Efficacy and Safety of Oral Deucrictibant for Prophylactic (CHAPTER-3) and for On-Demand (RAPIDe-3) Treatment of Hereditary Angioedema Attacks in Adolescents and Adults: Two Phase 3 Trial Designs

P.H. Li, E. Aygören-Pürsün, M. Cancian, H. Farkas, A.S. Grumach, M. Hide, C.H. Katelaris, H.J. Longhurst, W.R. Lumry, M. Magerl, R.D. Zwiener, J. Mendivil, P. Lu, M. Yu, L. Zhu, M.A. Riedl

EAACI Hong Kong Allergy School, 2025
Hong Kong, 27–29 August 2025

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

Conflicts of interest disclosure

Grants/research support, honoraria or consultation fees, sponsored speaker bureau

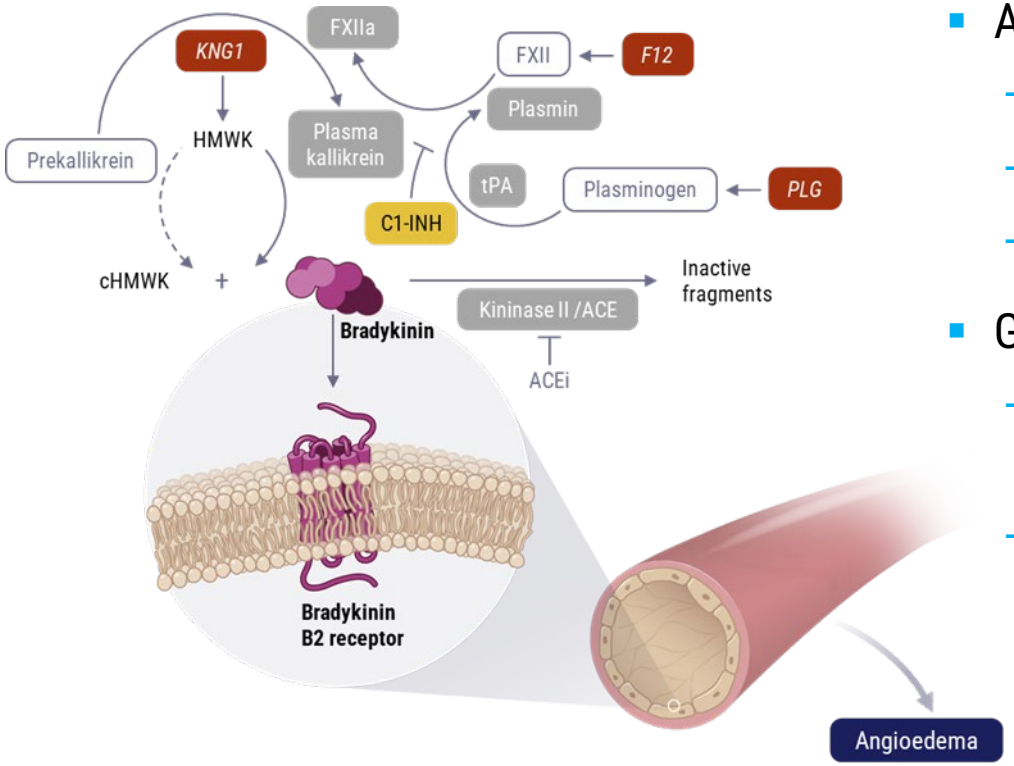
P.H.L.: no conflicts of interest to disclose relative to this work; **E.A-P.:** Astria, BioCryst, BioMarin, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Takeda; **M.C.:** BioCryst, CSL Behring, KalVista, Menarini, MSD, Novartis, Otsuka, Pharming, Pharvaris, Sobi, Takeda, UCB; **H.F.:** BioCryst, CSL Behring, Intellia, KalVista, ONO Pharmaceutical, Pharming, Pharvaris, Takeda; **A.S.G.:** Brazilian research Entity (CNPq), Catalyst, Takeda, The Binding Site; **M.H.:** CSL Behring, Pharvaris, Takeda; **C.H.K.:** CSL Behring, Takeda; **H.J.L.:** Astria Pharmaceuticals, CSL Behring, Intellia, KalVista, Pharvaris, Takeda; **W.R.L.:** AstraZeneca, Astria, BioCryst, BioMarin, CSL Behring, Fresenius-Kabi, GSK, Grifols, Intellia, Ionis, KalVista, Magellan, Optinose, Pharming, Pharvaris, Regeneron, Sanofi, Takeda, Teva; **M.M.:** Astria, BioCryst, CSL Behring, Intellia, KalVista, Novartis, Octapharma, Otsuka, Pharvaris, Takeda; **R.D.Z.:** AbbVie, Bago, CSL Behring, KalVista,Novartis, Panalab, Pint-Pharma, Pharvaris, Sanofi, Takeda; **J.M., P.L., M.Y., L.Z.:** employees of Pharvaris, hold stocks in Pharvaris; **M.A.R.:** Astria, BioCryst, BioMarin, Celldex, CSL Behring, Cycle Pharma, Grifols, Intellia, Ionis, KalVista, Novartis, Pharming, Pharvaris, Sanofi-Regeneron, Takeda.

Acknowledgments: Medical writing services were provided by Jonny Turner, PhD, of Envision Spark, an Envision Medical Communications agency, a part of Envision Pharma Group and funded by Pharvaris.

CHAPTER-3 and RAPIDe-3 are Pharvaris-sponsored clinical trials. ClinicalTrials.gov identifiers: NCT06669754, NCT06343779.

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

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

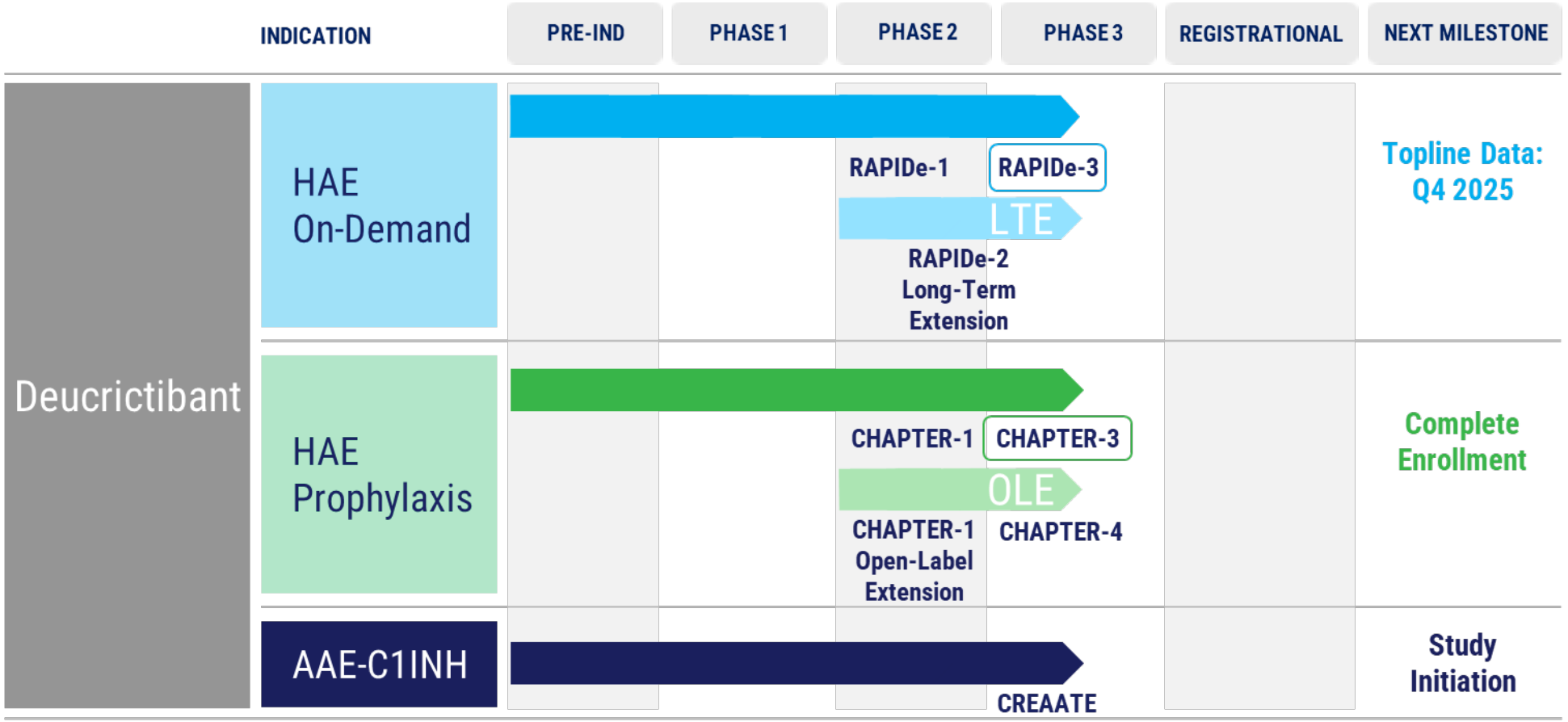


- An unmet need remains for additional **prophylactic therapies** combining[1-4]:
  - Injectable-like efficacy
  - A well-tolerated safety profile
  - Ease of administration
- Guidelines recommend HAE attacks are treated as early as possible.[4,5]
  - Parenteral administration often leads to **on-demand treatment** of HAE attacks being delayed or forgone.[3,5-7]
  - A rapid and sustained response to on-demand treatment through to complete resolution is paramount to abate the physical, functional, and emotional burden of attacks.[5,7,8]

ACE, angiotensin converting enzyme; ACEi, ACE inhibitor; C1INH, C1 inhibitor; cHMWK, cleaved HMWK; *F12*, gene encoding FXII; FXII, factor XII; FXIIa, factor XIIa; HAE, hereditary angioedema; HMWK, high-molecular-weight kininogen, *KNG1*, gene encoding HMWK; *PLG*, gene encoding plasminogen; tPA, tissue plasminogen activator.
1. Bouillet L, et al. *Allergy Asthma Proc*. 2022;43:406-12. **2**. Betschel SD, et al. *J Allergy Clin Immunol Pract*. 2023;11:2315-25. **3.** Covella B, et al. *Future Pharmacol*. 2024;4:41-53. **4.** Maurer M, et al. *Allergy*. 2022;77:1961-90. **5.** US Food and Drug Administration, Center for Biologics Evaluation and Research. The voice of the patient – hereditary angioedema. May 2018. https://www.fda.gov/media/113509/download. Accessed August 25, 2025. **6.** Betschel SD, et al. *Allergy Asthma Clin Immunol*. 2024;20:43. **7.** Radojicic C, et al. *Allergy Asthma Proc*. 2021;42. **8.** 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.

Deucrictibant development program in bradykinin-mediated angioedema



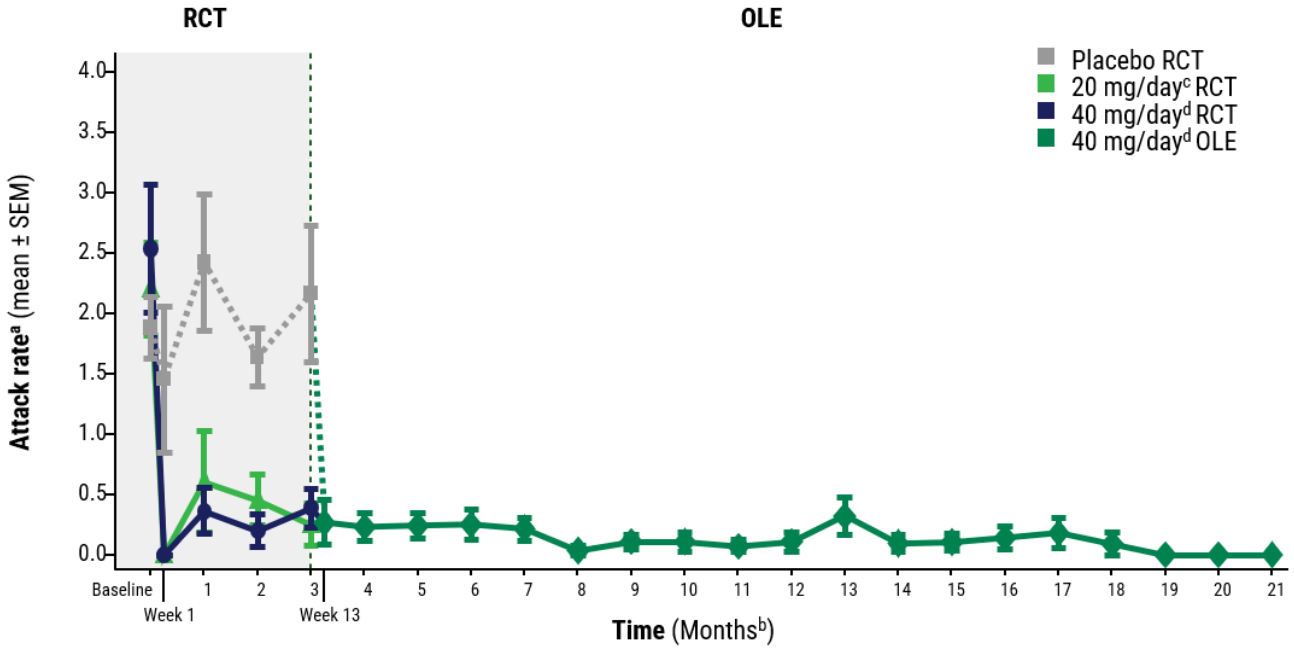
AAE-C1INH, acquired angioedema due to C1 inhibitor deficiency; HAE, hereditary angioedema; LTE, long-term extension; OLE, open-label extension; Q, quarter.
Study, ClinicalTrials.gov identifier: RAPIDe-1, NCT05396105; RAPIDe-2, NCT05396105; RAPIDe-3, NCT06343779; CHAPTER-1, NCT05047185; CHAPTER-3, NCT06669754. CHAPTER-4, NCT06679881.

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

Evidence for continued investigation of deucrictibant as a potential prophylactic treatment for HAE

Prophylaxis

- In the Phase 2 CHAPTER-1 trial (NCT05047185), deucrictibant IR capsule was dosed twice per day as a proof-of-concept for the once-daily deucrictibant XR tablet.[1,2]
- CHAPTER-1 results showed[1,2]:
  - Deucrictibant significantly reduced occurrence of attacks vs placebo in the randomized controlled trial (RCT).
  - Attack rate remained low through ≥1.5 years with long-term treatment during the open-label extension (OLE).



For more results from CHAPTER-1, please attend:
Lleonart et al. oral presentation
Friday 29 August, 16.05-16.15

SEM, standard error of the mean. [a]Based on time normalized number of attacks per 4 weeks. [b]1 month = 4 weeks. [c]Deucrictibant IR capsule, 10 mg twice daily. [d]Deucrictibant IR capsule, 20 mg twice daily. **1.** CHAPTER-1. Accessed August 25, 2025. https://www.clinicaltrials.gov/study/NCT05047185. **2.** Aygören-Pürsün, et al. Presented at: EAACI; May 31–June 3, 2024; Valencia, Spain.

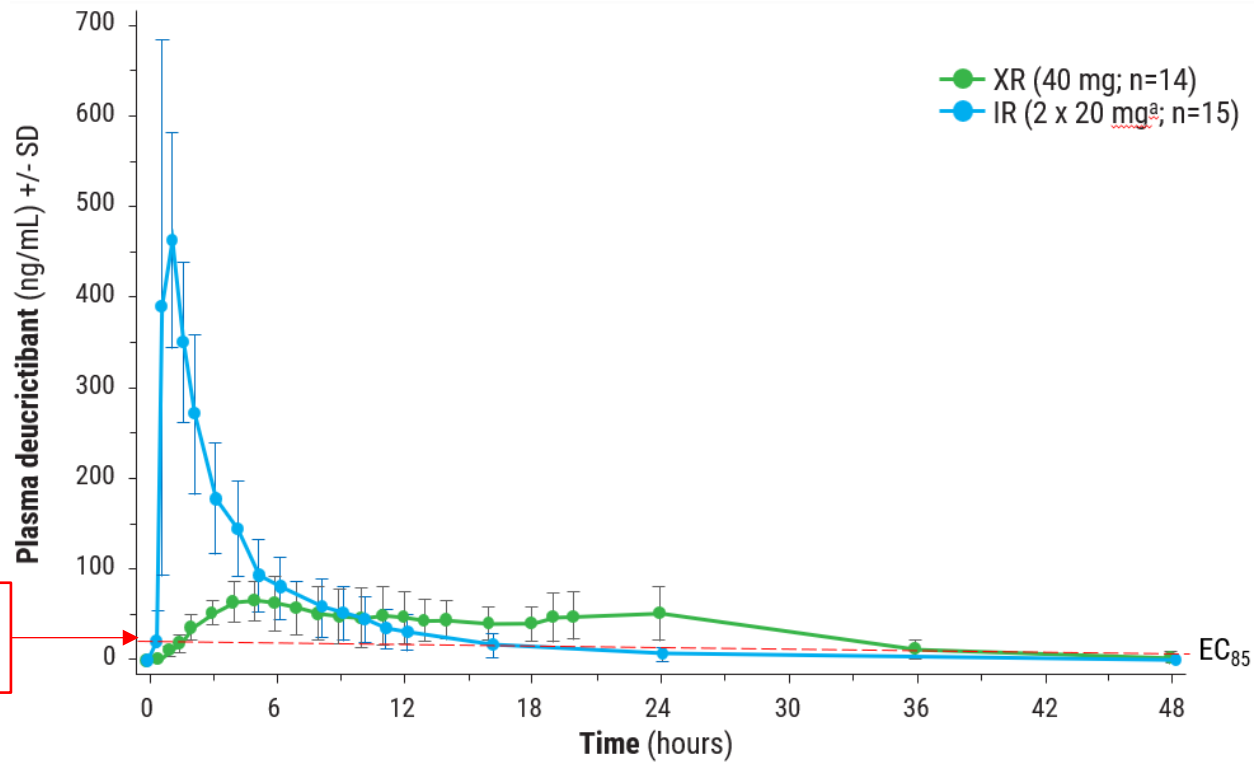
This presentation includes data for an investigational product not yet approved by regulatory authorities.

Sustained exposure through ≥24 hours supports once-daily dosing with deucricitbant XR tablet for prophylactic treatment

Prophylaxis

- In Phase 1 studies, deucrictibant XR tablet (40 mg):
  - Allowed for controlled release and absorption of deucrictibant in the small intestine and colon.[1]
  - Sustained mean concentrations in circulation above EC_{85} from ~1.5 to ≥24 hours post-dose.[1-3]
  - Showed more sustained exposure over time compared with single dose deucrictibant IR capsule (2x20 mg).[1-3]
    - Twice-daily IR capsule (20 mg) was used in CHAPTER-1 (NCT05047185).[4]

EC_{85} – anticipated therapeutic exposure threshold concentration estimated to provide 85% maximal response: 13.8 ng/mL.[1,2]



IR, immediate-release; XR, extended-release. [a]Single oral dose of 2 x 20 mg deucrictibant IR capsule. **1.** Lesage A, et al. Presented at IDDST; May 22–24, 2024; Otsaka, Japan. **2.** Groen K, et al. Presented at: ACAAI 2022. November 10–14, 2022; Louisville, KY, USA. **3.** Zhang Y-Z, et al. Presented at C1INH Deficiency & Angioedema Workshop; May 29–June 1, 2025; Budapest, Hungary. **4.** CHAPTER-1. Accessed August 25, 2025. https://www.clinicaltrials.gov/study/NCT05047185

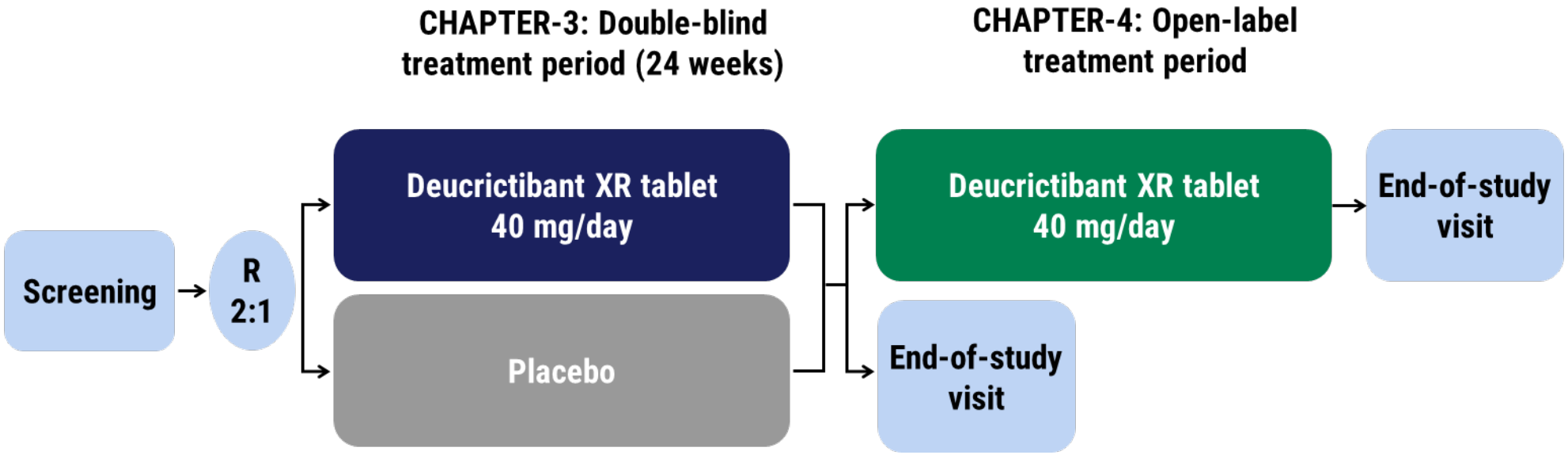
This presentation includes data for an investigational product not yet approved by regulatory authorities.

CHAPTER-3 (NCT06669754): Ongoing, phase 3, global, randomized, double-blind, placebo-controlled trial

Prophylaxis

Key objective:

To evaluate the efficacy and safety of once-daily, orally administered deucrictibant XR tablet for prophylaxis against HAE attacks in adolescents and adults.



- Eligible participants are randomized 2:1 to receive deucrictibant XR tablet 40 mg or matching placebo once daily for 24 weeks. Stratified according to:
  - age group (≥12 to <18 years, ≥18 years)
  - baseline HAE attack rate (1 to <2 attacks per 4 weeks, ≥2 attacks per 4 weeks)

R, randomization; XR, extended-release.

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

CHAPTER-3: Key inclusion and exclusion criteria

Prophylaxis

Target enrollment: 81 adolescents and adults living with HAE.

Key inclusion criteria include	Key exclusion criteria include
▪ Aged ≥12 years ▪ Diagnosed with HAE (including HAE-C1INH and HAE-nC1INH) ▪ History of ≥3 HAE attacks within the 3 consecutive months prior to screening visit ▪ Access and ability to use standard-of-care on-demand treatment to manage HAE attacks	▪ Pregnancy or breastfeeding ▪ Receiving long-term prophylactic therapy for HAE within the specified time-period before screening: – 2 weeks: C1 inhibitor, berotralstat, or anti-fibrinolytic – 4 weeks: Attenuated androgens – 5 half-lives: Monoclonal antibody therapy ▪ Received prior HAE prophylactic treatment with deucrictibant ▪ Participation in any other investigational drug study

C1INH, C1 inhibitor; HAE, hereditary angioedema; nC1INH, normal C1 inhibitor.

CHAPTER-3: Study objectives and endpoints

Prophylaxis

Primary objective evaluated:

- efficacy of deucrictibant XR tablet for prevention of angioedema attacks vs placebo.

Secondary objectives evaluated:

- efficacy
- safety and tolerability
- pharmacokinetics
- impact on health-related quality of life and disease control

Primary endpoint	▪ Time-normalized (per 4 weeks) number of investigator-confirmed HAE attacks during the 24-week treatment period
Secondary efficacy endpoints	▪ Number of attacks treated with on-demand medication ▪ Number of "moderate or severe" and "severe" attacks[a] ▪ Proportion of participants achieving ≥50%, ≥70%, or ≥90% reduction in attack rate relative to baseline and proportion remaining attack free ▪ Proportion of time without angioedema symptoms
Patient-reported outcomes	▪ Angioedema Quality of Life (AE-QoL) questionnaire ▪ Patient Global Assessment of Change (PGA-Change) ▪ Angioedema Control Test 4-week version (AECT-4wk) ▪ Treatment Satisfaction Questionnaire for Medication (TSQM-9)
Safety	▪ TEAEs including serious TEAEs and TEAEs leading to study drug discontinuation ▪ Change from baseline in clinical laboratory tests, vital signs, and ECG parameters

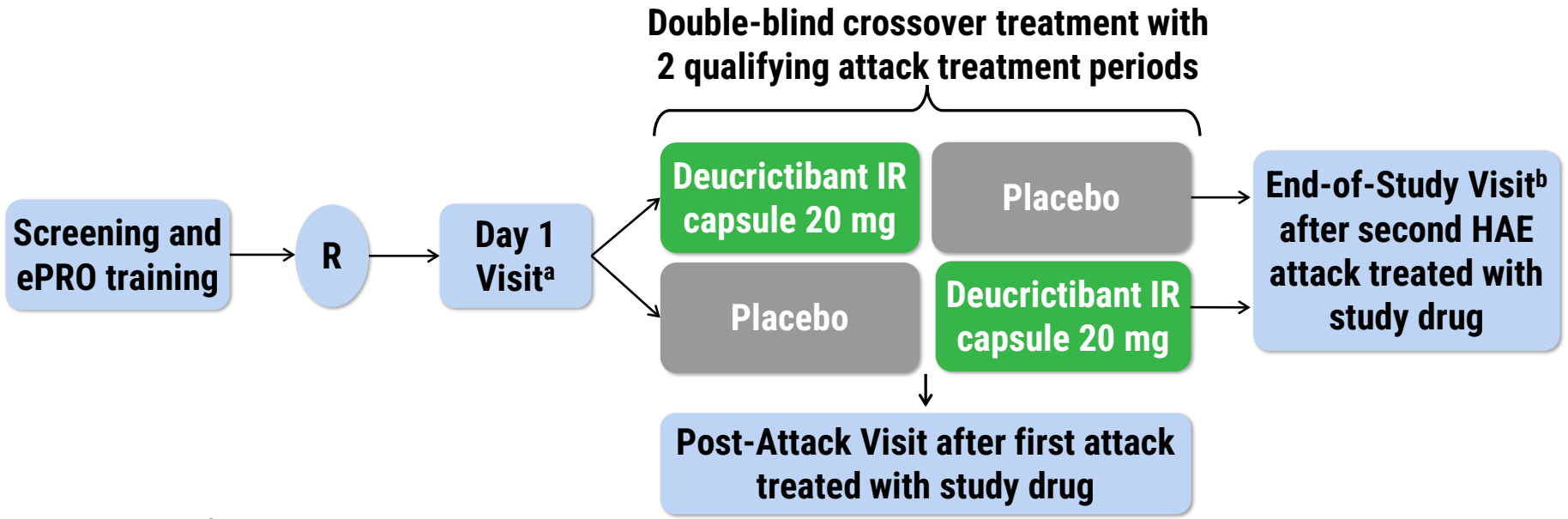
ECG, electrocardiogram; HAE, hereditary angioedema; TEAE, treatment-emergent adverse event. [a]Moderate attacks defined as an HAE attack that limits/interferes with the participant's ability to attend work/school or participate in family life and social/recreational activities. Severe attack defined as an HAE attack that significantly limits the participant's ability to attend work/school or participate in family life and social/recreational activities.

RAPIDe-3 (NCT06343779): Ongoing, phase 3, global, randomized, double-blind, placebo-controlled, crossover trial

On-demand

Key objective:

To evaluate the efficacy and safety of the deucrictibant IR capsule for on-demand treatment of HAE attacks in adolescents and adults.



- Randomization is stratified according to:
  - age (≥12 to <18 years, ≥18 years)
  - long-term HAE prophylaxis use (Yes/No)
- Qualifying attacks include non-laryngeal attacks and non-severe laryngeal attacks not associated with breathing difficulties or stridor.

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 R. [b]Data from the End-of-Study Visit may be used to qualify the participant for an open-label extension study with deucrictibant.

RAPIDe-3: Key inclusion and exclusion criteria

On-demand

Target enrollment: 120 adolescents and adults living with HAE.

Key Inclusion Criteria	Key Exclusion Criteria
▪ Aged ≥12 to ≤75 years ▪ Diagnosed with HAE (including HAE-C1INH and HAE-nC1INH) ▪ 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 (<200 mg/day danazol) ≥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 on-demand treatment with deucrictibant ▪ Participation in any other investigational drug study

C1INH, C1 inhibitor; HAE, hereditary angioedema; nC1INH, normal C1 inhibitor.

RAPIDe-3: Study endpoints

On-demand

Primary	▪ 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	▪ 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

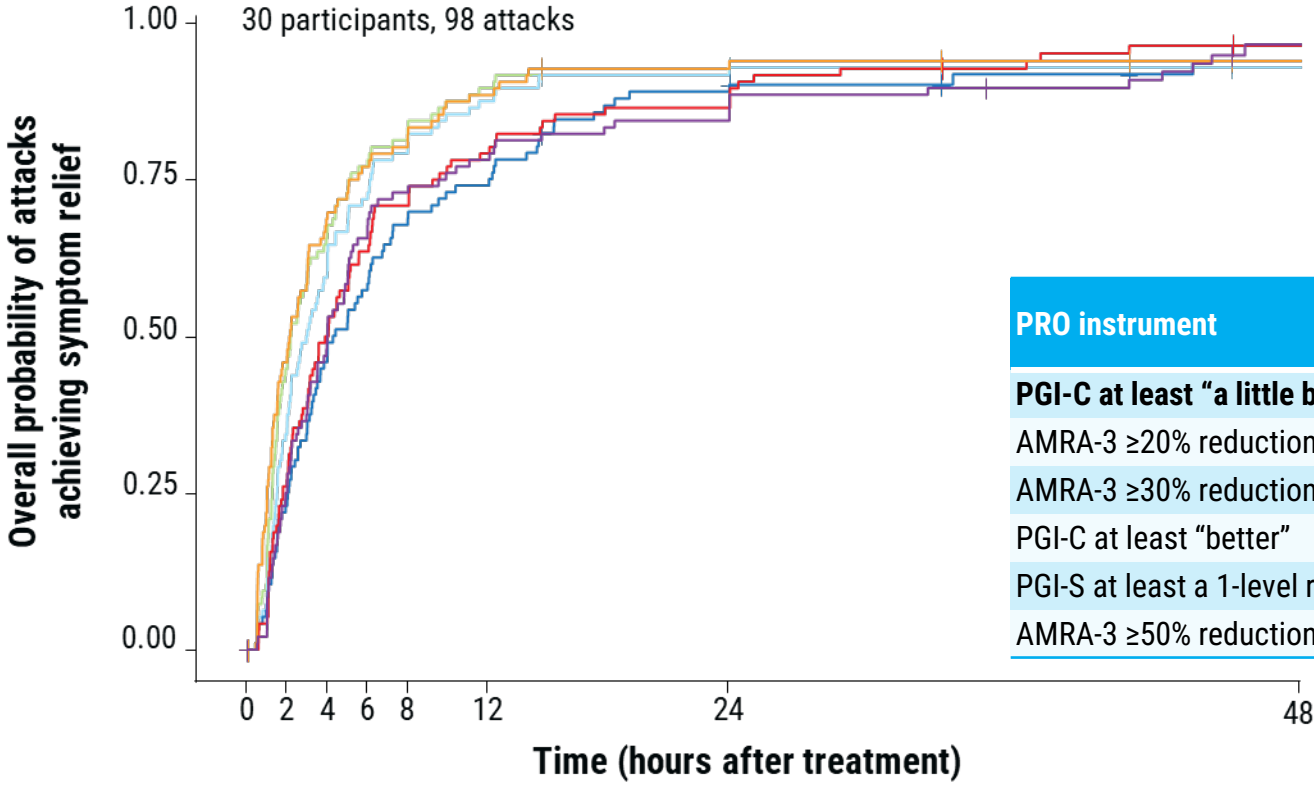
AMRA, Angioedema syMptom Rating scAle; ECG, electrocardiogram; EQ-5D-5L, EuroQoL 5-dimensions 5-levels assessment; HAE, hereditary angioedema; HRQoL, health-related quality of life; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; TEAE, treatment-emergent adverse event. [a]End of progression is defined as the earliest post-treatment timepoint, after which all subsequent PGI-C ratings are stable or improved.

Rationale for primary endpoint selection in RAPIDe-3

On-demand

In a real-world validation study of on-demand HAE endpoints using standard-of-care therapies[1], the most sensitive measure of onset of symptom relief was:

Time to onset of symptom relief as defined by PGI-C rating of at least "a little better" for two consecutive timepoints



PRO instrument	Number of events	Median time to, hours (95% CI)
PGI-C at least "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 at least "better"	92	3.925 (2.969, 5.055)
PGI-S at least a 1-level reduction	91	4.012 (3.015, 5.026)
AMRA-3 ≥50% reduction from pre-treatment	88	4.354 (3.256, 6.093)

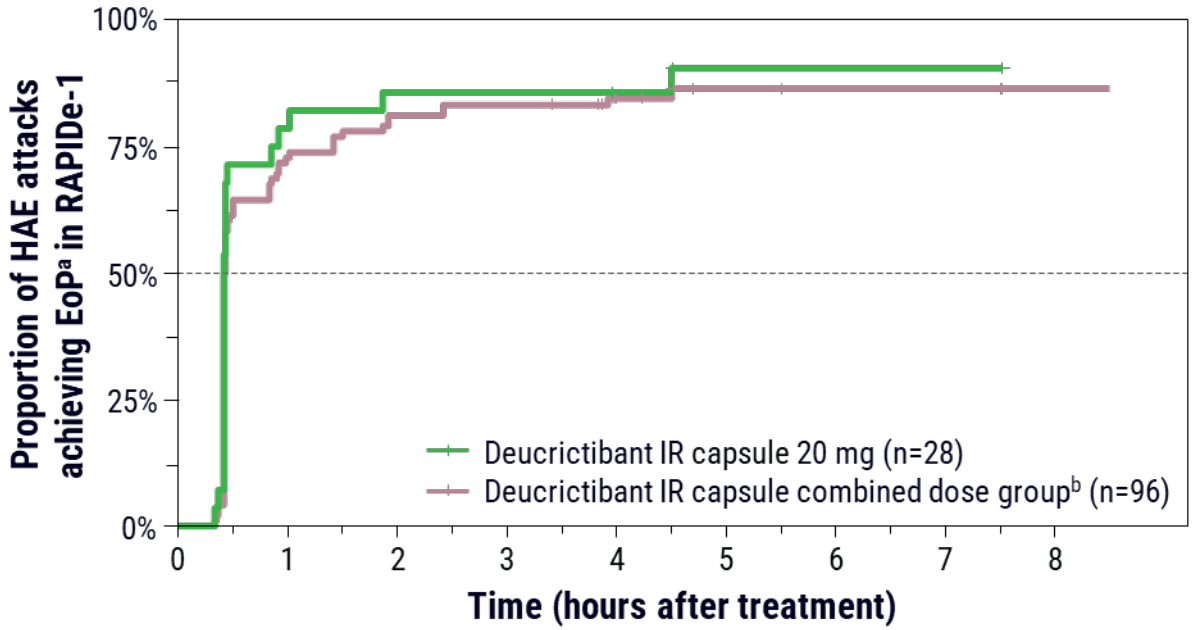
AMRA, Angioedema syMptom Rating scAle; CI, confidence interval; HAE, hereditary angioedema; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcome. **1.** Mendivil J, et al. Presented at GA²LEN UCARE Conference 2023. December 8, 2023; São Paulo, Brazil.

Rationale for early timing of PRO measurements in RAPIDe-3

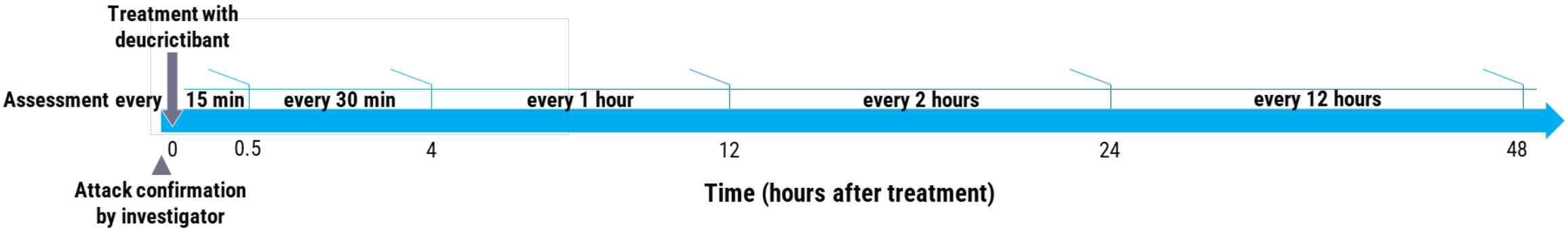
On-demand

RAPIDe-1 phase 2 trial post-hoc analysis

- Deucrictibant IR capsule treatment showed rapid onset of action, achieving end of progression (EoP) at a median time of 25–26 minutes post-treatment.
- These findings informed the first post-dose PRO measurement time of 15 minutes in RAPIDe-3.



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 with 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

	CHAPTER-3 (NCT06669754)	RAPIDe-3 (NCT06343779)
Treatment	▪ Prophylactic	▪ On-demand
Deucrictibant	▪ Deucrictibant extended-release (XR) tablet	▪ Deucrictibant immediate-release (IR) capsule
Participants	▪ Adolescents (≥12 to <18 years) ▪ Adults (≥18 years)	▪ Adolescents (≥12 to <18 years) ▪ Adults (≥18 years)
Trial design	▪ Global, Phase 3, multicenter, randomized, double-blind, placebo-controlled trial	▪ Global, Phase 3, multicenter, randomized, double-blind, placebo-controlled, crossover trial
Primary endpoint	▪ Time-normalized (per 4 weeks) number of investigator-confirmed HAE attacks during the 24-week treatment period	▪ Time to onset of symptom relief using PGI-C[a], with a first PRO measurement time at 15 minutes

The Authors and the Sponsor would like to thank all the people with HAE,
as well as all study site staff who have been participating in the CHAPTER-3 and RAPIDe-3 trials.

HAE, hereditary angioedema; PGI-C, Patient Global Impression of Change; PRO, patient-reported outcome. [a]PGI-C rating of at least "a little better."