Efficacy and Safety of Oral Deucrictibant Immediate-Release Capsule in Hereditary Angioedema: RAPIDe-3 Phase 3 Clinical Trial Design

M. Hide, J. Anderson, M. Cancian, D.M. Cohn, H. Farkas, A. Fukunaga, A.S. Grumach, C.H. Katelaris, P.H. Li, W.R. Lumry, M. Mager, M.A. Riedl, R.D. Zwiener, M. Yu, R. Crabbé, E. Omli, L. Zhu, J. Mendivil, P. Lu, M. Maurer*

73rd Annual Meeting of the Japanese Society of Allergology
Kyoto, Japan; 18 – 20 October 2024

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

*Our distinguished colleague and friend, Prof. Marcus Maurer, sadly passed away during the finalization of this slide presentation.

Form1-A

Japanese Society of Allergology COI Disclosure

Name of all presenters : ◎M. Hide, J. Anderson, M. Cancian, D.M. Cohn, H. Farkas, A. Fukunaga, A.S. Grumach, C.H. Katelaris, P.H. Li, W.R. Lumry, M. Mager, M.A. Riedl, R.D. Zwiener, M. Yu, R. Crabbé, E. Omli, L. Zhu, J. Mendivil, P. Lu, M. Maurer *(◎Corresponding author)*

Enterprises, etc. with which there is a COI relationship to be disclosed pertaining to the topic presentation:

(1) Employment/Leadership position/Advisory role : No

(2) Stock ownership or options : No

(3) Patent royalties/licensing fees : No

(4) Honoraria (e.g. lecture fees) : BioCryst, CSL Behring, KalVista, Pharvaris, Takeda, Torii

(5) Fees for promotional materials (e.g. manuscript fee) : No

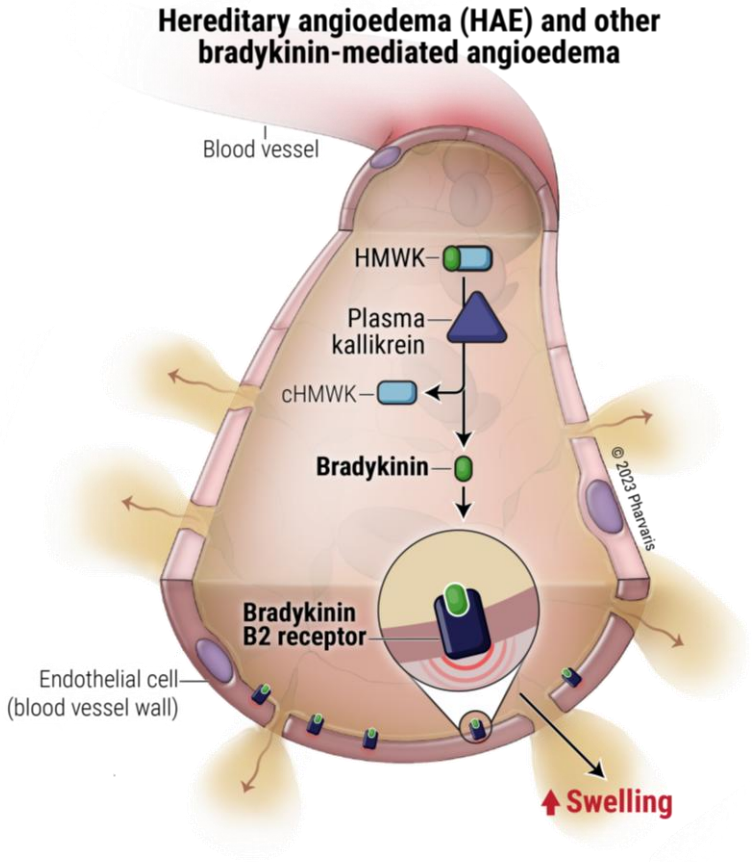
(6) Research funding (clinical trial, contract and collaborative researches) : No

(7) Scholarship donation : No

(8) Donated fund laboratory : No

(9) Others (e.g. trips, travel, or gifts, which are not related to research) : No

Hereditary angioedema (HAE) is a bradykinin-mediated condition with unmet medical needs



- International guidelines recommend that HAE attacks are **treated as early as possible**.[1-3]
- Burden associated with **parenteral administration** of currently approved on-demand medications[4-8] leads to treatment of a number 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 enabling prompt administration.[13]

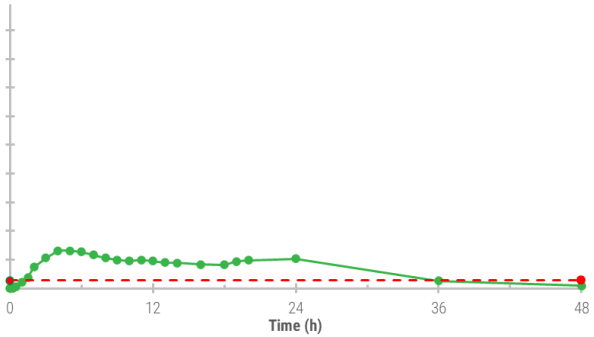
cHMWK, cleaved HMWK; HMWK, high-molecular-weight kininogen.**1**. Betschel S, et al. *Allergy Asthma Clin Immunol.* 2019;15:72. **2**. Busse PJ, et al. *J Allergy Clin Immunol Pract.* 2021;9:132-50. **3**. Maurer M. et al. *Allergy.* 2022;77:1961-90. **4**. Berinert®. Package insert. Accessed September 16, 2024. https://labeling.cslbehring.com/pi/us/berinert/en/berinert-prescribing-information.pdf; **5**. Cinryze®. Summary of product characteristics. Accessed September 27. https://www.ema.europa.eu/en/documents/product-information/cinryze-epar-product-information_en.pdf; **6**. Firazyr®. Package insert. Accessed September 27, 2024. https://www.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf; **7**. Kalbitor®. Package insert. Accessed September 27, 2024. https://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf; **8**. Ruconest®. Package insert. Accessed September 27, 2024. https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf; **9**. Burnette A, et al. Presented at: AAAAI; February 24–27, 2023; San Antonio, TX, USA. **10**. Tuong LA, et al. *Allergy Asthma Proc* 2014;35:250-4. **11.** Center for Biologics Evaluation and Research. The voice of the patient–Hereditary angioedema. US Food and Drug Administration. Accessed September 27, 2024. https://www.fda.gov/media/113509/download; **12**. Radojicic C, et al. Presented at: AAAAI; February 24–27, 2023; San Antonio, TX, USA. **13**. Mendivil J, et al. Presented at: ACAAI; November 9–13, 2023; Anaheim, CA, USA.

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

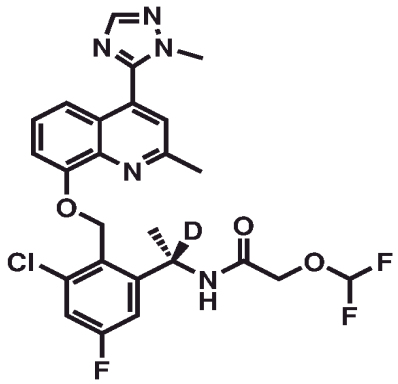
Two investigational oral therapies with the same active ingredient for the prophylactic and on-demand treatment of HAE attacks

DEUCRICTIBANT extended-release (XR) tablet

sustained absorption[1]



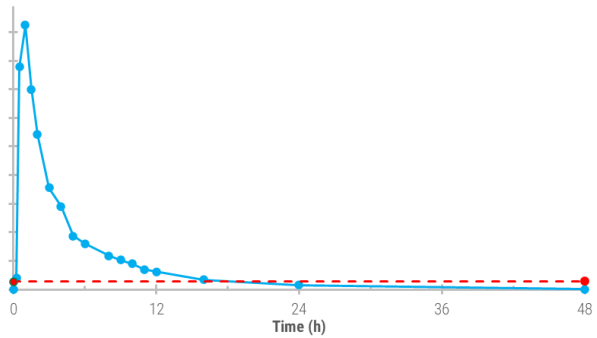
Maintains sustained therapeutic exposure over 24 hours[2] from day one, allowing for once-daily oral treatment to prevent HAE attacks[a]



deucrictibant

DEUCRICTIBANT immediate-release (IR) capsule

rapid absorption[3]



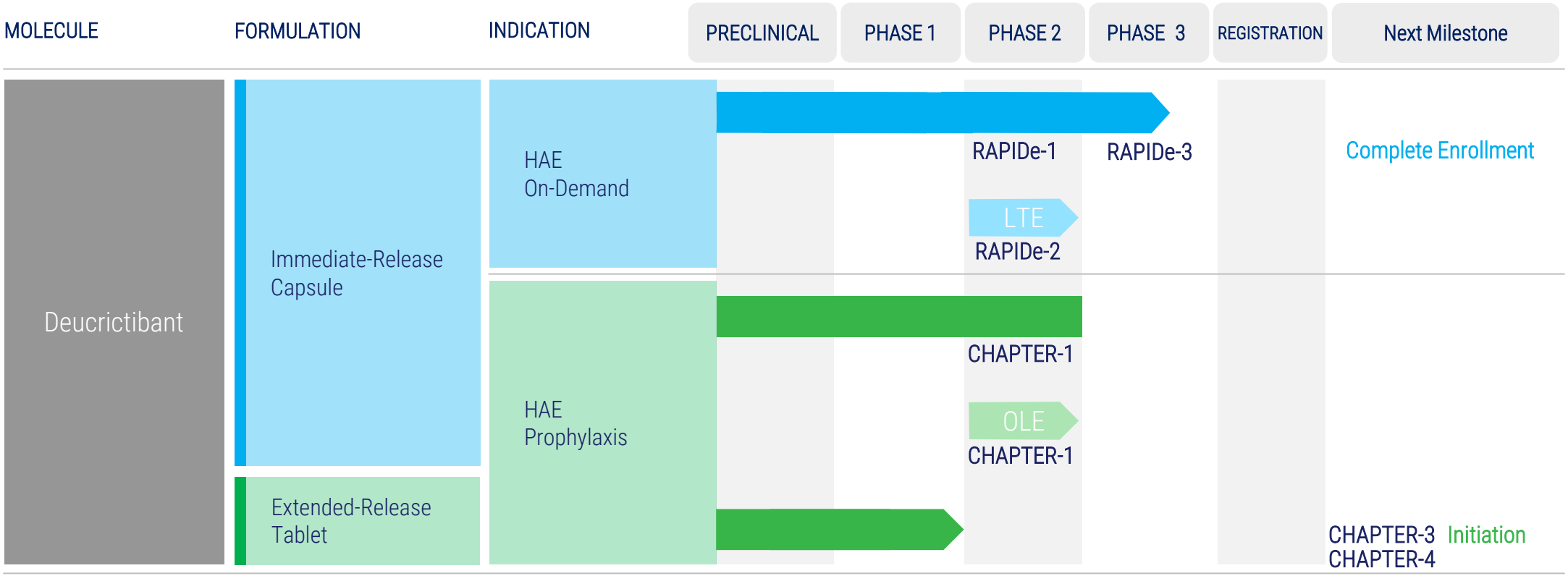
Rapidly reaches therapeutic exposure within 15-30 minutes[4], making it suitable for on-demand oral treatment of HAE attacks[a]

Two oral products with the same active ingredient for the prevention and treatment of HAE attacks

HAE, hereditary angioedema. [a]Aspirational; to be confirmed with clinical data from Phase 3 studies. **1.** Company data: single-dose cross-over PK study in healthy volunteers (n=14) under fasting conditions. **2.** Lesage A et al. Presented at IDDST; May 22-24, 2024. **3.** Crabbe et al. Presented at AAAAI; Feb 26-Mar 1, 2021. **4.** Maurer M, et al. Presented at AAAAI; Feb 24-27, 2023; San Antonio, TX, USA.

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

Deucrictibant development program in HAE

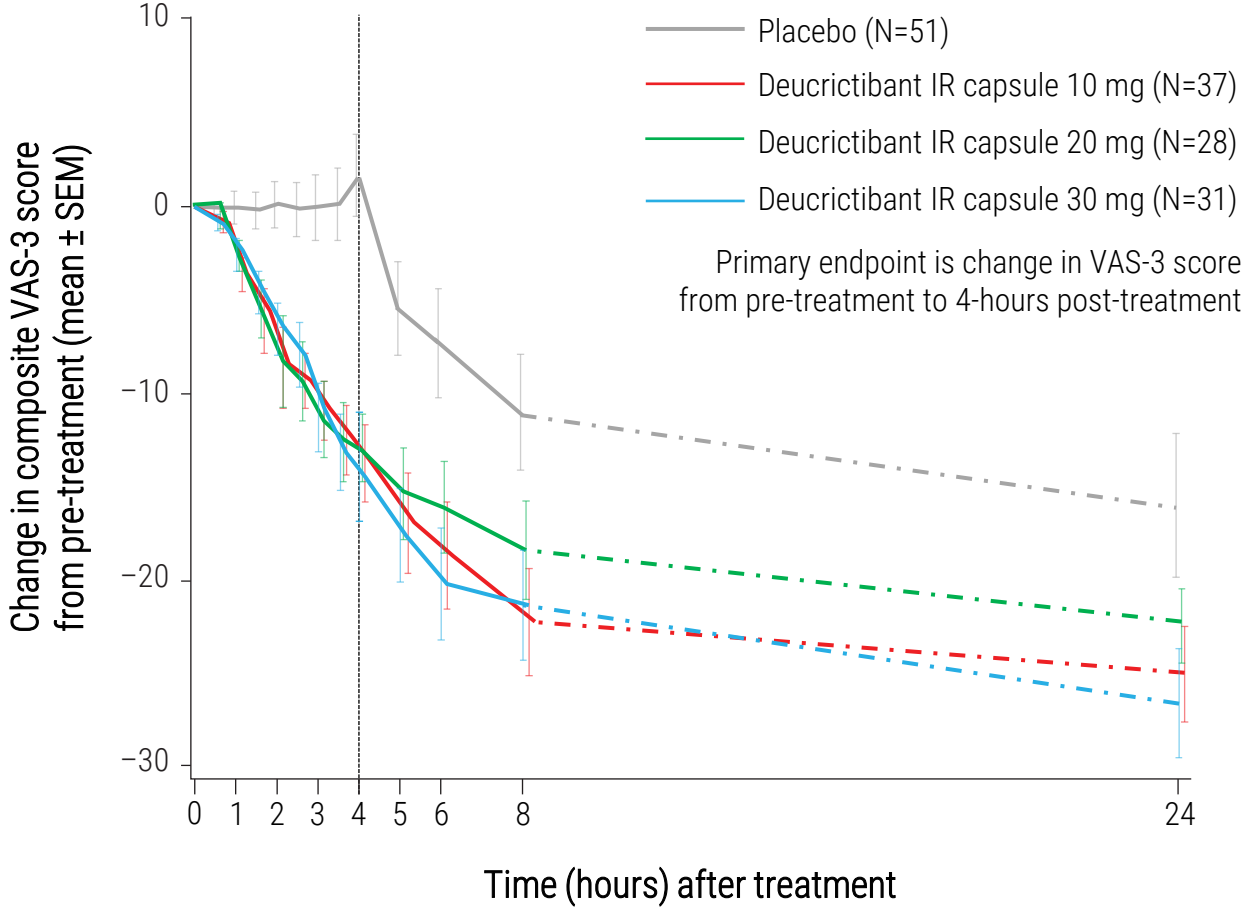


HAE, hereditary angioedema; LTE, long-term extension; OLE, open-label extension; RCT, randomized controlled trial. **1.** RAPIDe-1. ClinicalTrials.gov identifier: NCT04618211. https://www.clinicaltrials.gov/study/NCT04618211. Accessed September 27, 2024. **2.** RAPIDe-2. ClinicalTrials.gov identifier: NCT05396105. Accessed September 27, 2024. https://www.clinicaltrials.gov/study/NCT05396105. **3.** RAPIDe-3. ClinicalTrials.gov identifier: NCT06343779. Accessed September 27, 2024. https://www.clinicaltrials.gov/study/NCT06343779. **4.** CHAPTER-1. ClinicalTrials.gov identifier: NCT05047185. Accessed September 27, 2024. https://www.clinicaltrials.gov/study/NCT05047185.

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

RAPIDe-1 Phase 2 trial supported further development of deucrictibant IR capsule as a potential on-demand treatment for HAE attacks

- A total of 147 attacks were treated by 62 participants with double-blinded placebo or deucrictibant IR capsule 10, 20 or 30mg.[1]
- Deucrictibant IR capsule treatment resulted in:
  - rapid onset of action
  - reduced time to onset of symptom relief and to resolution of HAE attacks
  - substantial reduction in use of rescue medication
- Deucrictibant IR capsule treatment was well tolerated at all doses.
- Deucrictibant IR capsule 20mg was the selected dose for the RAPIDe-3 Phase 3 study.[2]



HAE: hereditary angioedema; IR: immediate-release; SEM, standard error of the mean; VAS, Visual Analogue Scale.

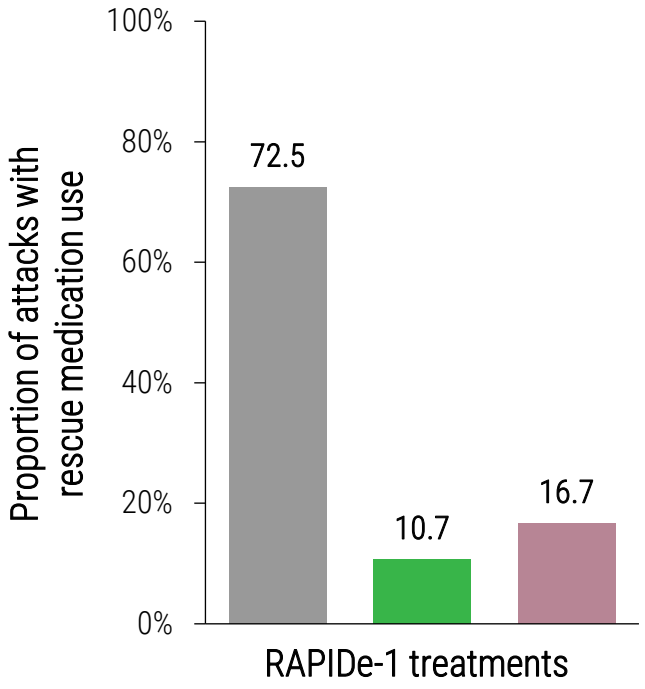
1. Maurer M, et al. Presented at AAAAI 2023. February 23–26, 2023; San Antonio, TX, USA. **2.** RAPIDe-3. ClinicalTrials.gov identifier: NCT06343779. Accessed September 29, 2024. https://www.clinicaltrials.gov/study/NCT06343779.

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

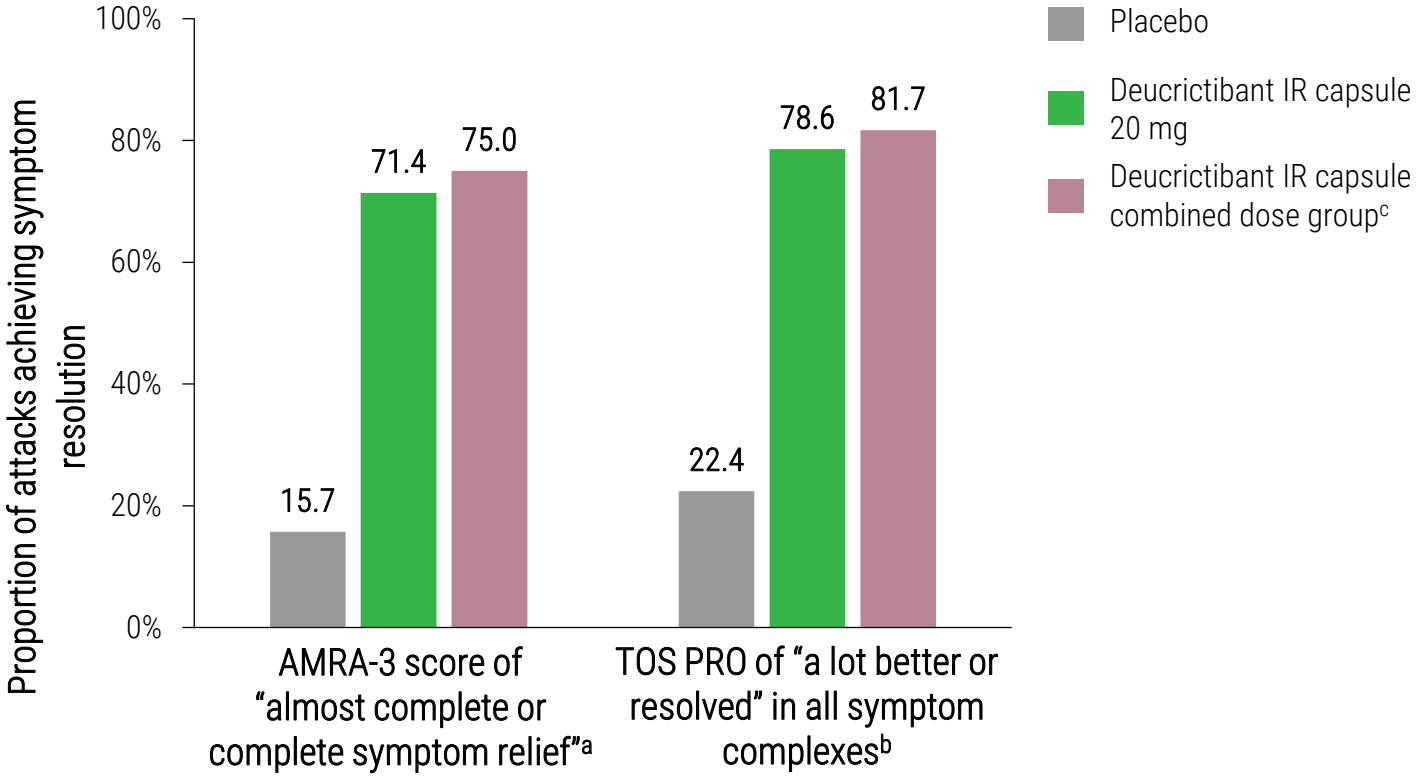
RAPIDe-1: Rescue medication use and symptom resolution

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

Attacks **treated with rescue medication** by 24 hours after treatment in **RAPIDe-1**



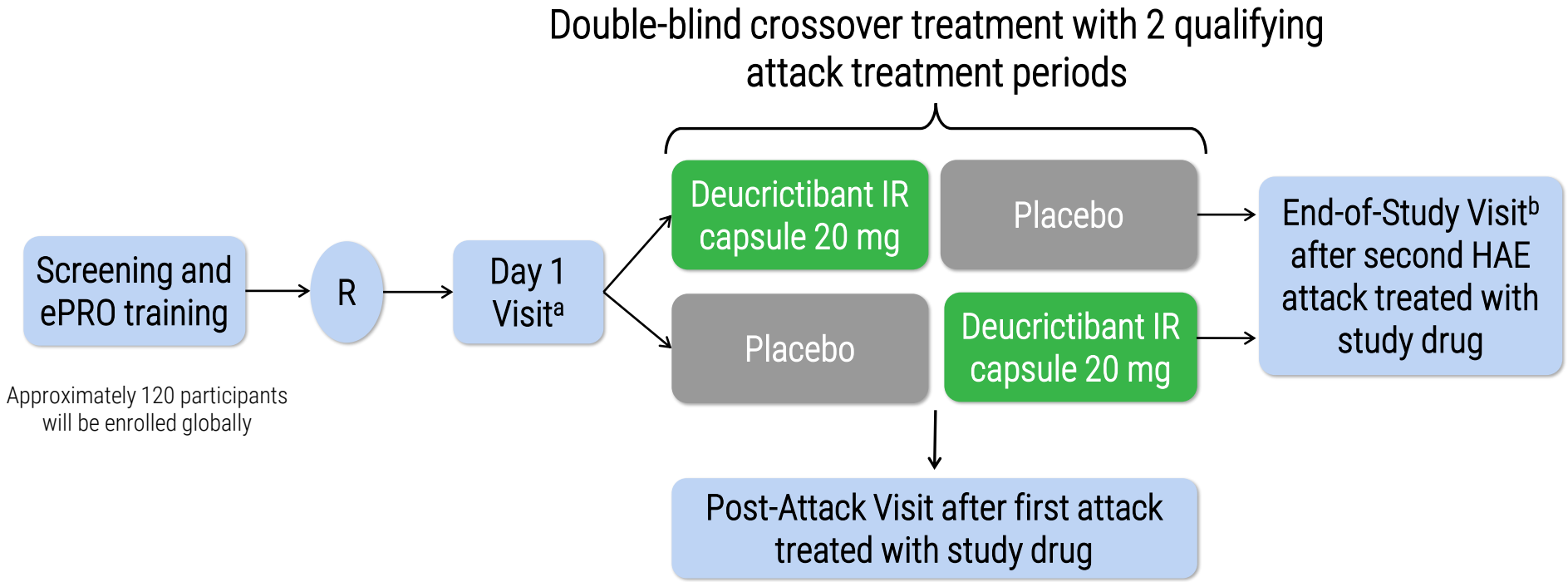
Attacks **achieving symptom resolution** with a single dose by 24 hours in **RAPIDe-1**



AMRA, Angioedema syMptom Rating scAle; IR, immediate-release; TOS PRO, Treatment Outcome Score patient-reported outcome. [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 deucrictibant 10 mg, 20 mg, and 30 mg dose groups.

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

RAPIDe-3 is an ongoing Phase 3 randomized, double-blind, placebo-controlled, crossover trial of deucrictibant IR capsule for on-demand treatment of HAE attacks



Primary objective	Efficacy of deucrictibant IR capsule as on-demand treatment vs placebo on the onset of symptom relief during HAE attacks
Secondary objectives	Efficacy of deucrictibant IR capsule as on-demand treatment vs placebo on symptom relief and resolution of HAE attacks Safety and tolerability of deucrictibant IR capsule vs placebo Pharmacokinetics in adolescent participants (aged ≥12 to <18 years) in a non-attack state[a]
Exploratory objective	Participants' HRQoL

ePRO, electronic patient-reported outcome; HAE, hereditary angioedema; HRQoL, health-related quality of life; IR, immediate-release; 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.

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

RAPIDe-3: 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).
- Qualifying attacks could be either non-laryngeal attacks or non-severe laryngeal attacks not associated with breathing difficulties or stridor.
  - 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.
- Participants who complete RAPIDe-3 can elect to continue deucrictibant IR capsule treatment in an open-label extension.

HAE: hereditary angioedema; IR: immediate-release.

RAPIDe-3: Eligibility criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Aged ≥12 to ≤75 years • Diagnosed with HAE type 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 prophylaxis 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 on-demand treatment with deucrictibant • Participation in any other investigational drug study

HAE, hereditary angioedema.

RAPIDe-3: Study endpoints

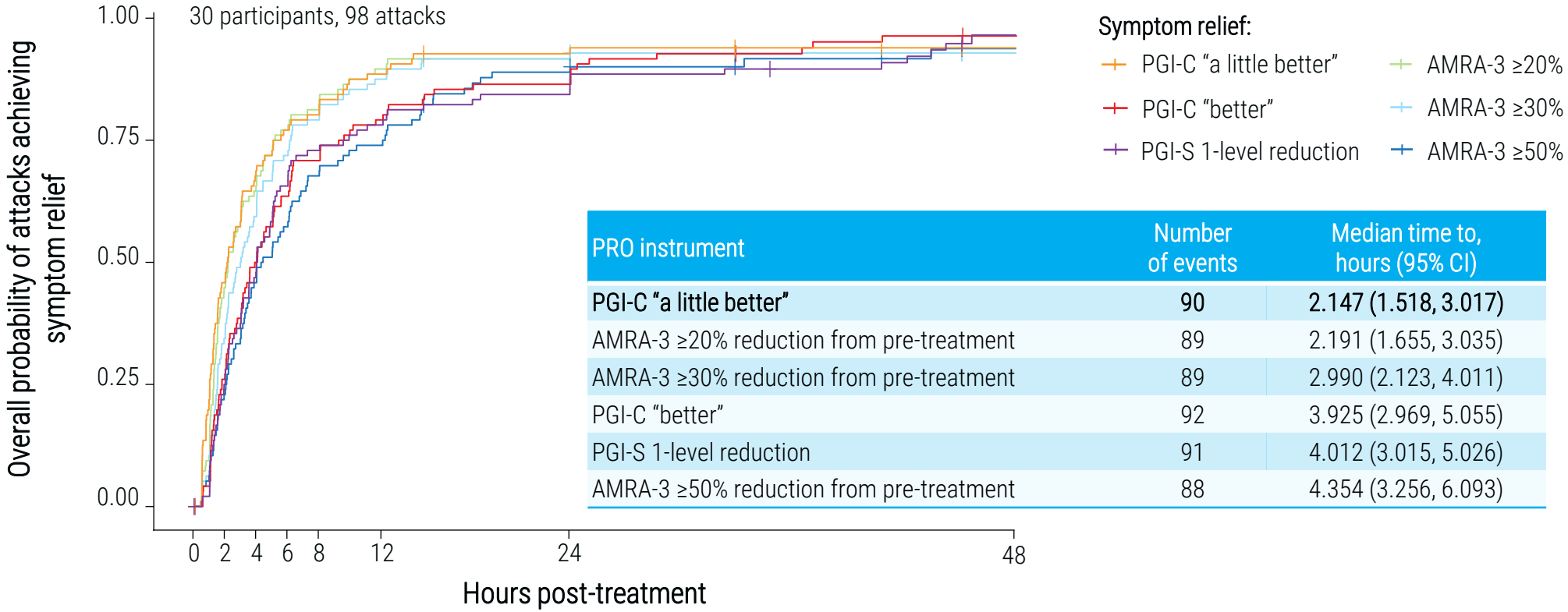
Primary	• Time to onset of symptom relief, defined as PGI-C rating of at least "a little better" for 2 consecutive timepoints by 12 hours post-treatment
Selected secondary	• Proportion of study drug-treated attacks achieving PGI-C rating of at least "a little better" at 4 hours post-treatment • Time 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] of 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
Patient-reported outcomes	• Qualitative interviews to determine participant experiences with HAE medications, treatment preferences, non-localized symptoms the participant typically experiences with HAE attacks (e.g., fatigue or anxiety), impairment of daily activities • HRQoL (using EQ-5D-5L) at ≥48 hours to ≤10 days following each of the two attacks treated with study drug
Safety	• 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; EQ-5D-5L, EuroQoL 5-dimensions 5-levels assessment; HAE, hereditary angioedema; HRQoL, health-related quality of life; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; TEAE, treatment-emergent adverse event. [a]Time to end of progression is defined as the earliest post-treatment timepoint after which all subsequent PGI-C ratings are stable or improved.

RAPIDe-3: Rationale for primary endpoint selection

- In a real-world validation study of on-demand HAE endpoints using standard-of-care therapies, the most sensitive measure of onset of symptom relief was time to onset of symptom relief as defined by PGI-C "a little better" in two consecutive timepoints.[1]

Time to symptom relief in a validation study of on-demand HAE endpoints[1]



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.

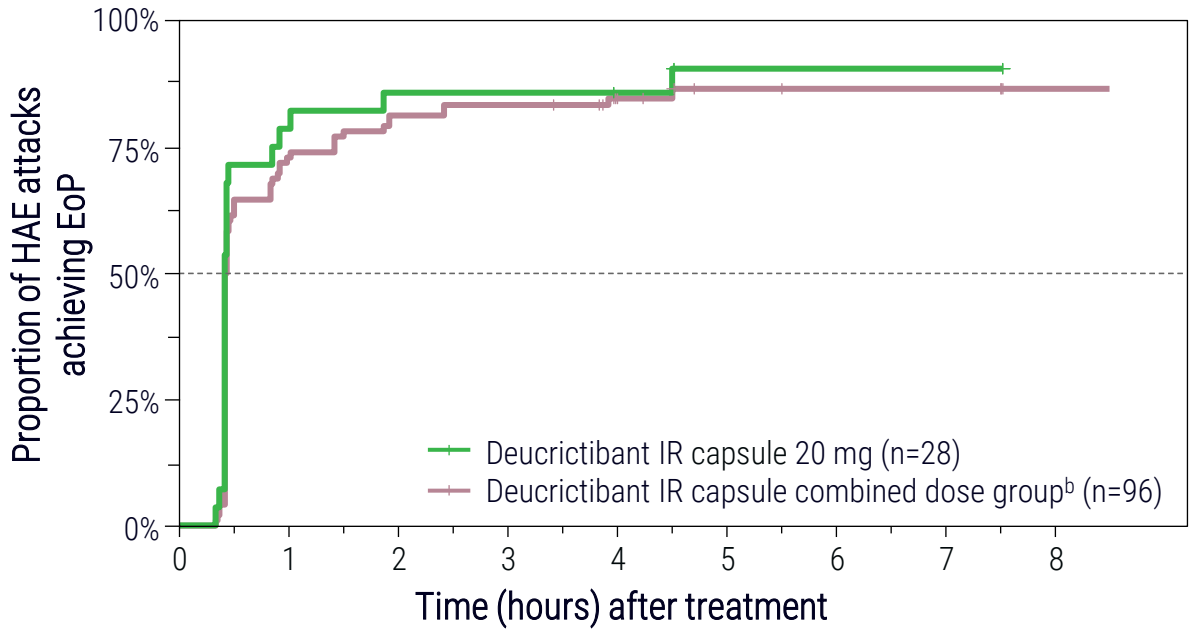
1. Mendivil J, et al. Presented at GA²LEN UCARE Conference 2023. December 8, 2023; São Paulo, Brazil.

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

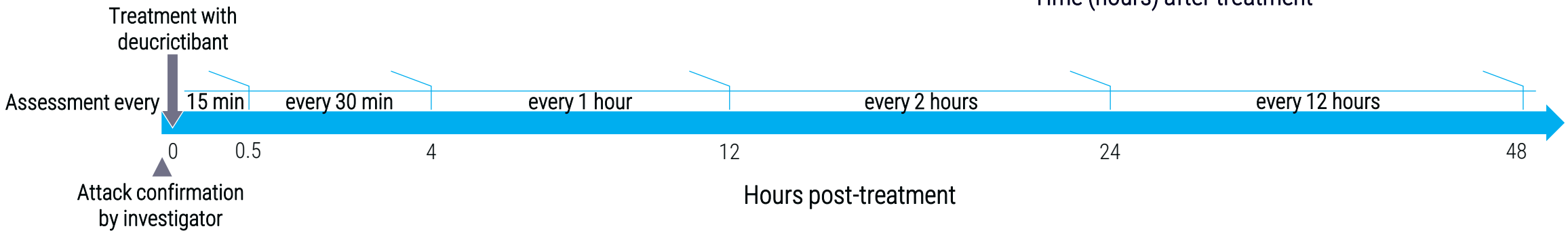
RAPIDe-3: Rationale for early timing of PRO measurements

- 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.
- This informed the first post-dose PRO measurement time of 15 minutes in RAPIDe-3.

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



PRO assessment timeline in RAPIDe-3



HAE, hereditary angioedema; IR, immediate-release; PRO, patient-reported outcome. [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 deucrictibant 10 mg, 20 mg, and 30 mg dose groups.

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

Conclusions

- RAPIDe-3 is an ongoing, global, Phase 3, randomized, double-blind, placebo-controlled, crossover trial.
- The study is 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.
- The primary endpoint is time to onset of symptom relief, using PGI-C, with a first PRO measurement time of 15 minutes.
- Results from the RAPIDe-1 Phase 2 study and a real-world HAE endpoint validation study support the RAPIDe-3 study design.

HAE, hereditary angioedema; IR, immediate-release; PGI-C, Patient Global Impression of Change; PRO, patient-reported outcome.