Clinical Cardiovascular Safety Assessment of Oral Deucrictibant

Anne Lesage[1], Rafael Crabbé[2], Nieves Crespo[3], Brigitte Loenders[4], Peng Lu[5]

[1]GrayMatters Consulting, Schilde, Belgium; [2]RC Consultancy, Bassins, Switzerland; [3]Pharvaris GmbH, Zug, Switzerland; [4]BLC, Sint-Huibrechts-Lille (Pelt), Belgium; [5]Pharvaris Inc., Lexington, MA, USA.

Key takeaways

There was no evidence of QTc prolongation or other cardiovascular safety concerns across Phase 1, 2, and 3 studies of oral deucrictibant in healthy participants and participants with hereditary angioedema.

- **~570** unique participants exposed to deucrictibant to date
- **No evidence** of QTc prolongation in clinical concentration-QTc modeling based on 3 Phase 1 trials
- No cardiovascular concerns at high clinical deucrictibant exposure
- No 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

- **Hereditary angioedema (HAE):** painful swelling attacks affecting multiple locations in the body caused by excess bradykinin activating bradykinin B2 receptors.[1]
- **Oral deucrictibant:** a selective bradykinin B2 receptor antagonist under development for both prophylactic and on-demand treatment (ODT) of bradykinin-mediated angioedema attacks.[2–11]
- **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.[12,13]
  - A manual patch-clamp assay at physiological temperature confirmed the absence of relevant inhibition of the hERG-mediated current at deucrictibant concentrations 162-fold above the highest estimated clinical exposure.[13]

Objective

- To assess the relationship between the deucrictibant plasma concentration and the QT interval corrected (QTc) for heart rate (HR) using the 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 (of non-childbearing potential) participants, 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 across 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.
    - Day 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.
- ECGs were centrally interpreted and analyzed by the same core lab in all three studies.
- 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 pre-dose baseline in QTcF.
- Based on the model results, the mean placebo-corrected change from baseline in QTcF (ΔΔQTcF) for plasma concentration (C) was calculated.

Methods

CV outcomes

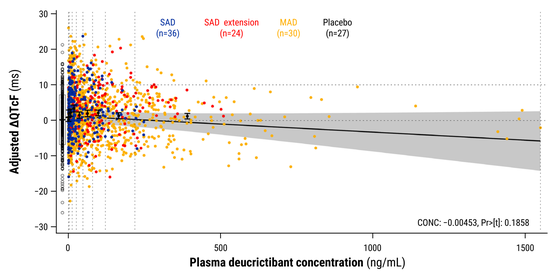
- An integrated analysis assessed CV outcomes across all deucrictibant Phase 1, Phase 2, and Phase 3 clinical studies with data available up to a cutoff of June 10, 2025, including:
  - CHAPTER-1: a randomized, placebo-controlled trial (RCT), and open-label extension (OLE) study of deucrictibant for long-term prophylaxis of HAE attacks in adults:
    - RCT: placebo or deucrictibant 20 or 40 mg/day for 12 weeks.[8]
    - OLE: 30 participants rolled over from the RCT, switching to deucrictibant 40 mg/day.[14]
  - RAPIDe-1: pharmacokinetics and safety part followed by a double-blind, randomized, placebo-controlled, crossover, dose-ranging trial of the deucrictibant immediate-release capsule for ODT of HAE attacks in adults.[4]
    - Placebo or ≤3 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.[5]
    - 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 Phase 3 trial of deucrictibant immediate-release capsule for ODT of HAE attacks in adolescents and adults.[6]
    - Placebo or deucrictibant 20 mg, in a crossover design to treat two qualifying attacks.

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 for 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 display 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 ΔQTcF 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 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.[15]

CV outcomes

- As of June 10, 2025, ~570 unique participants had been exposed to deucrictibant across 24 Pharvaris-sponsored clinical studies (based 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 ~190 were participants with HAE.
- There were no reports of sudden death, torsades de pointes, ventricular tachycardia, ventricular fibrillation or flutter, QT prolongation, or other cardiac arrhythmias.
- There were no cases of clinical seizures, convulsions, or syncope in participants treated with deucrictibant.

Results

Table 1. Total TEAEs, CV TEAEs, and blood pressure TEAEs across deucrictibant clinical studies in the integrated analysis, regardless of relationship to study treatment

Phase 1 single-dose studies in healthy participants, deucrictibant doses ranged from 1–50 mg

	Placebo (N=24)	Deucrictibant (N=107)
Participants with any TEAE, n (%)	**6 (25.0)**	**24 (22.4)**
SOC cardiac disorders, n	**0**	**0**

Phase 1 multiple-dose studies in healthy participants, total daily deucrictibant doses of 20–100 mg

	Placebo (N=8)	Deucrictibant (N=232)
Participants with any TEAE, n (%)	**5 (62.5)**	**112 (48.3)**
SOC cardiac disorders, preferred term, n (%)	**0**	**2 (0.9)**
Atrioventricular block first degree[a]	0	1 (0.4)
Postural orthostatic tachycardia syndrome[a]	0	1 (0.4)
SOC vascular disorders, preferred term, n (%)	**1 (12.5)**	**1 (0.4)**
Orthostatic hypotension[b]	1 (12.5)	1 (0.4)
Hypotension	1 (12.5)	0

RAPIDe-1 trial in participants with HAE: TEAEs within 5 days post-treatment

	Non-attack trial phase		
	Deucrictibant 10 mg (N=23)	Deucrictibant 20 mg (N=24)	Deucrictibant 30 mg (N=25)
Participants with any TEAE, n (%)	**2 (8.7)**	**2 (8.3)**	**4 (16.0)**
SOC cardiac disorders, n	**0**	**0**	**0**

	Attack treatment trial phase			
	Placebo (53 attacks; n'=53)	Deucrictibant 10 mg (38 attacks; n'=21)	Deucrictibant 20 mg (29 attacks; n'=16)	Deucrictibant 30 mg (36 attacks; n'=22)
Attacks with any TEAE, attacks (%)	**3 (5.7)**	**3 (7.9)**	**1 (3.4)**	**2 (5.6)**
SOC cardiac disorders, attacks	**0**	**0**	**0**	**0**

CHAPTER-1 RCT in participants with HAE: All TEAEs

	Placebo (N=11)	Deucrictibant 20 mg/day (N=11)	Deucrictibant 40 mg/day (N=12)
Participants with any TEAE, n (%)	**7 (63.6)**	**6 (54.5)**	**7 (58.3)**
SOC cardiac disorders, n	**0**	**0**	**0**

RAPIDe-2 trial in participants with HAE, Part A: TEAEs within 3 days post-treatment

	Deucrictibant 10 mg (N=4, 87 attacks)	Deucrictibant 20 mg (N=8, 103 attacks)	Deucrictibant 30 mg (N=7, 275 attacks)
Participants with any TEAE, n (%)	**1 (25.0)**	**1 (12.5)**	**5 (71.4)**
Attacks with any TEAE, attacks (%)	**1 (1.1)**	**1 (1.0)**	**10 (3.6)**
SOC cardiac disorders, attacks	**0**	**0**	**0**

RAPIDe-3 trial in participants with HAE: TEAEs within 3 days post-treatment

	Placebo (N=101)	Deucrictibant 20 mg (N=100)
Participants with any TEAE, n (%)	**2 (2.0)**	**15 (15.0)**
SOC cardiac disorders, n	**0**	**0**

CV, cardiovascular; HAE, hereditary angioedema; n, number of participants with a TEAE; n', number of participants with at least one attack treated with the study drug; N, total number of participants treated with at least 1 dose of study drug; RCT, randomized clinical trial; SOC, system organ class; TEAE, treatment-emergent adverse event. [a]Deemed not related to treatment. [b]Deemed related to treatment.

Table 2. Total TEAEs, CV TEAEs, and blood pressure TEAEs in the CHAPTER-1 OLE, regardless of relationship to study treatment

	Placebo to deucrictibant 40 mg/day[a] (N=9)	Deucrictibant 20 mg/day[b] to 40 mg/day[a] (N=11)	Deucrictibant 40 mg/day[a] to 40 mg/day[a] (N=10)
Participants with any TEAE, n (%)	**8 (88.9)**	**8 (72.7)**	**8 (80.0)**
SOC cardiac disorders, n (%)	**0**	**0**	**1 (10.0)**
Palpitations[c]	0	0	1 (10.0)
SOC vascular disorders, n (%)	**0**	**0**	**1 (10.0)**
Hypertension[c]	0	0	1 (10.0)

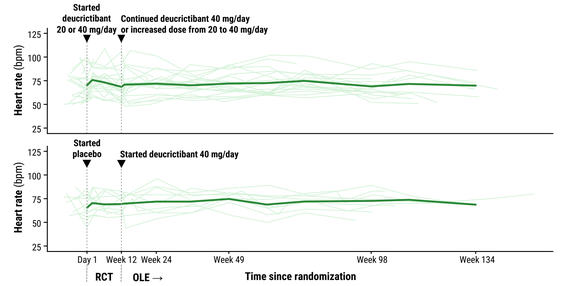
CV, cardiovascular; IR, immediate-release; n, number of participants with a TEAE; N, number of participants who received at least 1 dose of study treatment in the OLE by the cutoff date; OLE, open-label extension; SOC, system organ class; TEAE, treatment-emergent adverse event. [a]Deucrictibant IR capsule, 20 mg twice daily. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Both were deemed not related to treatment.

Results

CHAPTER-1 OLE CV outcomes

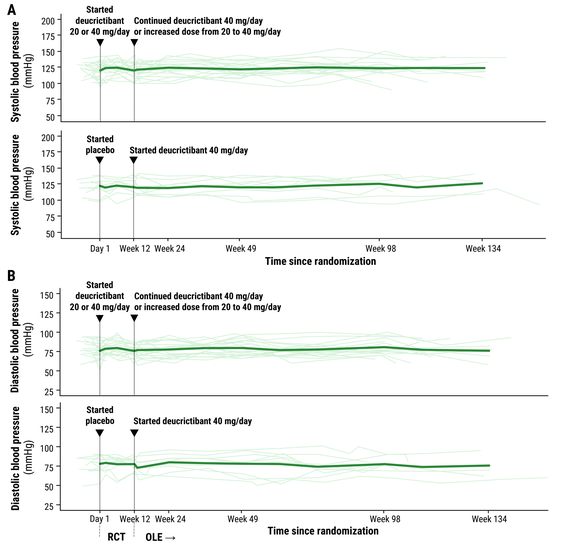
- In the CHAPTER-1 OLE, participants received deucrictibant for a mean (standard deviation) duration of 22.2 (8.1) months, with a maximum exposure across the entire CHAPTER-1 study of 33.8 months.
- Deucrictibant was generally well tolerated, with no treatment-related severe or serious TEAEs, and no TEAEs leading to study drug discontinuation, study withdrawal, or death.
- There were no clinically significant abnormalities in laboratory parameters or ECG findings.

Figure 2. Heart rate remained stable in participants with HAE during long-term treatment with deucrictibant in the RCT and OLE of CHAPTER-1



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

Figure 3. Systolic (A) and diastolic (B) blood pressure remained stable in participants with HAE during long-term treatment with deucrictibant in the RCT and OLE of CHAPTER-1



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.

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COIs: 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; **B.L.:** consultant to Pharvaris, holds stocks/stock options in Pharvaris; **N.C., P.L.:** employee of Pharvaris, holds stocks in Pharvaris.

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