RAPIDe-3 Phase 3 Trial Design: Oral Deucrictibant Immediate-Release Capsule in Treatment of Hereditary Angioedema Attacks

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

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

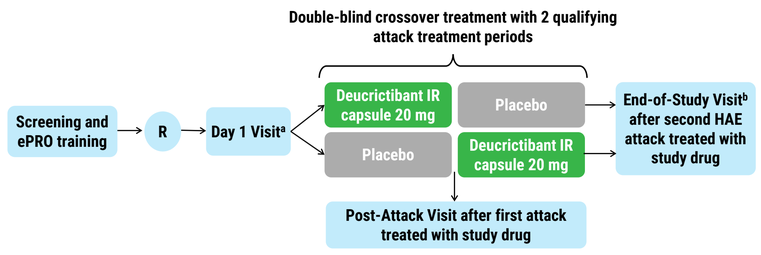
Rationale

- 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.[11-18]
- 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 (1) efficacy of deucrictibant IR capsule as an ODT compared with placebo on symptom relief and resolution of HAE attacks, (2) safety and tolerability of deucrictibant IR capsule compared with placebo, and (3) 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; IR, immediate release; R, randomization. [a]Adolescent participants receive a non-attack dose for pharmacokinetic sampling at day 1 visit prior to randomization. [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 breastfeeding • 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.

- 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,[19] this was the most sensitive measure of onset of symptom relief (**Figure 2** and **Table 3**).

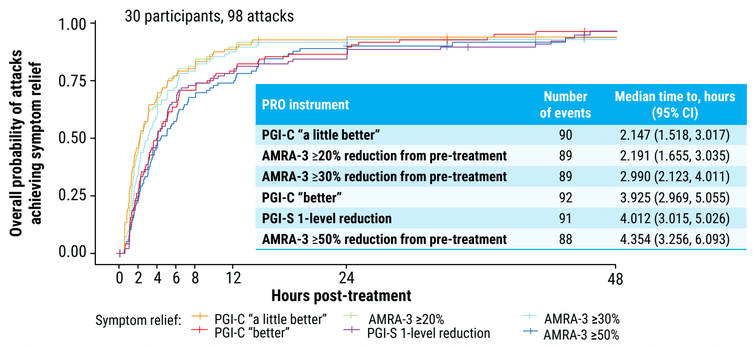
Clinical trial overview (continued)

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 two consecutive timepoints by 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 using PGI-C by 12 hours post-treatment. • Time to substantial symptom relief using PGI-S by 12 hours post-treatment. • Time to complete symptom resolution using PGI-S by 48 hours post-treatment. • Time to end of progression (EoP)[a] in attack symptoms using PGI-C by 12 hours. • Proportion of study drug-treated attacks requiring rescue medication by 24 hours post-treatment. • Proportion of attacks achieving symptom resolution using PGI-S with 1 dose of study drug at 24 hours post-treatment. • Time to substantial symptom relief using AMRA by 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; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; TEAE, treatment-emergent adverse event. [a]Time to EoP is defined as the earliest post-treatment timepoint after which all subsequent PGI-C ratings are stable or improved.

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

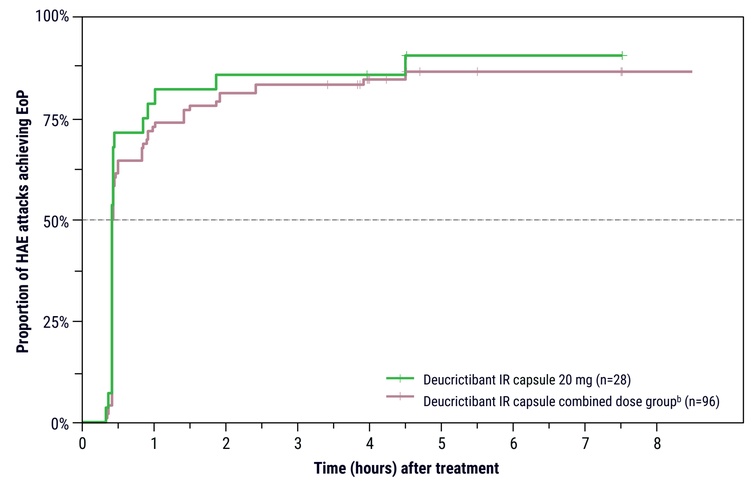


PRO instrument	Number of events	Median time to, hours (95% CI)
PGI-C "a little better"	90	2.147 (1.518, 3.017)
AMRA-3 ≥20% reduction from pre-treatment	89	2.191 (1.655, 3.035)
AMRA-3 ≥30% reduction from pre-treatment	89	2.990 (2.123, 4.011)
PGI-C "better"	92	3.925 (2.969, 5.055)
PGI-S 1-level reduction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

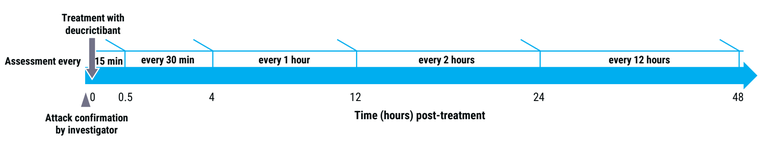
- Approximately 120 participants will be enrolled globally.
- In the Phase 2 RAPIDe-1 trial, deucrictibant IR capsule treatment showed rapid onset of action, achieving end of progression (EoP) at a median time of 25–26 minutes post-treatment (**Figure 3**).
- This informed a first post-dose patient-reported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



AMRA, Angioedema syMptom Rating scAle; EoP, end of progression; 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) AMRA-3 score and no use of rescue medication. (AMRA-3 was called the 3-symptom composite VAS-3 in the RAPIDe-1 trial.) [b]Includes 10 mg, 20 mg, and 30 mg dose groups.

Figure 4. Timeline of PRO assessments in RAPIDe-3



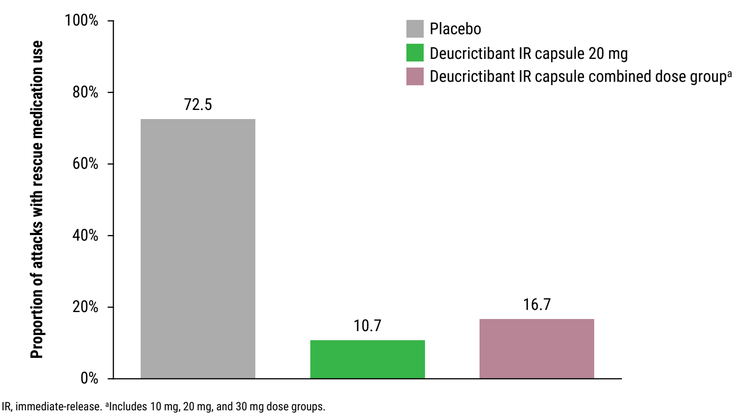
PRO, patient-reported outcome.

- 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.

Results

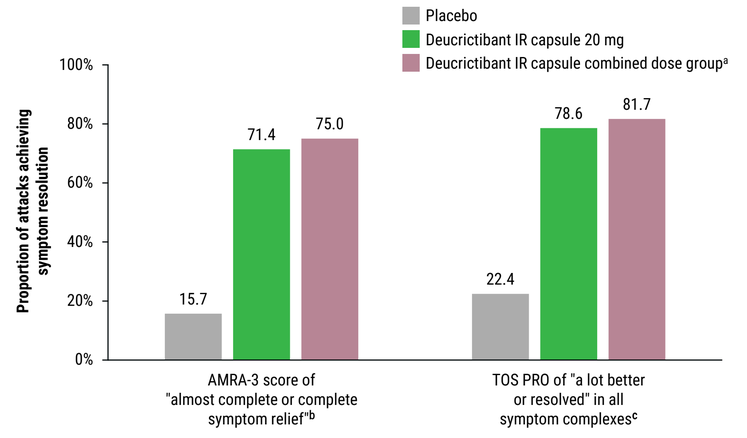
- In the Phase 2 RAPIDe-1 trial, although a second dose was not permitted, the majority of attacks did not result in rescue medication use (**Figure 5**) and resolved with a single dose of deucrictibant IR capsule by 24 hours (**Figure 6**).

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



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

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



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

- 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 an ongoing, global, Phase 3 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

1. Busse PJ, et al. *N Engl J Med*. 2020;382:1136-48. **2.** Berinert® [package insert]. https://labeling.cslbehring.com/pi/us/berinert/en/berinert-prescribing-information.pdf. Accessed November 26, 2024. **3.** Firazyr® [package insert]. https://www.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf. Accessed November 26, 2024. **4.** Kalbitor® [package insert]. https://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf. Accessed November 26, 2024. **5.** Ruconest® [package insert]. https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf. Accessed November 26, 2024. **6.** Mendivil J, et al. Presented at: ACAAI; Nov 9–13, 2023; Anaheim, CA, USA. **7.** Mendivil J, et al. Presented at: AAAAI; February 28–March 3, 2024; San Diego, CA, USA. **8.** Center for Biologics Evaluation and Research. The voice of the patient – hereditary angioedema. US Food and Drug Administration; May 2018. https://www.fda.gov/media/113509/download. Accessed November 26, 2024. **9.** Betschel SD, et al. *J Allergy Clin Immunol Pract*. 2023;11:2315-23. **10.** Covella B, et al. *Future Pharmacol*. 2024;4:41-53. **11.** https://clinicaltrials.gov/study/NCT04618211. Accessed November 26, 2024. **12.** Maurer M, et al. Presented at: AAAAI; February 24–27, 2023; San Antonio, TX, USA. **13.** https://www.clinicaltrials.gov/study/NCT06343779. Accessed November 26, 2024. **14.** https://www.clinicaltrials.gov/study/NCT05396105. Accessed November 26, 2024. **15.** E. Aygören-Pürsün, et al. Presented at: EAACI; May 31–June 3, 2024; Valencia, Spain. **16.** https://www.clinicaltrials.gov/study/NCT05047185. Accessed November 26, 2024. **17.** https://www.clinicaltrials.gov/study/NCT06669754. Accessed November 29, 2024. **18.** https://www.clinicaltrials.gov/study/NCT06679881. Accessed November 29, 2024. **19.** Mendivil J, et al. Presented at: GA²LEN UCARE Conference; Dec 8, 2023; São Paulo, Brazil.

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

COI: Grants/research support, honoraria or consultation fees, sponsored speaker bureau – **P.H.L.**: none; **J.A.**: BioCryst, BioMarin, CSL Behring, Cycle Pharma, KalVista, Pharming, Pharvaris, Takeda; **M.C.**: BioCryst, CSL Behring, KalVista, Menarini, MSD, Novartis, Pharming, Pharvaris, Sobi, Takeda, UCB; **D.M.C.**: Astria, BioCryst, CSL Behring, Ionis, KalVista, Pharming, Pharvaris, Takeda; **H.F.**: BioCryst, CSL Behring, Intellia, KalVista, ONO Pharmaceutical, Pharming, Pharvaris, Takeda; **A.F.**: Kaken, Kyorin, Kyowa-Kirin, Mitsubishi-Tanabe, Novartis, Sanofi, Taiho, Takeda; **A.S.G.**: The Binding Site, BioMarin, Brazilian research entity (CNPq), Catalyst, CSL Behring, Exeltis, KalVista, Multicare, Pharvaris, Pint-Pharma, Takeda; **M.H.**: BioCryst, CSL Behring, KalVista, Pharvaris, Takeda, Torii; **C.H.K.**: CSL Behring, Takeda; **W.R.L.**: AstraZeneca, Astria, BioCryst, BioMarin, CSL Behring, Fresenius-Kabi, Grifols, GSK, Intellia, Ionis, KalVista, Magellan, Optinose, Pharming, Pharvaris, Regeneron, Sanofi, Takeda, Teva; **M.Mag.**: BioCryst, CSL Behring, Intellia, KalVista, Novartis, Octapharma, Pharming, Pharvaris, Takeda; **M.A.R.**: Astria, BioCryst, BioMarin, CSL Behring, Cycle Pharma, Fresenius-Kabi, Grifols, Ionis, Ipsen, KalVista, Ono Pharma, Pfizer, Pharming, Pharvaris, RegenxBio, Sanofi/Regeneron, Takeda; **R.D.Z.**: AbbVie, Bago, CSL Behring, KalVista, Novartis, Panalab, Pint-Pharma, Sanofi, Takeda; **M.Y., E.O., L.Z., J.M.**: employee of Pharvaris, holds stocks in Pharvaris; **R.C.**: employee of CG Consultancy and consultant to Pharvaris, holds stocks in Pharvaris; **P.L.**: employee of Pharvaris, holds stocks/stock options in Pharvaris; **M.Mau.**: Averum, Attune, BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, Takeda.
Acknowledgments: Medical writing support was 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-3 is a Pharvaris-sponsored clinical trial. ClinicalTrials.gov identifier: NCT06343779.**