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

Marcus Maurer[1,2]*, John Anderson[3], Mauro Cancian[4], Danny M. Cohn[5], Henriette Farkas[6], Atsushi Fukunaga[7], Anete S. Grumach[8], Michihiro Hide[9], Constance H. Katelaris[10], **Philip H. Li[11],** William R. Lumry[12], Markus Magerl[1,2], Ricardo D. Zwiener[13], Ming Yu[14], Raf Crabbé[15], Eivind Omli[16], Li Zhu[14], Joan Mendivil[17], Peng Lu[14], Marc A. Riedl[18]

[1]Charité-Universitätsmedizin Berlin, Institute of Allergology, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin; [2]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany; [3]AllerVie Health, Clinical Research Center of Alabama, Birmingham, AL, USA; [4]Univ. Hospital of Padua, Dept. of Systems Medicine, Padua, Italy; [5]Amsterdam UMC, Univ. of Amsterdam, Dept. of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands; [6]Hungarian Angioedema Center of Reference and Excellence, Dept. of Internal Medicine and Haematology, Semmelweis Univ., Budapest, Hungary; [7]Kobe Univ. Graduate School of Medicine, Div. of Dermatology, Dept. of Internal Related, Chuo-ku, Kobe, Japan, and Osaka Medical and Pharmaceutical University, Dept. of Dermatology, Div. of Medicine for Function and Morphology of Sensory Organs, Faculty of Medicine, Takatsuki, Osaka, Japan; [8]Centro Universitario FMABC, Clinical Immunology, Sao Paulo, Brazil; [9]Hiroshima Univ. and Hiroshima Citizens Hospital, Dept. of Dermatology, Hiroshima, Japan; [10]Campbelltown Hospital and Western Sydney Univ., Dept. of Medicine, Sydney, New South Wales, Australia; [11]Queen Mary Hospital, Univ. of Hong Kong, Div. of Rheumatology and Clinical Immunology, Dept. of Medicine, Hong Kong; [12]AARA Research Center, Dallas, TX, USA; [13]Hospital Universitario Austral, Servicio de Alergia e Inmunología, Buenos Aires, Argentina; [14]Pharvaris Inc., Lexington, MA, USA; [15]RC Consultancy, Bassins, Switzerland; [16]Pharvaris Netherlands BV, Leiden, The Netherlands; [17]Pharvaris GmbH, Zug, Switzerland; [18]Univ. of California San Diego, Div. of Allergy and Immunology, La Jolla, CA, USA

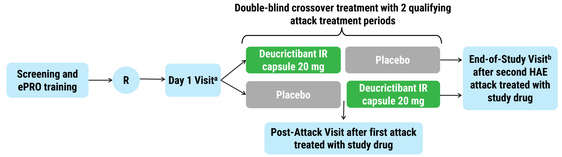
Rationale

- Hereditary angioedema (HAE) attacks are caused by excess bradykinin activating bradykinin B2 receptors.[1]
- The 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, well tolerated, and reduce treatment burden, enabling prompt administration.[6-10]
- Deucrictibant is a selective, orally administered bradykinin B2 receptor antagonist under development for prophylactic and on-demand treatment of HAE attacks.[11-16]
- In the RAPIDe-1 Phase 2 trial (NCT04618211),[11] deucrictibant immediate-release (IR) capsule reduced time to onset of symptom relief and to resolution of HAE attacks vs placebo and treatment was well tolerated.[12]

Clinical trial overview

- **RAPIDe-3** (NCT06343779)[13†] is an ongoing Phase 3 randomized, double-blind, placebo-controlled, crossover trial of oral deucrictibant IR capsule for the ODT of HAE attacks (**Figure 1**).
  - **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 IR capsule as an ODT compared with placebo on symptom relief and resolution of HAE attacks; to evaluate the safety and tolerability of deucrictibant IR capsule compared with placebo; to assess the pharmacokinetics of deucrictibant IR capsule in adolescent participants (aged ≥12 to <18 years) in a non-attack state.
  - **Exploratory objective:** to evaluate participants' health-related quality of life (HRQoL).

Figure 1. RAPIDe-3 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 IR capsule.

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

Table 1. RAPIDe-3 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 with 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.

Clinical trial overview (continued)

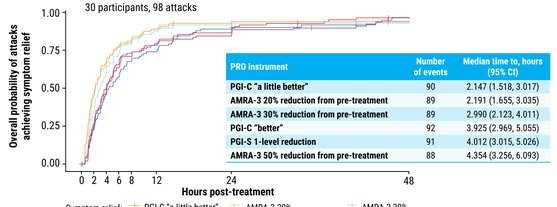
- The study includes a proportion of participants on long-term prophylactic treatment for HAE.
- Randomization is stratified according to age (≥12 to <18 years, ≥18 years) and use of long-term HAE prophylaxis (Yes/No).
- During the treatment phase, participants self-administer the double-blinded study drug (deucrictibant IR capsule 20 mg or placebo, in a crossover fashion) to treat two qualifying attacks (**Figure 1**).
- Qualifying attacks could be either non-laryngeal attacks or non-severe laryngeal attacks not associated with breathing difficulties or stridor.
- After participants self-administer study drug, they 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 (**Figure 1**).
- Time to onset of symptom relief as defined by Patient Global Impression of Change (PGI-C) "a little better" in two consecutive timepoints was selected as the primary endpoint for RAPIDe-3 (**Table 2**). The rationale for this choice was the observation that, in a recent real-world validation study of on-demand HAE endpoints using standard-of-care therapies[17], this was the most sensitive measure of onset of symptom relief (**Figure 2** and **Table 3**).

Table 2. Study endpoints in RAPIDe-3

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
Selected 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, electrocardiogram; EoP, end of progression; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; TEAE, treatment-emergent adverse event.

Figure 2 and Table 3. Time to symptom relief in a validation study of on-demand HAE endpoints[17]



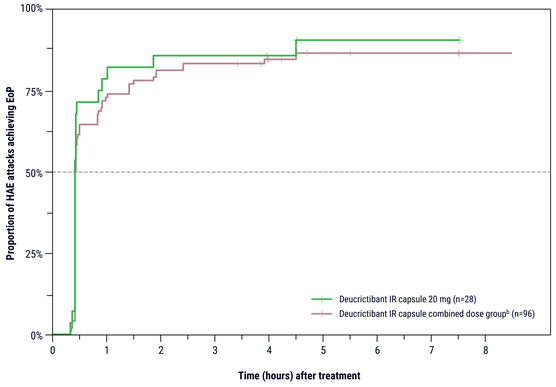
PRO instrument	Number of events	Median time to, hours (95% CI)
PGI-C "a little better"	90	2.147 (1.518, 3.017)
AMRA-3 20% reduction from pre-treatment	89	2.191 (1.655, 3.035)
AMRA-3 30% reduction from pre-treatment	89	2.990 (2.123, 4.011)
PGI-C "better"	92	3.925 (2.969, 5.055)
PGI-S 1-level reduction	91	4.012 (3.015, 5.026)
AMRA-3 50% reduction from pre-treatment	88	4.354 (3.256, 6.093)

AMRA, Angioedema syMptom Rating scAle; CI, confidence interval; HAE, hereditary angioedema; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcome.

Clinical trial overview (continued)

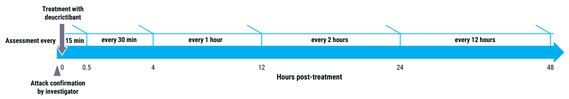
- Approximately 120 participants will be enrolled globally.
- In the Phase 2 RAPIDe-1 trial, deucrictibant IR capsule treatment showed rapid onset of action, achieving end of progression (EoP) at a median time of 25–26 minutes post-treatment (**Figure 3**), informing a first post-dose patient-reported outcome (PRO) measurement time of 15 minutes in RAPIDe-3 (**Figure 4**).

Figure 3. Kaplan-Meier plot of time to end of progression (EoP)[a] in the RAPIDe-1 Phase 2 trial



HAE, hereditary angioedema; IR, immediate-release. [a]EoP was assessed in a post-hoc analysis of RAPIDe-1 and defined as the earliest post-treatment timepoint with highest 3-symptom composite (skin pain, skin swelling, abdominal pain) Angioedema syMptom Rating scAle (AMRA-3) score and no use of rescue medication. [b]Includes 10 mg, 20 mg, and 30 mg dose groups.

Figure 4. Timeline of PRO assessments in RAPIDe-3



PRO, patient-reported outcome.

- For qualifying 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.

Clinical trial overview (continued)

- In the Phase 2 RAPIDe-1 trial, although a second dose was not permitted, the majority of attacks did not require rescue medication (**Figure 5**) and resolved with a single dose of deucrictibant IR capsule within 24 hours (**Figure 6**).

Figure 5. Attacks treated with rescue medication by 24 hours after treatment in RAPIDe-1

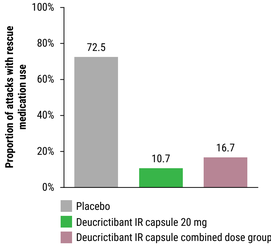
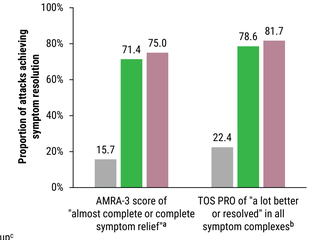


Figure 6. Attacks achieving symptom resolution with a single dose within 24 hours in RAPIDe-1



AMRA, Angioedema syMptom Rating scAle; IR, immediate-release; TOS PRO, Treatment Outcome Score patient-reported outcome. [a]All 3 individual AMRA scores ≤10 (key secondary endpoint). AMRA-3 was called the 3-symptom composite Visual Analogue Scale (VAS-3) in the RAPIDe-1 trial. [b]TOS PRO was assessed in a post-hoc analysis of RAPIDe-1. [c]Includes 10 mg, 20 mg, and 30 mg dose groups.

- HRQoL is evaluated as an exploratory endpoint.
  - Qualitative interviews examine 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), impairment of daily activities, as well as HRQoL as measured using EQ-5D-5L, are conducted ≥48 hours to ≤10 days following each of the two 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 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.**
- **Results from the RAPIDe-1 Phase 2 study and a real-world HAE endpoint validation study support the RAPIDe-3 study design.**

References

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