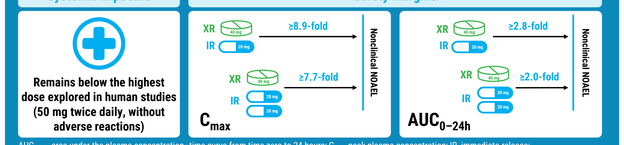
Evaluations of Safety Margins and Response to Deucrictibant Extended-Release (XR) Tablet in Combination With Deucrictibant Immediate-Release (IR) Capsule

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

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

Key takeaways

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



AUC_{0-24h}, 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]
- **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 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 by 6 hours after the XR tablet, such that the peak plasma concentrations (C_{max}) for the XR tablet and IR capsule would be reached at the same time, providing a maximum peak of exposure.
- A post-hoc analysis of the CHAPTER-1 study[12,16] assessed mean duration of breakthrough attacks, in the placebo group from the randomized clinical trial (RCT) part and the deucrictibant group from the RCT and the open label extension (OLE) parts, that were treated with a single dose of subcutaneous icatibant, another bradykinin B2 receptor antagonist indicated for on-demand treatment of attacks.

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) in humans

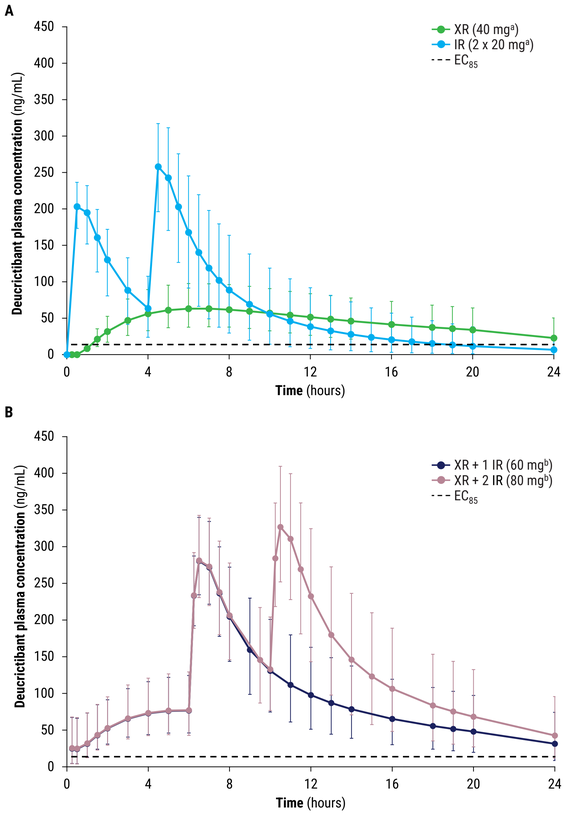
	Total dose (mg)	Total C_{max} (ng/mL)	Total AUC_{0-24h} (ng·h/mL)
XR + 1 IR[a]	60	281	1923
XR + 1 IR + 1 IR[a]	80	327	2683

AE-BK, bradykinin-mediated angioedema; AUC_{0-24h}, 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 IR it was assumed that the first IR dose was taken by 6 hours after the XR tablet at the time where both T_{max} values are expected to coincide, providing a maximum peak of exposure.

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. Error bars represent 90% prediction interval. [a]Single oral dose of deucrictibant XR tablet 40 mg or two doses of deucrictibant IR capsule 20 mg (4h apart). [b]One or two doses of IR capsule (4h 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} (281 ng/mL) resulted in a margin of 8.9- 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_{0-24h}) in humans was estimated at 1923 ng·h/mL with a margin of 2.8- to 11-fold the AUC_{0-24h} at the nonclinical NOAEL in different species (**Table 3, Figure 2B**).
- 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 327 ng/mL was between 7.7- and 16-fold the nonclinical C_{max} at the NOAEL in different species (**Table 2, Figure 2A**).
  - The human AUC_{0-24h} was estimated to be 2683 ng·h/mL with a margin of 2- to 7.9-fold the AUC at the NOAEL in different species (**Table 3, Figure 2B**).

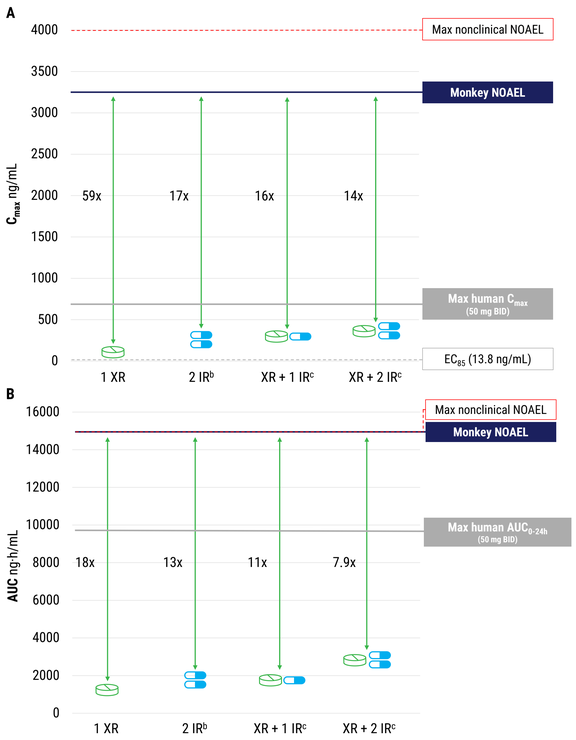
Results

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[b]
Total dose (mg)		40	40	60	80
Human C_{max} (ng/mL)[c]		78	267	281	327
Species	**NOAEL C_{max} (ng/mL)**	**Clinical safety margins to nonclinical NOAEL, as unbound exposure[d]**			
Mouse	4000	69	20	19	16
Rat	2000	34	9.8	9.3	8.0
Rabbit	1500	32	9.4	8.9	7.7
Monkey	3250	59	17	16	14

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 and IR it was assumed that the first IR dose was taken by 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]The estimated systemic mean exposures in humans based on population pharmacokinetics modeling. [d]Safety margins 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-related effects[a] of deucrictibant



AUC, area under plasma concentration–time curve; 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 and IR it was assumed that the first IR dose was taken by 6 hours after the XR tablet at the time where both T_{max} values are expected to coincide, providing a maximum peak of exposure.

Results

Table 3. Safety margins for AUC 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[b]
Total dose (mg)		40	40	60	80
Human AUC_{0-24h} (ng·h/mL)[c]		1151	1620	1923	2683
Nonclinical assessment[d]	**Species**	**NOAEL AUC (ng·h/mL)**	**Clinical safety margins to nonclinical NOAEL, as unbound exposure**		
Chronic toxicity[e]	Rat	7570	8.4	5.9	5.0	3.6
	Monkey	15000	18	13	11	7.9
Embryo fetal development	Rat	14900	16	12	9.8	7.1
	Rabbit	7870	13	9.1	7.6	5.5
Carcinogenicity[e]	Rat	11800	13	9.3	7.8	5.6
	Mouse	5520	4.7	3.3	2.8	2.0

AE-BK, bradykinin-mediated angioedema; AUC, 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; popPK, population pharmacokinetics; 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 and IR, it was assumed the first IR dose was taken by 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]The estimated systemic mean exposures in humans based on popPK modeling. [d]In all nonclinical assessments the NOAEL was the highest dose tested. [e]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 remains below the highest exposure explored in humans following clinical administration of deucrictibant in a SMEDDS solution at 50 mg BID, for 10 days (**Table 4, Figure 2A and B**), 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)

Exposure	Clinical study	Combination of deucrictibant XR with IR[a]		Safety margins[a]	
Formulation	**Deucrictibant 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	281	327	2.5	2.1
AUC_{0-24h} (ng·h/mL)	9716[b]	1923	2683	5.1	3.6

AUC_{0-24h}, 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]For the combined use of XR and IR it was assumed that the first IR dose was taken by 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]In BID regimen, $AUC_{0-24} = 2*AUC_{0-12}$

- In the CHAPTER-1 study, mean attack duration was comparable for icatibant-treated attacks in the placebo group from the RCT part (1.12 days, n=25) and for icatibant-treated attacks in the deucrictibant group from the RCT/OLE parts (1.01 days, n=21), suggesting no evident impairment of efficacy of on-demand treatment with a bradykinin B2 receptor antagonist when used for breakthrough attacks during exposure to a prophylactic treatment with the same mechanism of action.

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COI: A.L.: employee of GrayMatters Consulting and consultant to Pharvaris, holds stocks/stock options in Pharvaris, advisor to Kosa Pharma; **J.B., Z-Y.Z., P.L.,** and **N.C.:** employees of Pharvaris, hold stocks/stock options in Pharvaris; **M.R.:** employee of CTI and consultant to Pharvaris.
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