# CHAPTER-3 Phase 3 Trial Design: Efficacy and Safety of the Oral Bradykinin B2 Receptor Antagonist Deucrictibant Extended-Release Tablet for Prophylaxis of Hereditary Angioedema Attacks

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## Key takeaways

- CHAPTER-3 is an ongoing, global, Phase 3 study designed to evaluate the efficacy and safety of once-daily, oral deucrictibant extended-release (XR) tablet for prophylaxis of attacks in adolescents and adults with hereditary angioedema (HAE).
- Results from the CHAPTER-1 Phase 2 study support the CHAPTER-3 study design.

| Deucrictibant | Primary efficacy endpoint | Safety endpoints | Patient-reported outcomes |
|---|---|---|---|
| XR<br>Deucrictibant XR once-daily tablet | 24 weeks<br>Time-normalized number of investigator-confirmed HAE attacks during the 24-week treatment period | TEAEs, clinical laboratory tests, vital signs, and ECG parameters | Health-related quality of life, disease control, work productivity and activity impairment, and treatment satisfaction |

ECG, electrocardiogram; HAE, hereditary angioedema; TEAE, treatment-emergent adverse event; XR, extended-release.

## Background

- **Hereditary angioedema (HAE):** a rare genetic condition caused by excess bradykinin production and characterized by painful, often disabling, swelling attacks affecting multiple locations in the body.[1-3]
- **Unmet need:** additional prophylactic treatments combining injectable-like efficacy, a well-tolerated profile, and ease of administration.[4-7]
- **Deucrictibant:** deucrictibant is a selective, orally administered antagonist of the bradykinin B2 receptor under development for prophylactic and on-demand treatment of hereditary angioedema (HAE) attacks.[8-18]

## Objective

The CHAPTER-3 study (NCT06669754) is an ongoing, global, Phase 3 study designed to evaluate the efficacy and safety of once-daily, oral deucrictibant XR tablet for prophylaxis of attacks in adolescents and adults with HAE.

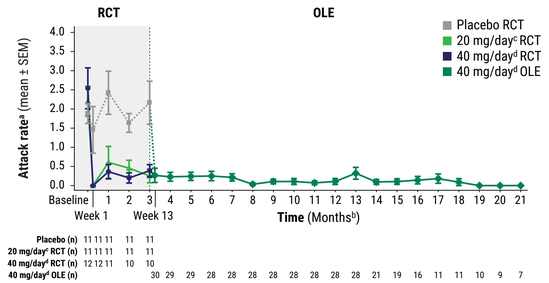
## Previous studies

### CHAPTER-1

- In the placebo-controlled Phase 2 trial (NCT05047185), deucrictibant significantly reduced occurrence of attacks, induced clinically meaningful improvement in disease control and in health-related quality of life, and was generally well tolerated.[14,15]
- Attack rate was significantly reduced with deucrictibant in the RCT and remained low over long-term treatment in the OLE.
- Immediate-release (IR) capsule was dosed twice per day as a proof-of-concept for the once-daily deucrictibant XR tablet (intended formulation for prophylactic HAE treatment).
- CHAPTER-1 results supported further development of deucrictibant as a potential prophylactic treatment for HAE.[15]

## Previous studies

**Figure 1. Reduced attack rate by week 1 in the CHAPTER-1 RCT remained low in the OLE**

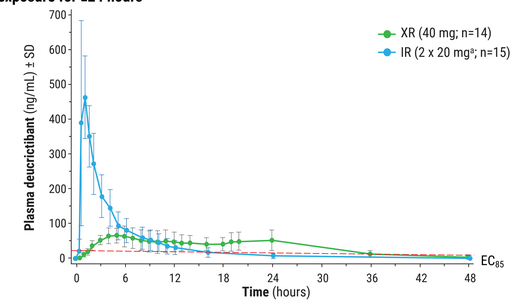



IR, immediate-release; OLE, open-label extension; RCT, randomized controlled trial; SEM, standard error of the mean. n = number of patients analyzed at each timepoint. [a]Based on time normalized number of attacks per 4 weeks. [b]1 month = 4 weeks. [c]Deucrictibant IR capsule, 10 mg twice daily. [d]Deucrictibant IR capsule, 20 mg twice daily.

### Phase 1 studies

- In Phase 1 studies, deucrictibant XR tablet (40 mg):
  - Allowed for controlled release and absorption of deucrictibant in the small intestine and colon.[18]
  - Sustained mean concentrations in circulation above threshold levels of therapeutic exposure from ~1.5 to ≥24 hours post-dose.[18-20] Effective concentration estimated to provide 85% maximal response ($EC_{85}$) is 13.8 ng/mL.[19]
  - Showed more sustained exposure over time compared with twice-daily IR capsule (2 x 20 mg) used in proof-of-concept Phase 2 CHAPTER-1 study.[18-20]
- Maintenance of exposure through 24 hours supports once-daily dosing with XR tablet for prophylactic treatment.

**Figure 2. Deucrictibant XR tablet maintains exposure above threshold level of therapeutic exposure for ≥24 hours**

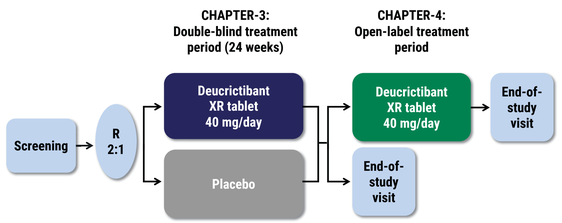



$EC_{85}$, concentration estimated to provide 85% maximal response; IR, immediate-release; SD, standard deviation; XR, extended-release. [a]Single oral dose of 2 x 20 mg deucrictibant IR capsule.

## CHAPTER-3 study overview

- **CHAPTER-3 (NCT06669754):** an ongoing Phase 3, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of orally administered deucrictibant XR tablet once daily for prophylaxis of HAE attacks in adolescents and adults.
- **Target enrollment:** 81 adolescents and adults living with HAE.
- **Randomization:** participants stratified according to:
  - age group (≥12 to <18 years, ≥18 years) and
  - baseline HAE attack rate (1 to <2 attacks per 4 weeks, ≥2 attacks per 4 weeks).

**Figure 3. CHAPTER-3 and CHAPTER-4 study design**




R, randomization; XR, extended-release.

### Participants

**Table 1. CHAPTER-3 key inclusion and exclusion criteria**

| Key inclusion criteria include | Key exclusion criteria include |
|---|---|
| • Aged ≥12 years<br>• History of ≥3 HAE attacks within the 3 consecutive months prior to screening visit<br>• Access and ability to use standard-of-care on-demand treatment to manage HAE attacks | • Participation in any other investigational drug study<br>• Received prior HAE prophylactic treatment with deucrictibant<br>• Receiving long-term prophylactic therapy for HAE within the specified time period before screening:<br>– 2 weeks: C1 inhibitor, berotralstat, or anti-fibrinolytic<br>– 4 weeks: Attenuated androgen<br>– 5 half-lives: Lanadelumab<br>• Pregnant or breastfeeding |

HAE, hereditary angioedema.

## Results

### Objectives and endpoints

- **Primary objective:** evaluate efficacy of deucrictibant XR tablet for prevention of angioedema attacks vs placebo.
- **Secondary objectives:**
  - evaluate efficacy
  - evaluate safety and tolerability
  - evaluate pharmacokinetics
  - evaluate impact on health-related quality of life

**Table 2. CHAPTER-3 key inclusion and exclusion criteria**

| | |
|---|---|
| **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<br>• Number of "moderate or severe" and "severe" attacks[a]<br>• Proportion of participants achieving ≥50%, ≥70%, or ≥90% reduction in attack rate relative to baseline and proportion remaining attack free<br>• Proportion of time without angioedema symptoms |
| **Patient-reported outcomes** | • Angioedema Quality of Life (AE-QoL) questionnaire<br>• Patient Global Assessment of Change (PGA-Change)<br>• Angioedema Control Test 4-week version (AECT-4wk)<br>• Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP)<br>• Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) |
| **Safety** | • Treatment-emergent adverse events (TEAEs) including serious TEAEs and TEAEs leading to study drug discontinuation<br>• 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.

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

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**COI: W.R.L.:** AstraZeneca, Astria, BioCryst, BioMarin, CSL Behring, Fresenius-Kabi, GSK, Grifols, Intellia, Ionis, KalVista, Magellan, Optinose, Pharming, Pharvaris, Regeneron, Sanofi, Takeda, Teva. **H.F.:** BioCryst, CSL Behring, Intellia, KalVista, ONO Pharmaceutical, Pharming, Pharvaris, Takeda; **A.S.G.:** Brazilian research Entity (CNPq), Catalyst, CSL Behring, Exeltis, KalVista, Kedrion, Multicare, Pharvaris, Pint-Pharma, Takeda, The Binding Site; **M.H.:** BioCryst, CSL Behring, KalVista, Pharvaris, Takeda, Torii; **J.S.J.:** BioCryst, CSL Behring, Cycle Pharma, Oasis, Pharming, Pharvaris, Takeda; **L.L., P.H.L.:** no conflicts of interest to disclose relative to this work; **R.L.:** BioCryst, CSL Behring, Ionis, KalVista, Novartis, Pharming, Pharvaris, Takeda; **H.J.L.:** CSL Behring, Intellia, KalVista, Pharvaris, Takeda; **M.M.:** BioCryst, CSL Behring, Intellia, KalVista, Novartis, Octapharma, Pharming, Pharvaris, Takeda; **I.M.S.:** BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, Octapharma, Takeda; **J.P.:** Pharming, Takeda; **S.S.:** AstraZeneca, BioCryst, Celldex, CSL Behring, KalVista, Novartis, Pharvaris, Sobi, Takeda, member of the board of trustees and chair of clinical immunology for the British Society for Immunology; **M.S.:** BioCryst, CSL Behring, KalVista, Pharming, Takeda; **R.T.:** Astria, BioCryst, CSL Behring, Ionis, Kalvista, Pharming, Pharvaris, Takeda; **A.V.:** AstraZeneca, Berlin-Chemie/Menarini Group, CSL Behring, KalVista, Novartis, Pharming, Pharvaris, Sobi, Takeda; **H.J.W.:** BioCryst, BioMarin, CSL Behring, Genentech, GSK, Takeda; **A.Z.:** BioCryst, CSL Behring, KalVista, Pharming, Takeda; **R.Z.:** AbbVie, Bago, CSL Behring, KalVista, Novartis, Panalab, Pint-Pharma, Pharvaris, Sanofi, Takeda; **C.C., L.Z., U.F., J.M., M.Y.:** employees of Pharvaris, hold stocks in Pharvaris; **P.L.:** employee of Pharvaris, holds stocks/stock options in Pharvaris; **E.A-P.:** Astria, BioCryst, CSL Behring, Intellia, Kalvista, Otsuka, Pharvaris, Takeda.

**Acknowledgments:** Medical writing services were provided by Rebecca Jarvis, PhD, CMPP, of Two Labs Pharma Services, and were funded by Pharvaris.

**CHAPTER-3 and CHAPTER-4 are Pharvaris-sponsored clinical trials. ClinicalTrials.gov identifiers: NCT06669754 and NCT06679881.**