Evaluation of Safety Margins and Response to Deucrictibant Immediate-Release Capsule Combined With Deucrictibant Extended-Release Tablet

Anne Lesage[1], Juan Bravo[2], Monica Rodriguez[3], Peng Lu[4], Zhi-Yi Zhang[4]

[1]GrayMatters Consulting, Schilde, Belgium; [2]Pharvaris GmbH, Zug, Switzerland; [3]CTI Facts, Bilbao, Spain; [4]Pharvaris Inc., Lexington, MA, USA

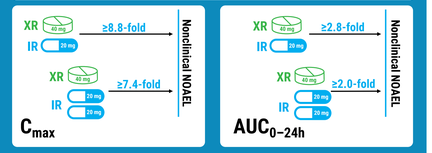
Key takeaways

The combined use of deucrictibant extended-release (XR) tablet 40 mg and immediate-release (IR) capsule(s) 20 mg in the event of a bradykinin-mediated angioedema attack occurring during prophylactic treatment with XR tablet is supported by adequate safety margins, subject to approval of each formulation by regulatory authorities.

Human systemic exposure

Remains below the C_{max} and $AUC_{0\text{-}24h}$ recorded at the highest dose explored in human studies (50 mg twice daily, well tolerated)

Nonclinical safety margins



$AUC_{0\text{-}24h}$, area under the plasma concentration–time curve from time zero to 24 hours; C_{max}, peak plasma concentration; IR, immediate-release; NOAEL, no observed adverse-effect level; XR, extended-release. Images are not a direct representation of the deucrictibant XR tablet or IR capsule.

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]
- **Deucrictibant:** a selective, orally administered bradykinin B2 receptor antagonist under development for prophylactic (extended-release [XR] tablet) and on-demand (immediate-release [IR] capsule) treatment of AE-BK attacks.[6-15]
- **Long-term prophylaxis** with deucrictibant 40 mg/day reduced HAE attack rates by 84.5% compared with placebo in the Phase 2 CHAPTER-1 trial.[12]
- **Combined use** of deucrictibant IR capsule and deucrictibant XR tablet may occur in the real-world setting, subject to regulatory approval of each formulation, if deucrictibant IR capsule is used in the event of an attack occurring during prophylactic treatment with deucrictibant XR tablet.

Objective

To derive exposures in humans across the anticipated dosing scenarios involving once-daily XR tablet combined with one or two IR capsules and to characterize corresponding safety margins based on available nonclinical and clinical data.

Methods

- Safety margins for the combined scenarios were calculated using simulations of exposure in humans performed with a population pharmacokinetic model combining XR and IR administration, clinical exposure at the highest dose tested (50 mg twice daily [BID]), and animal systemic exposure at the no observed adverse-effect level (NOAEL) in toxicity studies in different species.
- The evaluated scenarios (**Table 1**) included once daily deucrictibant XR tablet (40 mg, at steady state) combined with one deucrictibant IR capsule (20 mg), or two deucrictibant IR capsules taken 4 hours apart.
  - Scenarios assumed that the first IR capsule was taken 6 hours (if only one capsule) or 2 hours (if two capsules) after the XR tablet, such that the peak plasma concentrations (C_{max}) for the XR tablet and IR capsule(s) would be reached at the same time, providing a maximum peak of exposure in each scenario.

Table 1. Estimated systemic concentrations for combined use of deucrictibant XR tablet and deucrictibant IR capsule (for prophylactic and on-demand treatment of AE-BK attacks, respectively) in humans

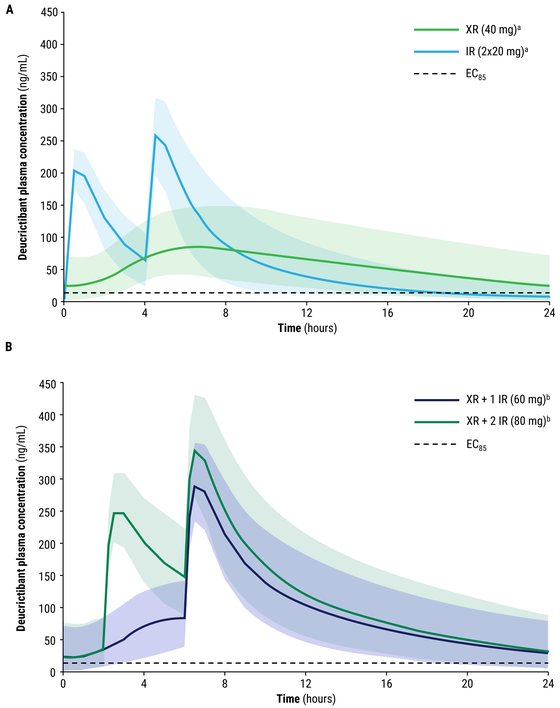
	Total dose (mg)	Total C_{max} (ng/mL)	Total $AUC_{0\text{-}24h}$ (ng·h/mL)
XR + 1 IR[a]	60	287	1912
XR + 1 IR + 1 IR[b]	80	342	2726

AE-BK, bradykinin-mediated angioedema; $AUC_{0\text{-}24h}$, area under the plasma concentration–time curve from time zero to 24 hours; C_{max}, peak plasma concentration; IR, immediate-release; T_{max}, time to peak maximum concentration; XR, extended-release. [a]For the combined use of XR and 1 x IR, it was assumed that the IR dose was taken 6 hours after the XR tablet at the time where both T_{max} values are expected to coincide, providing a maximum peak of exposure. [b]For the combined use of XR and 2 x IR, it was assumed that the first IR dose was taken 2 hours after the XR tablet and the second IR dose 6 hours after the XR tablet, so that the T_{max} values of the XR tablet and the second IR capsule coincide.

Results

- Deucrictibant XR tablet is formulated for prophylaxis and maintains plasma concentrations above the effective concentration estimated to provide 85% of the maximal response (EC_{85}, 13.8 ng/mL) for >24 hours. Deucrictibant IR capsule is formulated for on-demand treatment and rapidly exceeds EC_{85} (**Figure 1A**).
- Plasma concentration–time profiles for evaluated combined use scenarios are presented in **Figure 1B**.

Figure 1. Linear plasma concentration–time profiles of deucrictibant



EC_{85}, effective concentration estimated to provide 85% of the maximal response; IR, immediate-release; XR, extended-release. Mean values shown, with shaded areas representing 95% prediction interval. [a]Single oral deucrictibant XR tablet 40 mg or two deucrictibant IR capsules 20 mg (4 hours apart). [b]One or two IR capsules (4 hours apart) on top of XR tablet at steady state.

- In the scenario where one IR capsule was taken in addition to one XR tablet (XR + 1 IR):
  - The anticipated human C_{max} (287 ng/mL) resulted in a margin of 8.8- to 19-fold the nonclinical C_{max} at the NOAEL in different species (**Table 2, Figure 2A**).
  - The total area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24h}$) in humans was estimated at 1912 ng·h/mL with a margin of 2.8- to 11-fold the $AUC_{0\text{-}24h}$ at the nonclinical NOAEL in different species (**Table 3, Figure 2B**).

Results

- In the scenario where a second IR capsule was administered 4 hours after the first IR capsule in addition to one XR tablet (XR + 2 IR):
  - The margin for the estimated human C_{max} of 342 ng/mL was between 7.4- and 16-fold the nonclinical C_{max} at the NOAEL in different species (**Table 2, Figure 2A**).
  - The human $AUC_{0\text{-}24h}$ was estimated to be 2726 ng·h/mL with a margin of 2.0- to 7.7-fold the AUC at the NOAEL in different species (**Table 3, Figure 2B**).

Table 2. Safety margins for C_{max} to the nonclinical NOAEL in different species for combined use of deucrictibant for prophylactic and on-demand treatment of AE-BK

	XR	2 IR[a]	XR + 1 IR[b]	XR + 2 IR[c]
Total dose (mg)	40	40	60	80
Human C_{max} (ng/mL)[d]	85	267	287	342

Species	NOAEL C_{max} (ng/mL)	Clinical safety margins to nonclinical NOAEL, as multiples of human unbound exposure[e]			
Mouse	4000	63	20	19	16
Rat	2000	31	9.8	9.1	7.7
Rabbit	1500	30	9.4	8.8	7.4
Monkey	3250	54	17	16	13

AE-BK, bradykinin-mediated angioedema; C_{max}, maximum plasma concentration; IR, immediate-release; NOAEL, no observed adverse effect level; T_{max}, time to maximum concentration; XR, extended-release. [a]Two deucrictibant IR capsules taken 4 hours apart. [b]For the combined use of XR + 1 IR, it was assumed that the IR capsule was taken 6 hours after the XR tablet at the time where both T_{max} values are expected to coincide, providing a maximum peak of exposure. [c]For the combined use of XR + 2 IR, it was assumed that the IR capsules were taken at 2 and 6 hours after the XR tablet, so that the T_{max} values of the XR tablet and the second IR capsule coincide. [d]The estimated systemic mean exposures in humans based on population pharmacokinetics modeling. [e]Safety margins were calculated using the free plasma fraction, applying percentage of plasma protein binding in human and animal species.

Figure 2. Safety margins for (A) C_{max}- and (B) $AUC_{0\text{-}24h}$-related effects of deucrictibant in monkeys[a]



$AUC_{0\text{-}24h}$, area under plasma concentration–time curve from time zero to 24 hours; BID, twice daily; C_{max}, maximum plasma concentration; EC_{85}, effective concentration estimated to provide 85% of the maximal response; IR, immediate-release; Max, maximum; NOAEL, no observed adverse effect level; XR, extended-release. [a]Images are not a direct representation of the deucrictibant XR tablet or IR capsule. [b]Two deucrictibant IR capsules taken 4 hours apart. [c]For the combined use of XR + 1 IR, it was assumed that the IR capsule was taken 6 hours after the XR tablet where both T_{max} values are expected to coincide, providing a maximum peak of exposure. [d]For the combined use of XR + 2 IR, it was assumed that the IR capsules were taken at 2 and 6 hours after the XR tablet, so that the T_{max} values of the XR tablet and the second IR capsule coincide.

Results

Table 3. Safety margins for $AUC_{0\text{-}24h}$ to the nonclinical NOAEL in different species for combined use of deucrictibant for prophylactic and on-demand treatment of AE-BK, as unbound exposure

		XR	2 IR[a]	XR + 1 IR[b]	XR + 2 IR[c]
	Total dose (mg)	40	40	60	80
	Human $AUC_{0\text{-}24h}$ (ng·h/mL)[d]	1129	1620	1912	2726
Nonclinical assessment	**Species**	**NOAEL $AUC_{0\text{-}24h}$ (ng·h/mL)**	**Clinical safety margins to nonclinical NOAEL, as multiples of human unbound exposure**			
Chronic toxicity[e,f]	Rat	7570	8.5	5.9	5.0	3.5
	Monkey	15000	19	13	11	7.7
Embryo fetal development[e]	Rat	14900	17	12	9.9	6.9
	Rabbit	7870	13	9.1	7.7	5.4
Carcinogenicity[e,f]	Rat	11800	13	9.3	7.8	5.5
	Mouse	5520	4.8	3.3	2.8	2.0

AE-BK, bradykinin-mediated angioedema; $AUC_{0\text{-}24h}$, area under the plasma concentration–time curve from time zero to 24 hours or the last measured concentration; IR, immediate-release; NOAEL, no observed adverse effect level; T_{max}, time to maximum plasma concentration; XR, extended-release. [a]Two deucrictibant IR capsules taken 4 hours apart. [b]For the combined use of XR + 1 IR, it was assumed that the IR capsule was taken 6 hours after the XR tablet at the time where both T_{max} values are expected to coincide, providing a maximum peak of exposure. [c]For the combined use of XR + 2 IR, it was assumed that the IR capsules were taken at 2 and 6 hours after the XR tablet, so that the T_{max} values of the XR tablet and the second IR capsule coincide. [d]The estimated systemic mean exposures in humans based on population pharmacokinetics modeling. [e]In all nonclinical assessments the NOAEL was the highest dose tested. [f]No evidence of sex-related differences in toxicologic response was identified, therefore only the sex with higher exposure is presented.

- In both combined scenarios, the estimated systemic exposure remained below the highest exposure explored in humans following clinical administration of deucrictibant as an oral solution at 50 mg BID for 10 days (**Table 4, Figure 2A and 2B**), a dose that was not associated with adverse reactions.

Table 4. Exposure coverage and safety margins of potential administration of deucrictibant IR capsule with XR tablet to the highest dose tested in humans (100 mg)

PK parameter	Maximum exposure in clinical trials	Combination of deucrictibant XR with IR		Safety margins	
Formulation	**Oral solution (50 mg BID)**	**XR + 1 IR**	**XR + 2 IR**	**XR + 1 IR**	**XR + 2 IR**
Total dose	**100 mg**	**60 mg**	**80 mg**	**60 mg**	**80 mg**
C_{max} (ng/mL)	693	287	342	2.4	2.0
$AUC_{0\text{-}24h}$ (ng·h/mL)	9716[a]	1912	2726	5.1	3.6

$AUC_{0\text{-}24h}$, area under the plasma concentration–time curve from 0 to 24 hours; BID, twice daily; C_{max}, peak plasma concentration; IR, immediate-release; T_{max}, time to maximum plasma concentration; XR, extended-release. [a]In BID regimen at steady state, $AUC_{0\text{-}24h} = 2*AUC_{0\text{-}12h}$.

References

1. Busse PJ, et al. *N Engl J Med*. 2020;382:1136-48. **2.** Banerji A, et al. *Ann Allergy Asthma Immunol*. 2020;124:600-7. **3.** Betschel SD, et al. *J Allergy Clin Immunol Pract*. 2023;11:2315-25. **4.** Maurer M, et al. *Allergy*. 2022;77:1961-90. **5.** Reshef A, et al. *J Allergy Clin Immunol*. 2024;154(2):398-411. **6.** Lesage A, et al. *Front Pharmacol*. 2020;11:916. **7.** Lesage A, et al. *Int Immunopharmacol*. 2022;105:108523. **8.** Maurer M, et al. *Lancet Haematol*. 2026;13(4):e200-14. **9.** RAPIDe-2. https://www.clinicaltrials.gov/study/NCT05396105. Accessed October 23, 2026. **10.** Riedl MA, et al. *Lancet*. 2026; doi: 10.1016/S0140-6736(26)01296-1. **11.** Riedl MA, et al. Presented at: AAAAI; February 27 to March 2, 2026; Philadelphia, PA, USA. **12.** Aygören-Pürsün E, et al. *Lancet Haematol*. 2026;13(4):e215-26. **13.** CHAPTER-3. https://clinicaltrials.gov/study/NCT06669754. Accessed October 23, 2026. **14.** CHAPTER-4. https://clinicaltrials.gov/study/NCT06679881. Accessed October 23, 2026. **15.** CREAATE. https://clinicaltrials.gov/study/NCT07266805. Accessed October 23, 2026.

COI: A.L.: employee of GrayMatters Consulting and consultant to Pharvaris, holds stocks/stock options in Pharvaris, advisor to Kosa Pharma; **J.B., P.L., Z-Y.Z.,:** employees of Pharvaris, hold stocks options in Pharvaris; **M.R.:** employee of CTI Facts and consultant to Pharvaris.
Acknowledgments: Medical writing services were provided by Jonny Turner, PhD, of Envision Medical Communications, and funded by Pharvaris.

This study was sponsored by Pharvaris