Clinical Cardiovascular Safety Evaluation of Oral Deucrictibant

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Key takeaways

To date there has been no evidence of QTc prolongation or other cardiovascular safety concerns across completed and ongoing Phase 1, 2, and 3 studies of oral deucrictibant in healthy participants and participants with hereditary angioedema.

- **>740** unique participants exposed to deucrictibant to date
- **No evidence** of QTc prolongation in clinical concentration-QTc modeling based on 3 Phase 1 trials
- **No evidence of increased risks of cardiovascular events with either intended commercial formulation**
- **No evidence of cardiovascular concerns in participants dosed daily for a mean >22 months**

QTc, corrected QT interval.

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

Background

- **Bradykinin-mediated angioedema (AE-BK):** includes hereditary angioedema (HAE) with C1 inhibitor deficiency (HAE-C1INH) or with normal C1 inhibitor (HAE-nC1INH) and acquired angioedema due to C1 inhibitor deficiency (AAE-C1INH).[1-5] AE-BK is characterized by recurrent, unpredictable, often painful and disabling swelling attacks.[1-5]
- **Oral deucrictibant:** a selective bradykinin B2 receptor antagonist under development for both prophylactic and on-demand treatment (ODT) of AE-BK attacks.[6-13]
- **Nonclinical cardiovascular (CV) safety assessments:**
  - Deucrictibant had no evident effects on cardiac electrophysiology, hemodynamic parameters, cardiac morphology, and histopathology evaluation in acute and chronic nonclinical safety studies in non-human primates.[14,15]
  - A manual patch-clamp assay at physiologic temperature confirmed the absence of relevant inhibition of the hERG-mediated current at deucrictibant concentrations 162-fold above the highest estimated clinical exposure.[15]

Objectives

- To assess the relationship between the deucrictibant plasma concentration and the QT interval corrected (QTc) for heart rate (HR) using Fridericia formula (QTcF) in humans.
- To assess the effects of deucrictibant on CV outcomes, including blood pressure, HR, electrocardiogram (ECG), and adverse events, using data from clinical pharmacology Phase 1, Phase 2, and Phase 3 clinical studies to date.

Methods

Concentration QTc (C-QTc) analysis

- A meta-analysis of pooled data from two single ascending dose (SAD) and one multiple ascending dose (MAD) Phase 1 studies.
- Eligible participants: healthy male and female participants (of non-childbearing potential), between 18 and 65 years of age (inclusive) with a body mass index between 18.0 and 30.0 kg/m^2 (inclusive).
- SAD: placebo or 1, 2, 4.5, 12, or 22 mg deucrictibant in fasting condition and 22 mg after a high-calorie, high-fat breakfast.
- SAD extension: placebo or 22, 33, or 50 mg deucrictibant in fed condition and 40 mg in fasting condition.
- MAD: placebo or 12, 22, 33, or 50 mg deucrictibant administered twice daily at 12-hour intervals in fed condition for 9 days with a last dose in the morning of Day 10.
- Digital triplicate 12-lead ECGs were acquired from participants in a supine position using the same equipment, and centrally interpreted and analyzed by the same core lab across all three studies.
- Pharmacokinetic and ECG assessment time points were aligned across the three studies:
  - SAD: Predose, 0.5, 1, 2, 3, 4, 8, 10, and 24 hours post dose.
  - MAD:
    - Day 1: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 14, 16, and 24 hours post first dose.
    - Days 3–9: 48, 72, 96, 120, 144, 168, and 192 hours post first dose on Day 1.
    - Day 10 (only one morning dose): Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, and 72 hours after the last dose.
- Fridericia's formula was used for the HR correction of the QT interval for each ECG.
- ΔQTcF was defined as the change from the individual predose baseline in QTcF.
- Based on the model results, the mean placebo-corrected change from baseline in QTcF (ΔΔQTcF) for plasma concentration was calculated.

Methods

CV outcomes

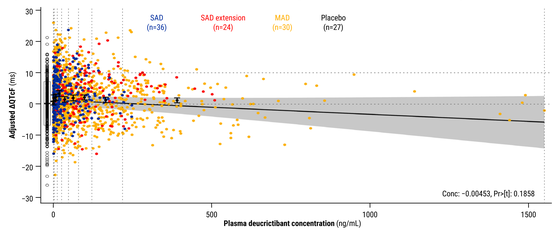
- An integrated analysis assessed CV outcomes across all completed and ongoing deucrictibant Phase 1, Phase 2, and Phase 3 clinical studies with data available up to a cutoff of June 10, 2026, including the following.
- RAPIDe-1: pharmacokinetics and safety assessments following a single dose administered in a non-attack state, followed by a double-blind, randomized, placebo-controlled, crossover, dose-ranging trial of deucrictibant immediate-release capsule for ODT of HAE attacks in adults.[7]
  - Placebo or up to three single doses of deucrictibant 10 mg, 20 mg, or 30 mg across both parts.
- RAPIDe-2: a two-part, Phase 2/3 long-term extension study of deucrictibant immediate-release capsule for ODT of repeat HAE attacks in adults.[8]
  - Part A: double-blind deucrictibant 10 mg, 20 mg, or 30 mg.
  - Part B, which also included adolescents: open-label deucrictibant 20 mg.
- RAPIDe-3: randomized, placebo-controlled, crossover, Phase 3 trial of deucrictibant immediate-release capsule for ODT of HAE attacks in adolescents and adults.[9]
  - Placebo or deucrictibant 20 mg in a crossover design to treat two qualifying attacks.
- CHAPTER-1: a randomized, placebo-controlled trial (RCT) and an open-label extension (OLE) study of deucrictibant for long-term prophylaxis (LTP) of HAE attacks in adults:
  - RCT: placebo or deucrictibant 20 or 40 mg/day for 12 weeks.[10]
  - OLE: 30 participants completed the RCT and rolled into the OLE, during which all participants received deucrictibant 40 mg/day.[16]
- CHAPTER-3: a multicenter, double-blind, placebo-controlled, Phase 3 trial of deucrictibant for LTP of HAE attacks in participants aged ≥12 years:[11]
  - As of July 21, 2026, CV safety data were available from CHAPTER-3.
  - RCT: randomized 2:1 to receive placebo or deucrictibant extended-release (XR) tablet 40 mg/day for 24 weeks.[11]
  - Details of efficacy and safety of deucrictibant in CHAPTER-3 are in the presentation by Riedl et al. ACAAI 2026, presentation ID: LBA010.

Results

C-QTc

- C-QTc meta-analysis population received placebo (N=28; 22 men and 6 women; 16 fasted and 12 fed), or 1–50 mg deucrictibant (N=117; 98 men and 19 women; 47 fasted and 70 fed).
- The highest mean maximum plasma concentration (C_{max}) in the meta-analysis was 693 ng/mL, substantially higher than the concentration estimated to provide 85% maximal response (EC_{85}: 13.8 ng/mL).
- The maximum mean differences in mean QTcF changes between fasted and fed participants were approximately 6 ms with no overlapping 90% CIs, indicating that this assay had sufficient sensitivity and the probability of a false-negative result was small.
- The C-QTcF model estimated a slope of −0.00453 ms/(ng/mL) between deucrictibant plasma concentration and QTcF, which was statistically and clinically non-significant (P=0.1858 based on two-sided t-test).

Figure 1. Plasma deucrictibant concentration versus change in QTcF for all available data pairs



CI, confidence interval; Conc, concentration; MAD, multiple ascending dose; QTcF, corrected QT interval using Fridericia formula; SAD, single ascending dose. The vertical dashed lines indicate decile borders. The small thick lines with whiskers show the mean adjusted QTcF changes (±90% CI) at the mean plasma concentration within each decile. The regression line of the placebo-corrected changes in the QTcF for the pooled data is plotted as a thick black solid line with surrounding 90% CI. The black empty dots left of the minimum plasma concentrations show the individual adjusted QTcF changes for all placebo-treated participants. The thick line within the box shows the mean adjusted ΔΔQTcF for placebo-treated participants, and the box represents the standard deviation.

- In the highest estimated clinical exposure scenario, the expected mean C_{max} was approximately 840.6 ng/mL. The C-QTcF model dataset contained individual plasma concentrations up to 1550 ng/mL, nearly twice this value.
- The ΔΔQTcF in this scenario resulted in a slight negative value of −2.55 ms (upper 90% CI: +2.29 ms), below the 10 ms threshold for QTc prolongation set by regulatory agencies for a clinically meaningful change.[17]

Results

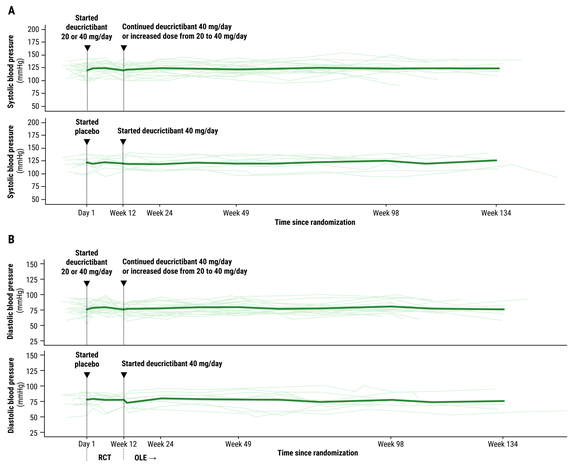
CV outcomes

- As of June 10, 2026, 743 unique participants are estimated to have been exposed to deucrictibant across 25 Pharvaris-sponsored clinical studies (based on number of participants treated with deucrictibant in open-label or completed studies and on randomization ratios for blinded trials ongoing at the time of data cutoff):
  - 339 were healthy participants, 16 had hepatic impairment, 24 had renal impairment, and approximately 312 were participants with HAE.
- There were no system organ class (SOC) cardiac disorder or SOC vascular disorder treatment-related treatment-emergent adverse events (TEAEs) across Phase 1 single-dose studies, RAPIDe-1, CHAPTER-1 RCT, RAPIDe-2 Part A, or RAPIDe-3.
- Of the 232 healthy participants receiving deucrictibant in Phase 1 multiple-dose studies, there were no SOC cardiac disorder treatment-related TEAEs, and 1 (0.4%) participant experienced an SOC vascular disorder TEAE of orthostatic hypotension considered related to treatment.
- Of 110 participants in the ongoing RAPIDe-2 Part B, there were no SOC vascular disorder treatment-related TEAEs, and 1 (0.9%) experienced an SOC cardiac disorder TEAE of tachycardia considered related to treatment.
- Overall, in these studies, no evidence of increased risk of CV events was observed.

CHAPTER-1 OLE CV outcomes

- In the CHAPTER-1 OLE, participants received deucrictibant for a mean (standard deviation) duration of 22.2 (8.1) months, with a maximum exposure across the entire CHAPTER-1 study of 33.8 months.
- Deucrictibant was generally well tolerated, with no treatment-related severe or serious TEAEs, and no TEAEs leading to study drug discontinuation, study withdrawal, or death.
- Of 30 participants receiving deucrictibant in the CHAPTER-1 OLE, no treatment-related SOC cardiac disorder or SOC vascular disorder TEAEs were reported.
- Two participants with a medical history of pharmacologically controlled hypertension showed no clinically significant changes in blood pressure, and their antihypertensive medication regimens remained unchanged during the OLE.
- There were no clinically significant abnormalities in laboratory parameters or ECG findings.

Figure 2. Systolic (A) and diastolic (B) peripheral blood pressure remained stable in participants with HAE during long-term treatment with deucrictibant in the RCT and OLE of CHAPTER-1



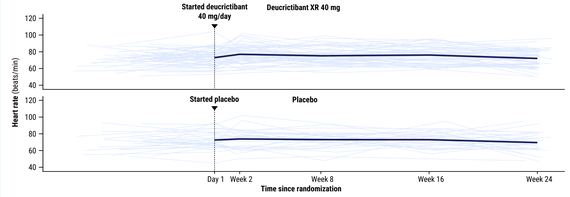
HAE, hereditary angioedema; OLE, open-label extension; RCT, randomized controlled trial. Thin green lines represent individual participant blood pressure. The thick green lines represent the group mean. Participants received placebo or deucrictibant immediate-release capsule, 10 or 20 mg twice daily.

Results

CHAPTER-3 safety outcomes

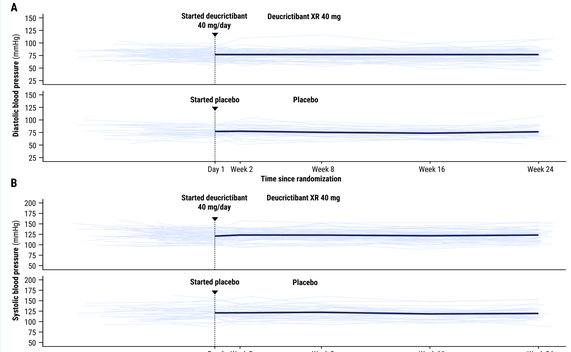
- In CHAPTER-3, 85 participants received deucrictibant (n=55) or placebo (n=30) with a median (IQR) treatment duration of 24.0 (23.7–24.0) weeks.
- Deucrictibant was generally well tolerated, with no treatment-related serious TEAEs and no deaths.
- Treatment-related TEAEs were experienced by 11 (20%) participants receiving deucrictibant and 3 (10%) receiving placebo, and 1 participant in each group discontinued study treatment due to an adverse event.
- There were no SOC cardiac disorder or vascular disorder TEAEs that were deemed related to deucrictibant.
- There were no treatment-related clinically significant abnormalities in heart rate, systolic and diastolic blood pressure, or ECG findings.

Figure 3. Heart rate remained stable in participants with HAE during treatment with deucrictibant in CHAPTER-3



HAE, hereditary angioedema; XR, extended release. Thin blue lines represent individual participant heart rate. The thick blue lines represent the group mean. Participants received placebo or deucrictibant XR capsule, 40 mg once daily. The Day 1 value is the last available record before the first dose.

Figure 4. Diastolic (A) and systolic (B) peripheral blood pressure remained stable in participants with HAE during treatment with deucrictibant in CHAPTER-3



HAE, hereditary angioedema; XR, extended release. Thin blue lines represent individual participant blood pressure. The thick blue lines represent the group mean. Participants received placebo or deucrictibant XR capsule, 40 mg once daily. The Day 1 value is the last available record before the first dose.

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These studies were all Pharvaris-sponsored. SAD/MAD studies: EudraCT 2018-004468-72, 2019-004544-30, and 2020-001533-12.
ClinicalTrials.gov identifiers: CHAPTER-1, NCT05047185; RAPIDe-1, NCT04618211; RAPIDe-2, NCT05396105 ; RAPIDe-3, NCT06343779; CHAPTER-3, NCT06669754.

COIs: B.L.: consultant to Pharvaris, holds stocks/stock options in Pharvaris; **A.L.:** employee of GrayMatters Consulting; consultant to Pharvaris; holds stocks/stock options in Pharvaris; advisor to Kosa Pharma; **R.C.:** employee of RC Consultancy and consultant to Pharvaris, holds stocks in Pharvaris; **P.L.:** employee of Pharvaris, holds stocks in Pharvaris.
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