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

Pharmacokinetics

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

~2-4-fold higher pre-dose plasma concentration than the estimated effective therapeutic threshold concentration with the once-daily regimen

Sustained exposure during repeat dosing and fasting/fed conditions

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

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

Background

- **Bradykinin-mediated angioedema (AE-BK):** includes hereditary angioedema 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 painful and often disabling swelling attacks.
- **Deucrictibant:** an investigational, selective, orally administered bradykinin B2 receptor antagonist under development for prophylactic and on-demand treatment of bradykinin-mediated angioedema.[6-16]
- **Clinical trials:** deucrictibant was efficacious and generally well tolerated when evaluated in Phase 2 clinical trials for prophylactic (CHAPTER-1, NCT05047185) and Phase 2 and 3 clinical trials for on-demand (RAPIDe-1, NCT04618211; RAPIDe-2, NCT05396105; RAPIDe-3, NCT06343779) 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.[12,15,17]

Objective

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*:** an 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 (period 1/period 2) 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 repeated administration of deucrictibant XR tablet (40 mg) once-daily under fed conditions.

Results

PHA022121-C020

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

Table 1. PK summary

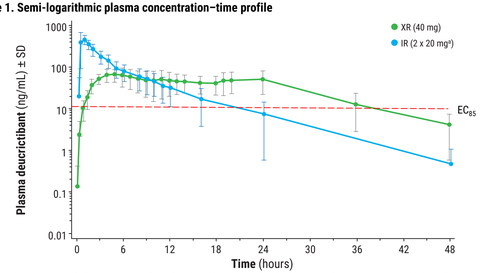
PK parameter	Deucrictibant XR tablet (40 mg) (N=14[a])	Deucrictibant IR capsule (2 x 20 mg) (N=14[b])
C_{max}, ng/mL	87.2 (25.5)	547 (193)
t_{max}, hours, median (range)	5.03 (3.98–24.00)	1.00 (0.50–1.50)
C_{12h}, ng/mL	47.3 (27.7)	31.1 (19.9)
C_{24h}, ng/mL	51.6 (29.7)	7.47 (6.88)
AUC_{12h}, ng·h/mL	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/hour	31.5 (14.7)	26.5 (12.7)

Mean (standard deviation) unless otherwise noted. $AUC_{0\text{-}x}$ area under the concentration–time curve from time of drug administration to x hours; $AUC_{0\text{-}t}$, area under the plasma concentration–time curve extrapolated to infinity; $AUC_{0\text{-}t}$, area under the plasma concentration–time curve to the last measurable plasma concentration; CL/F, oral clearance; C_{12h}, plasma concentration at 12 hours post-dose; C_{24h}, plasma concentration at 24 hours post-dose; C_{max}, maximum plasma concentration; IR, immediate-release; L, liter; PK, pharmacokinetic; t_{last}, time of last measurable concentration; t_{max}, actual sampling time to reach the maximum observed analyte concentration; $t_{1/2}$, terminal elimination half-life; XR, extended-release. [a]n=12 for AUC_{inf}, $t_{1/2}$, 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 tablet was ~4-fold higher than the effective concentration of drug estimated to provide 85% maximal response (EC_{85}; 13.8 ng/mL of deucrictibant) above which clinical effects are anticipated based on studies with the subcutaneously administered antagonist of bradykinin B2 receptor icatibant[18] (**Figure 1**).
  - C_{24h} of deucrictibant XR tablet 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 tablet 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 tablet 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.

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. [a]Single oral dose of 2 x 20 mg deucrictibant IR capsule.

Results

Relative bioavailability and overall exposure

- Plasma concentrations of deucrictibant XR tablet were maintained above the EC_{85} for 36 hours, resulting in highly efficacious plasma levels for the full 24-hour dosing period.
- Geometric least squares mean ratio (90% confidence interval) 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)
  - 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).

Safety

- Deucrictibant was generally well tolerated with no serious treatment-emergent adverse event (TEAEs) reported.

PHA022121-C021

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

Table 2. PK summary

PK parameter	Single oral dose of deucrictibant XR tablet (40 mg) under fasting conditions (N=17)	Single oral dose of deucrictibant XR tablet (40 mg) 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_{24h}, ng/mL	29.3 (19.6)	26.8 (17.4)
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_{24h}, area under the concentration–time curve from time of drug administration to 24 hours; AUC_{last}, area under the plasma concentration–time curve to the last measurable plasma concentration; C_{24h}, plasma concentration at 24 hours post-dose; C_{max}, maximum plasma concentration; PK, pharmacokinetic; t_{max}, actual sampling time to reach the maximum observed analyte concentration; $t_{1/2}$, terminal elimination half-life; XR, extended-release.

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

Safety

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

PHA022121-C017

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

Table 3. PK summary

PK parameter	Repeat doses of deucrictibant XR tablet (40 mg) once daily: Day 1 of administration (N=14[a])	Repeat doses of deucrictibant XR tablet (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_{24h}, ng/mL	39.1 (22.2)	38.2 (26.9)
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/hour	–	32.7 (13.4)

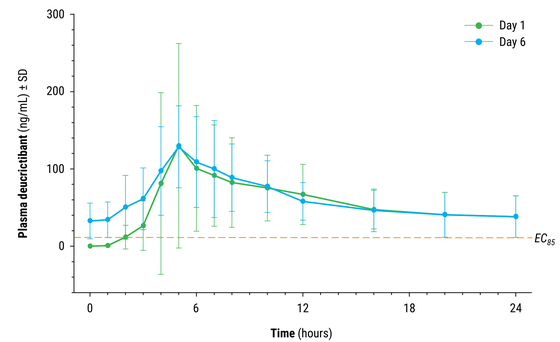
Mean (standard deviation) unless otherwise noted. AUC_{24h}, area under the concentration–time curve from time of drug administration to 24 hours; AUC_{last}, area under the plasma concentration–time curve to the last measurable plasma concentration; C_{24h}, plasma concentration at 24 hours post-dose; CL/F, oral clearance; C_{max}, maximum plasma concentration; L, liter; PK, pharmacokinetic; t_{last}, time of last measurable concentration; t_{max}, actual sampling time to reach the maximum observed analyte concentration; 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 tablet (40 mg) dosing resulted in sustained exposure, with mean C_{24h} (pre-dose) at concentrations ~3-fold higher (**Table 3**) than the EC_{85} of 13.8 ng/mL.

Results

- The mean pre-dose deucrictibant concentrations on Day 6 to Day 15 of daily doses of deucrictibant XR tablet varied between 29 ng/mL and 41 ng/mL, without a clear trend upwards or downwards.
- Deucrictibant XR tablet (40 mg) reached steady state within 2–3 days.
  - Based on deucrictibant half-life and extended absorption for XR tablet (t_{max}, ~5 hours).
- PK at steady state (Day 6), except for pre-dose baseline exposure, was similar to the single-dose PK on Day 1 (**Figure 2**).
- Deucrictibant XR tablet (40 mg) showed limited accumulation over time with repeat dosing.

Figure 2. Plasma concentration–time profile of daily doses of deucrictibant XR tablet 40 mg



EC_{85}, concentration estimated to provide 85% maximal response; SD, standard deviation; XR, extended-release. Error bars represent standard deviation.

Safety

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

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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.
Acknowledgments: Medical writing services were provided by Daniel East, PhD, CMPP, of Envision Spark, an Envision Medical Communications agency, a part of Envision Pharma Group and funded by Pharvaris Netherlands B. V.

*The PHA022121-C020, PHA022121-C021,and PHA022121-C017 studies were funded by Pharvaris.