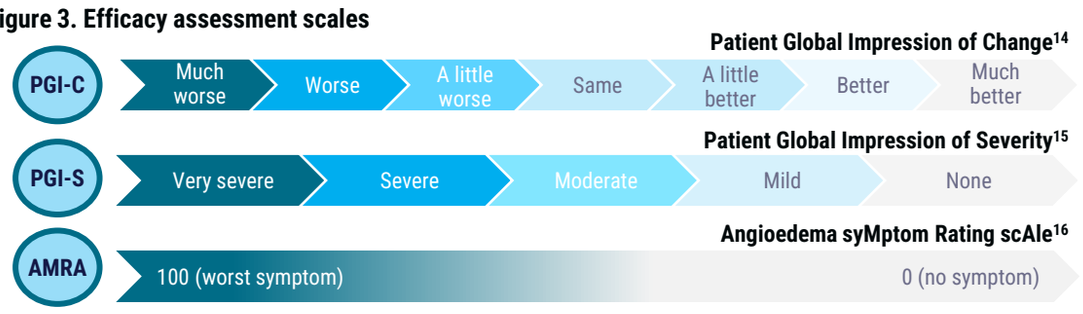
Table 2. Study endpoints

Primary endpoint	• Time to onset of symptom relief, defined as PGI-C rating of at least "a little better" for 2 consecutive timepoints within 12 hours post-treatment
Select secondary endpoints	• Proportion of study drug-treated attacks achieving PGI-C rating of at least "a little better" at 4 hours post-treatment • Time to substantial symptom relief by PGI-C within 12 hours post-treatment • Time to substantial symptom relief by PGI-S within 12 hours post-treatment • Time to complete symptom resolution by PGI-S within 48 hours post-treatment • Time to EoP in attack symptoms within 12 hours by PGI-C • Proportion of study drug-treated attacks requiring rescue medication within 24 hours post-treatment • Proportion of attacks achieving symptom resolution by PGI-S with 1 dose of study drug at 24 hours post-treatment • Time to substantial symptom relief by AMRA within 12 hours post-treatment
Safety endpoints	• Incidence of TEAEs and serious TEAEs • Change from baseline in clinical laboratory tests, vital signs, and ECG parameters

AMRA, Angioedema syMptom Rating scAle; ECG, electrocardiography; EoP, end of progression; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; TEAE, treatment-emergent adverse event.

- Patient-reported outcome (PRO) tools will be used to assess efficacy (**Figure 3**), with data collection at pre-specified timepoints ranging from the time at investigator-confirmed attack qualification to 48 (+6) hours post-dose and with the first post-dose measurement taken at 15 minutes.

Figure 3. Efficacy assessment scales



AMRA-3 assesses skin pain, skin swelling, and abdominal pain, as does AMRA-5, which additionally scores voice change and difficulty swallowing. Data to be collected at time of investigator-confirmed attack qualification and at 15 min, every 30 min from 30 min to 4 hr, every 1 hr from 5–11 hr, every 2 hr from 12–24 hr, 36 hr, and 48 (+6) hr post-dose.

- HRQoL will be evaluated as an exploratory endpoint.
  - Qualitative interviews will be conducted to determine participant experiences with HAE medications (including double-blinded study drug), treatment preferences, non-localized symptoms the participant typically experiences with HAE attacks (e.g., fatigue or anxiety), and impairment of daily activities, as well as HRQoL measured using the EQ-5D-5L questionnaire, ≥48 hours to ≤10 days following each of the 2 attacks treated with study drug.
- Participants who complete RAPIDe-3 can elect to continue deucrictibant IR capsule treatment in an open-label extension if inclusion and exclusion criteria are met.

Conclusions

- **RAPIDe-3 is a planned Phase 3 global study designed to evaluate the efficacy and safety of oral deucrictibant IR capsule for on-demand treatment of attacks in adolescent and adult patients with HAE.**

References

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

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