Sustained Therapeutic Exposure with Once-Daily Oral Deucrictibant Extended-Release Tablet for Prophylaxis of Hereditary Angioedema Attacks

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Key takeaways

Results of these Phase 1 pharmacokinetic (PK) studies in healthy volunteers support the once-daily administration of deucrictibant extended-release (XR) tablet in Phase 3 trials investigating its efficacy and safety for prophylaxis against bradykinin-mediated angioedema attacks.

Safety

Deucrictibant XR tablet was generally well tolerated with no serious TEAEs

Pharmacokinetic profile

Sustained therapeutic exposure through ≥24 hours supports once-daily dosing for attack prevention

~ 2-4-fold higher mean plasma concentration at 24 hours than the estimated threshold concentration for therapeutic exposure with a single dose of deucrictibant XR tablet

Sustained exposure during Repeat dosing and Fasting/fed conditions

TEAE, treatment-emergent adverse event; XR, extended-release.

Background

- **Bradykinin-mediated angioedema (AE-BK):** includes hereditary angioedema with C1 inhibitor deficiency (HAE-C1INH) or with normal levels of C1 inhibitor (HAE-nC1INH) and acquired angioedema due to C1 inhibitor deficiency (AAE-C1INH).[1-5]
  - AE-BK is characterized by painful and often disabling swelling attacks.[1-5]
- **Deucrictibant:** an investigational, selective, orally administered bradykinin B2 receptor antagonist under development for prophylactic and on-demand treatment of bradykinin-mediated angioedema.[6-15]
- **Clinical trials:** deucrictibant was efficacious and generally well tolerated when evaluated in Phase 2 clinical trials for prophylactic (CHAPTER-1, NCT05047185) and on-demand (RAPIDe-1, NCT04618211; RAPIDe-2, NCT05396105) treatment of HAE attacks.[8,9,11,12,15]
- **Deucrictibant extended-release (XR) tablet:**
  - In CHAPTER-1, deucrictibant was administered as immediate-release (IR) capsule formulation (20 mg), dosed twice daily, as a proof-of-concept for the once-daily deucrictibant XR tablet, which is the intended commercial formulation of deucrictibant for prophylactic HAE treatment.[12,15,16]

Objectives

Three open-label Phase 1 studies aimed to characterize the:

- Single-dose pharmacokinetics (PK) of deucrictibant XR tablet (40 mg) and deucrictibant IR capsule (2 x 20 mg) and to assess relative bioavailability, safety, and tolerability.
- Food effect on the PK of deucrictibant XR tablet (40 mg) and to assess safety and tolerability.
- Repeat-dose PK of deucrictibant XR tablet (40 mg) and to assess safety and tolerability.

Methods

Phase 1 studies

- **PHA022121-C020*:** a Phase 1, open-label, randomized, two-period, crossover study during which healthy volunteers received a single oral dose of deucrictibant XR tablet (40 mg) or deucrictibant IR capsule (2 x 20 mg taken simultaneously) in crossover fashion under fasting conditions.
- **PHA022121-C021*:** an open-label, randomized, two period, crossover study, during which healthy volunteers received, in randomized order, a single oral dose of deucrictibant XR tablet (40 mg) under fasting or fed conditions.
- **PHA022121-C017*:** a fixed sequence study, during which healthy volunteers received deucrictibant XR tablet (40 mg) once-daily under fed conditions.

COI: Z-Y.Z. and **P.L.**: employees of Pharvaris, hold stocks/stock options in Pharvaris; **K.G.:** employee of DGr Pharma and consultant to Pharvaris; **R.C.:** employee of RC Consultancy and consultant to Pharvaris, holds stocks in Pharvaris.
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Results

PHA0221210-C020

- A total of 15 participants were enrolled in the study.
- This analysis included 14 participants with evaluable PK data for both formulations.
- One person who received deucrictibant IR capsule in period 1 discontinued 4 hours post-dose due to problems with blood sample withdrawal.

Table 1. Summary of PK characteristics

PK parameter	Deucrictibant XR 40 mg tablet (N=14[a])	Deucrictibant IR 2 x 20 mg capsule (N=14[b])
C_{max}, ng/mL	87.2 (25.5)	547 (193)
t_{max}, hours, median (range)	5.03 (3.98–24.00)	1.00 (0.50–1.50)
C_{12h}, ng/mL	47.3 (27.7)	31.1 (19.9)
C_{24h}, ng/mL	51.6 (29.7)	7.47 (6.88)
AUC_{12h}, ng·h/mL	571 (188)	1509 (527)
AUC_{24h}, ng·h/mL	1124 (416)	1703 (660)
AUC_{last}, ng·h/mL	1609 (668)	1794 (742)
AUC_{inf}, ng·h/mL	1547 (699)	1799 (745)
t_{last}, hours, median (range)	47.64 (47.25–48.00)	47.55 (23.98–48.00)
$t_{1/2}$, hours	5.72 (1.70)	5.10 (1.28)
CL/F, L/hours	31.5 (14.7)	26.5 (12.7)
V_z/F, L	245 (129)	179 (52.1)

Mean ± standard deviation unless otherwise noted. AUC_{xh}, area under the concentration-time curve from time of drug administration to x hours; AUC_{inf}, area under the plasma concentration-time curve extrapolated to infinity; AUC_{last}, area under the plasma concentration-time curve to the last measurable plasma concentration; CL/F, oral clearance; C_{max}, maximum plasma concentration; C_{12h}, plasma concentration at 12 hours post-dose; C_{24h}, plasma concentration at 24 hours post-dose; IR, immediate-release; L, liter; PK, pharmacokinetic; $t_{1/2}$, terminal elimination half-life; t_{last}, time of last measurable concentration; t_{max}, actual sampling time to reach the maximum observed analyte concentration; V_z/F, volume of distribution during the terminal phase; XR, extended-release. [a]n=12 for AUC_{inf}, $t_{1/2}$, V_z/F, and CL/F. [b]n=15 for C_{max} and t_{max}.

Mean plasma concentration

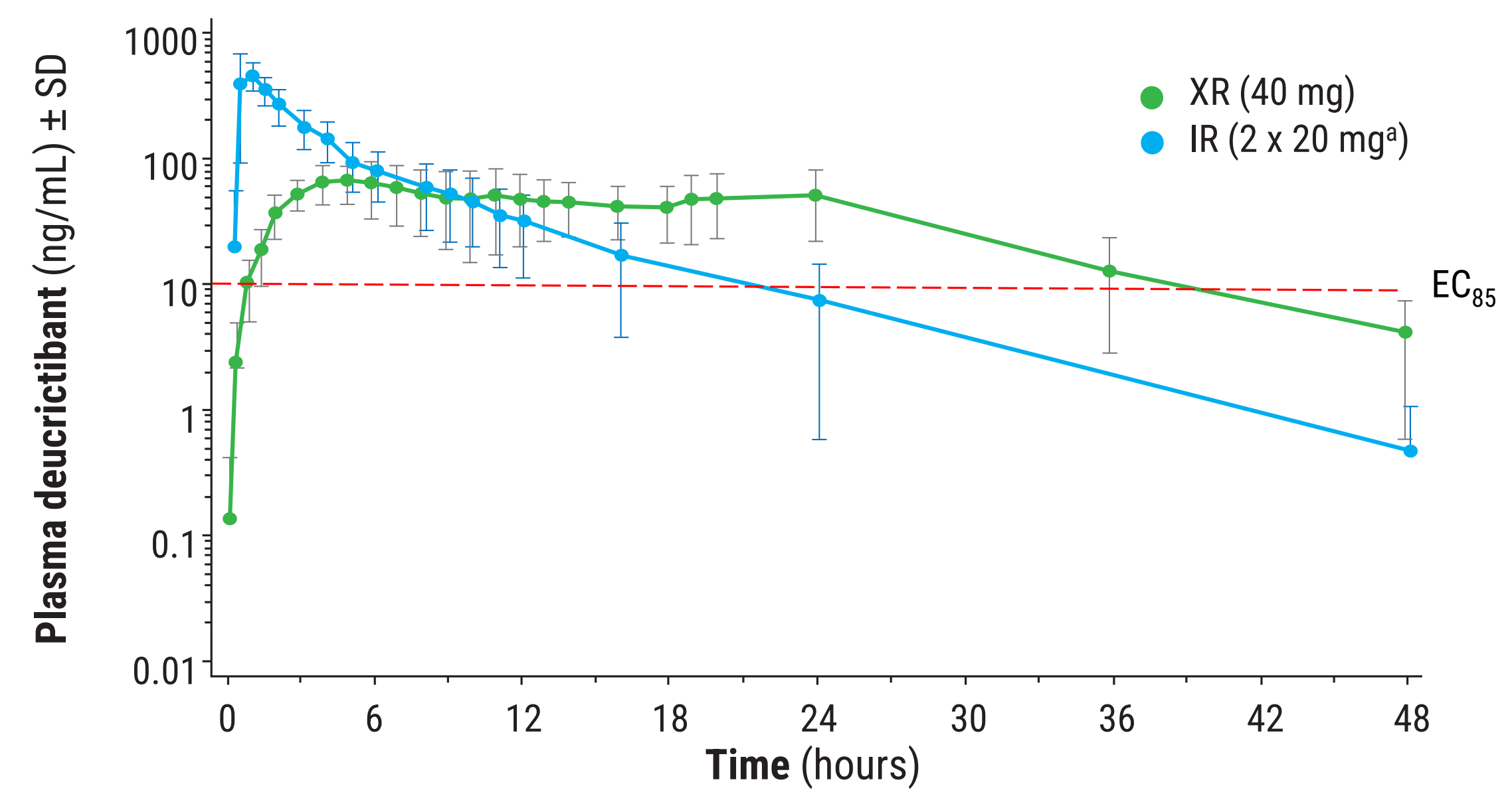
- Mean plasma concentration at 24 hours post-dose (C_{24h}) of deucrictibant XR was ~4-fold higher than the effective concentration of drug estimated to provide 85% maximal response (EC_{85}) of 13.8 ng/mL (above which clinical effects are anticipated based on icatibant studies[17]) **(Figure 1)**.
  - C_{24h} of deucrictibant XR was higher than EC_{85} in 12/14 participants and higher than the concentration estimated to provide 50% maximal response (EC_{50}; 2.4 ng/mL) in all participants.
- Deucrictibant XR resulted in sustained levels in circulation exceeding the EC_{85} therapeutic threshold from ~1.5 hours to at least 24 hours post-dose.
  - Deucrictibant XR resulted in a steady rise in mean plasma concentration to a maximum at 5 hours post-dose; the mean plasma concentration remained relatively stable between 4 and 24 hours post-dose.
  - Deucrictibant IR resulted in a mean plasma concentration exceeding EC_{85} within 15-30 minutes.

Relative bioavailability and overall exposure

- Geometric least square mean ratio (90% CIs) of AUC_{last} was 89.08 (73.30-108.27), which indicated that relative bioavailability and overall exposure of the two formulations were comparable.
- Deucrictibant XR tablet compared with deucrictibant IR capsule showed:
  - 83% lower mean values for C_{max} (86.2 vs. 513 ng/mL).
  - a longer median t_{max} (5.03 hours vs 1 hour).
- Mean $t_{1/2}$ was comparable for deucrictibant XR tablet (5.72 hours) and IR capsule (5.10 hours).

Results

Figure 1. Semi-logarithmic plasma concentration-time profile



EC_{85}, concentration estimated to provide 85% maximal response; IR, immediate-release; SD, standard deviation; XR, extended-release. Error bars represent standard deviation. n = number of participants in each group. [a]Single oral dose of 2 x 20 mg deucrictibant IR capsule.

Safety

- Deucrictibant was generally well tolerated with no serious TEAEs reported.

PHA022121-C021

- A total of 17 participants were included in the study.

PK data

Table 2. Summary of PK characteristics

PK parameter	Single oral dose of deucrictibant 40 mg XR under fasting conditions (N=17)	Single oral dose of deucrictibant 40 mg XR under fed conditions (N=17)
C_{max}, ng/mL	62.9 (18.2)	106 (35.3)
t_{max}, hours, median (range)	5.00 (3.97–25.98)	6.95 (3.98–19.98)
C_{12h}, ng/mL	29.1 (17.3)	51.2 (24.0)
C_{24h}, ng/mL	29.3 (19.6)	26.8 (17.4)
AUC_{12h}, ng·h/mL	396 (136)	630 (279)
AUC_{24h}, ng·h/mL	719 (264)	1050 (359)
AUC_{last}, ng·h/mL	962 (403)	1301 (470)
$t_{1/2}$, hours	5.96 (1.77)	6.07 (1.61)

Mean ± standard deviation unless otherwise noted. AUC_{xh}, area under the concentration-time curve from time of drug administration to x hours; AUC_{last}, area under the plasma concentration-time curve to the last measurable plasma concentration; C_{max}, maximum plasma concentration; C_{12h}, plasma concentration at 12 hours post-dose; C_{24h}, plasma concentration at 24 hours post-dose; PK, pharmacokinetic; $t_{1/2}$, terminal elimination half-life; t_{max}, actual sampling time to reach the maximum observed analyte concentration; XR, extended-release.

- Deucrictibant XR administered under fasting conditions compared with fed conditions showed:
  - The concentration of deucrictibant XR remained above EC_{85} for the entire dosing interval (24 hours) regardless of fasting or fed conditions.
  - C_{24h} was comparable (29.3 ± 19.6 vs 26.8 ± 17.4).
  - Median t_{max} was slightly longer under fed conditions (5 hours vs. 7 hours).
  - Mean $t_{1/2}$ was comparable (6.0 hours vs. 6.1 hours).

Safety

- Deucrictibant was generally well tolerated with no serious TEAEs reported.

Results

PHA022121-C017

- A total of 14 participants were included in the study.

PK data

Table 3. Summary of PK characteristics

PK parameter	Repeat doses of deucrictibant XR (40 mg) once daily: Day 1 of administration (N=14[a])	Repeat doses of deucrictibant XR (40 mg) once daily: Day 6 of administration (N=14[b])
C_{max}, ng/mL	142 (128)	141 (57)
t_{max}, hours, median (range)	6.00 (3.00–12.00)	5.01 (2.08–8.00)
C_{12h}, ng/mL	67.0 (39.0)	58.0 (24.4)
C_{24h}, ng/mL	39.1 (22.2)	38.2 (26.9)
AUC_{12h}, ng·h/mL	783 (563)	941 (432)
AUC_{24h}, ng·h/mL	1636 (1006)	1436 (653)
AUC_{last}, ng·h/mL	1306 (726)	1505 (680)
t_{last}, hours, median (range)	23.25 (23.25–23.28)	23.27 (23.25–23.37)
CL/F, L/hours	–	32.7 (13.4)

Mean ± standard deviation unless otherwise noted. AUC_{xh}, area under the concentration-time curve from time of drug administration to x hours; AUC_{inf}, area under the plasma concentration-time curve extrapolated to infinity; AUC_{last}, area under the plasma concentration-time curve to the last measurable plasma concentration; CL/F, oral clearance; C_{max}, maximum plasma concentration; C_{12h}, plasma concentration at 12 hours post-dose; C_{24h}, plasma concentration at 24 hours post-dose; IR, immediate-release; L, liter; PK, pharmacokinetic; $t_{1/2}$, terminal elimination half-life; t_{last}, time of last measurable concentration; t_{max}, actual sampling time to reach the maximum observed analyte concentration; V_z/F, volume of distribution during the terminal phase; XR, extended-release. [a]n=5 for AUC_{24h}. [b]n=13 for C_{24h}, AUC_{last}, and t_{last}; n=9 for AUC_{24h} and CL/F. Urine collected on Day 6 of administration only.

- Daily deucrictibant XR (40 mg) dosing resulted in sustained exposure, with mean C_{24h} (predose) at concentrations ~3-fold higher than EC_{85} (13.8 ng/mL).
- Deucrictibant XR (40 mg) showed limited accumulation over time with repeat dosing.
- The mean pre-dose deucrictibant concentrations on Days 9 to 22 varied between 29 ng/mL and 41 ng/mL, without a clear trend upwards or downwards.
- Median t_{max} was comparable for Days 8, 13, and 14 with median values varying between 5 and 6 hours.

Safety

- Deucrictibant was generally well tolerated with no serious TEAEs reported.

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

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