Evaluating Safety Margins of the Use of Deucrictibant Extended-Release Tablet in Combination with Deucrictibant Immediate-Release Capsule

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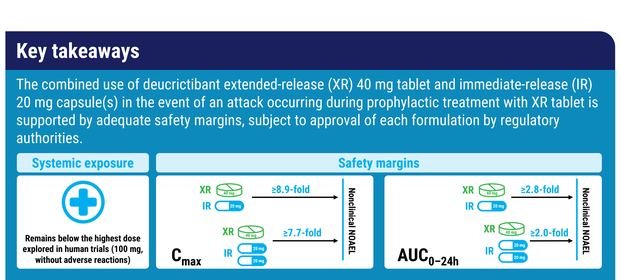
Key takeaways

The combined use of deucrictibant extended-release (XR) 40 mg tablet and immediate-release (IR) 20 mg capsule(s) 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; h, hours; IR, immediate-release; NOAEL, no observed adverse-effect level; XR, extended-release. Images 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 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 (extended-release [XR] tablet) and on-demand (immediate-release [IR] capsule) treatment of AE-BK attacks.[6-18]
- **Combined use:** of deucrictibant XR tablet and deucrictibant IR capsule 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 human exposures across the anticipated dosing scenarios involving once-daily XR tablet combined with one or two IR capsules and characterize corresponding safety margins based on available nonclinical and clinical data.

Methods

- Safety margins for the combined scenarios were calculated using human exposure simulations 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 daily-dose 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 CHAPTER-1[13,14] assessed mean duration of breakthrough attacks, in placebo and deucrictibant groups, that were treated with a single dose of icatibant, another bradykinin B2 receptor antagonist, for on-demand treatment of attacks.

Table 1. Estimated systemic concentrations for combined prophylactic and on-demand treatment of AE-BK in humans

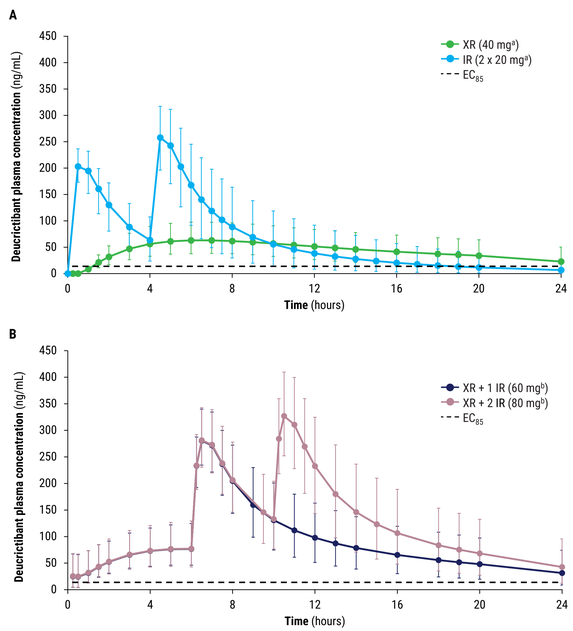
	Total dose (mg)	Total C_{max} (ng/mL)	Total AUC_{0-24h} (ng·h/mL)
XR + 1 IR[a]	60	281	1923
XR + 1 IR + 1 IR[a]	80	327	2683

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; h, hours; IR, immediate-release; T_{max}, time to peak maximum concentration; XR, extended-release. [a]For the combined use of XR and IR it is assumed that the first IR dose is taken 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



EC_{85}, 85% effective concentration; IR, immediate-release; XR, extended-release. Error bars represent 90% confidence interval. [a]Single oral dose of 40 mg XR tablet or two doses of 20 mg deucrictibant IR capsule. [b]One or two doses of IR capsules on top of XR tablet at steady state.

- In the scenario where 1 IR capsule is taken in addition to 1 XR tablet (XR + 1 IR):
  - The anticipated human C_{max} (281 ng/mL) would result 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 is 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 is administered 4 hours after the first IR capsule in addition to 1 XR tablet (XR + 2 IR):
  - The margin for the estimated human C_{max} of 327 ng/mL is maintained 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} is 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**).

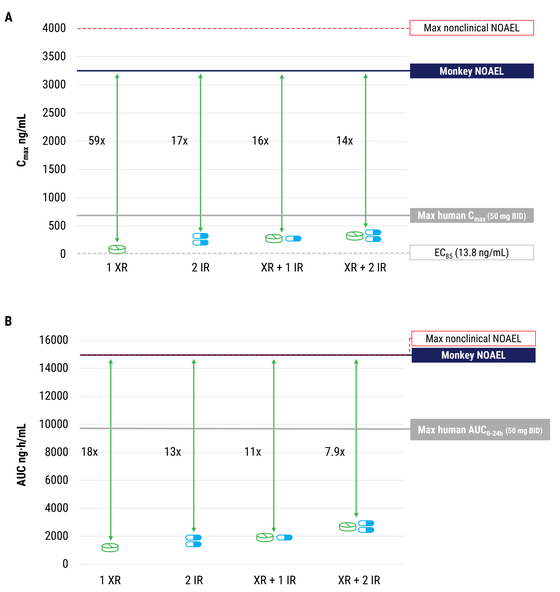
Results

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

	XR	2 IR[a]	XR + 1 IR[b]	XR + 1 IR + 1 IR after 4h[b]
Total dose (mg)	40	40	60	80
Human C_{max} (ng/mL)[c]	78	267	281	327
Species	**NOAEL C_{max} (ng/mL)**	**Safety margins to nonclinical NOAEL, as unbound exposure**		
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; h, hours; 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 is assumed that the first IR dose is taken 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.

Figure 2. Safety margins for (A) C_{max}- and (B) AUC-related effects[a]



AUC, area under plasma concentration–time curve; BID, twice daily; C_{max}, maximum plasma concentration; EC_{85}, 85% effective concentration; IR, immediate-release; Max, maximum; NOAEL, no observed adverse effect level; XR, extended-release. [a]Images not a direct representation of the deucrictibant XR tablet or IR capsule.

Results

Table 3. Safety margins to the nonclinical AUC at the NOAEL in different species for combined prophylactic and on-demand treatment of AE-BK, as unbound concentration

		XR	2 IR[a]	XR + 1 IR[b]	XR + 1 IR + 1 IR[b]
Total dose (mg)		40	40	60	80
Human AUC_{0-24h} (ng·h/mL)[c]		1151	1620	1923	2683
Nonclinical assessment	**Species**	**NOAEL AUC (ng·h/mL)**	**Clinical safety margins to nonclinical NOAEL, as unbound exposure**		
Chronic toxicity[d]	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[d]	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 is assumed the first IR dose is taken 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]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 100 mg (as 50 mg BID) (**Table 4, Figure 2A and B**), a dose that was not associated with adverse reactions.

Table 4. Exposure coverage of potential administration of deucrictibant XR tablet with IR capsule by highest dose tested in humans (50 mg BID)

Exposure	Clinical study	Combination of deucrictibant XR with IR[a]		Safety margin[a]	
	Deucrictibant 50 mg BID	XR + 1 IR	XR + 1 IR + 1 IR	XR + 1 IR	XR + 1 IR + 1 IR
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; h, hours; IR, immediate-release; T_{max}, time to maximum plasma concentration; XR, extended-release. [a]For the combined use of XR and IR it is assumed that the first IR dose is taken 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 CHAPTER-1, bradykinin B2 receptor antagonist icatibant as on-demand treatment of breakthrough attacks while on prophylactic treatment with deucrictibant still showed evidence of efficacy, since mean breakthrough attack duration was comparable for the placebo-icatibant (1.12 days, n=25) and the deucrictibant-icatibant (1.05 days, n=20) groups.

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.** RAPIDe-1. https://www.clinicaltrials.gov/study/NCT04618211. Accessed March 12, 2026. **9.** Maurer M, et al. *Lancet Haem*. 2026; DOI: 10.1016/S2352-3026(25)00341-2. **10.** RAPIDe-2. https://www.clinicaltrials.gov/study/NCT05396105. Accessed March 12, 2026. **11.** RAPIDe-3. https://clinicaltrials.gov/study/NCT06343779. Accessed March 12, 2026. **12.** Maurer M, et al. Presented at: AAAAI; February 24–27, 2023; San Antonio, TX, USA. **13.** CHAPTER-1.https://www.clinicaltrials.gov/study/NCT05047185. Accessed March 12, 2026. **14.** Aygören-Pürsün E, et al. *Lancet Haem*. 2026; DOI: 10.1016/S2352-3026(26)00004-9. **15.** CHAPTER-3. https://clinicaltrials.gov/study/NCT06669754. Accessed March 12, 2026. **16.** CHAPTER-4. https://clinicaltrials.gov/study/NCT06679881. Accessed March 12, 2026. **17.** Aygören-Pürsün, et al. Presented at: EAACI; May 31–June 3, 2024; Valencia, Spain. **18.** CREAATE. https://clinicaltrials.gov/study/NCT07266805. Accessed March 12, 2026.

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This study was sponsored by Pharvaris

Author disclosures

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Methods

- Safety margins for the combined scenarios were calculated using human exposure simulations 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 daily-dose 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 CHAPTER-1[13,14] assessed mean duration of breakthrough attacks, in placebo and deucrictibant groups, that were treated with a single dose of icatibant, another bradykinin B2 receptor antagonist, for on-demand treatment of attacks.

Table 1. Estimated systemic concentrations for combined prophylactic and on-demand treatment of AE-BK in humans

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

AE-BK, bradykinin-mediated angioedema; $AUC_{0\text{-}24h}$, area under the plasma concentration–time curve from time zero to 24 hours; C_{max}, peak plasma concentration; h, hours; IR, immediate-release; T_{max}, time to maximum plasma concentration; XR, extended-release. [a]For the combined use of XR and IR it is assumed that the first IR dose is taken 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**).
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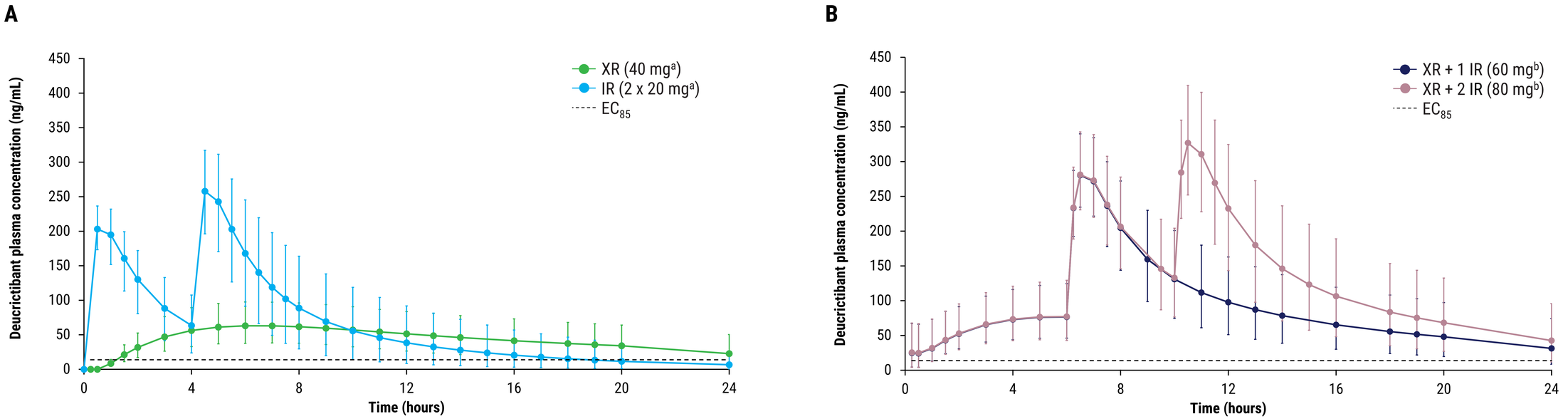
Figure 1. Linear plasma concentration–time profiles



EC_{85}, 85% effective concentration; IR, immediate-release; XR, extended-release. Error bars represent 90% confidence interval. [a]Single oral dose of 40 mg XR tablet or two doses of 20 mg deucrictibant IR capsule. [b]One or two doses of IR capsules on top of XR tablet at steady state.

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Results

- In the scenario where 1 IR capsule is taken in addition to 1 XR tablet (XR + 1 IR):
  - The anticipated human C_{max} (281 ng/mL) would result 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 ($AUC_{0\text{-}24h}$) in humans is estimated at 1923 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**).
- In the scenario where a second IR capsule is administered 4 hours after the first IR capsule in addition to 1 XR tablet (XR + 2 IR):
  - The margin for the estimated human C_{max} of 327 ng/mL is maintained between 7.7- and 16-fold the nonclinical C_{max} at the NOAEL in different species (**Table 2, Figure 2A**).
  - The human $AUC_{0\text{-}24h}$ is 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**).

AUC, area under the plasma concentration–time curve from time zero to the last measured or 24 hours concentration; C_{max}, maximum plasma concentration; IR, immediate-release; NOAEL, no observed adverse effect level; XR, extended-release.

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

		XR	2 IR[a]	XR + 1 IR[b]	XR + 1 IR + 1 IR after 4h[b]
Total dose (mg)		40	40	60	80
Human C_{max} (ng/mL)[c]		78	267	281	327
Species	**NOAEL C_{max} (ng/mL)**	**Safety margins to nonclinical NOAEL, as unbound exposure**			
Mouse	4000	69	20	19	16
Rat	2000	34	9.8	9.3	8.0
Rabbit	1500	32	9.4	8.9	7.7
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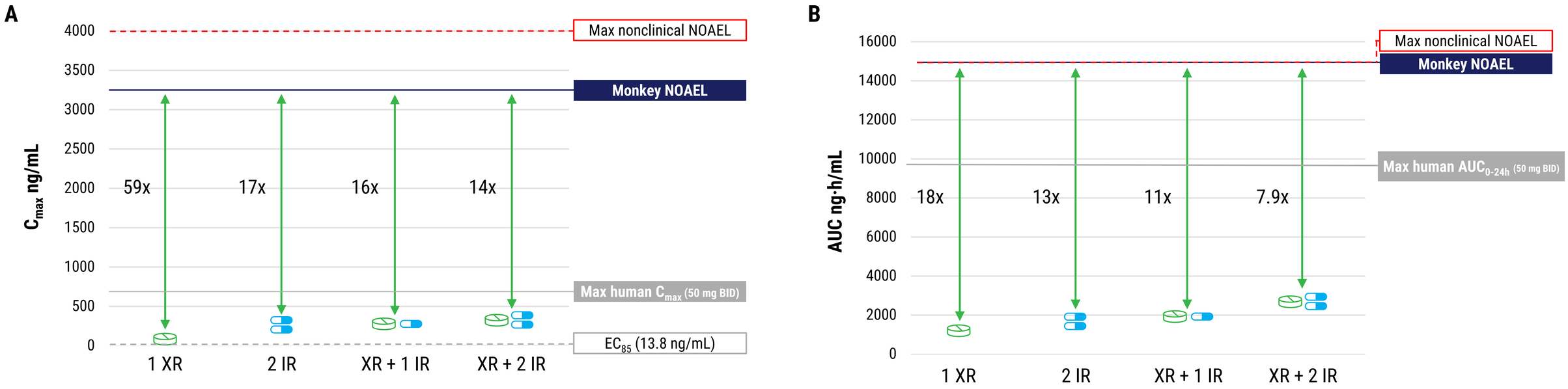
AE-BK, bradykinin-mediated angioedema; C_{max}, maximum plasma concentration; h, hours;IR, immediate-release; NOAEL, no observed adverse effect level; T_{max}, time to maximum plasma concentration; XR, extended-release. [a]Two deucrictibant IR capsules taken 4 hours apart. [b]For the combined use of XR and IR it is assumed that the first IR dose is taken 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.

Figure 2. Safety margins for (A) C_{max}- and (B) AUC-related effects[a]



AUC, area under plasma concentration–time curve; BID, twice daily; C_{max}, maximum plasma concentration; EC85, 85% effective concentration; IR, immediate-release; Max, maximum; NOAEL, no observed adverse effect level; XR, extended-release. [a]Images not a direct representation of the deucrictibant XR tablet or IR capsule.

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Table 3. Safety margins to the nonclinical AUC at the NOAEL in different species for combined prophylactic and on-demand treatment of AE-BK, as unbound concentration

			XR	2 IR[a]	XR + 1 IR[b]	XR + 1 IR + 1 IR[b]
		Total dose (mg)	40	40	60	80
		Human $AUC_{0\text{-}24h}$ (ng·h/mL)[c]	1151	1620	1923	2683
Nonclinical assessment	**Species**	**NOAEL AUC (ng·h/mL)**	**Clinical safety margins to nonclinical NOAEL, as unbound exposure**			
Chronic toxicity[d]	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[d]	Rat	11800	13	9.3	7.8	5.6
	Mouse	5520	4.7	3.3	2.8	2.0

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Table 4. Exposure coverage of potential administration of deucrictibant XR tablet with IR capsule by highest dose tested in humans (50 mg BID)

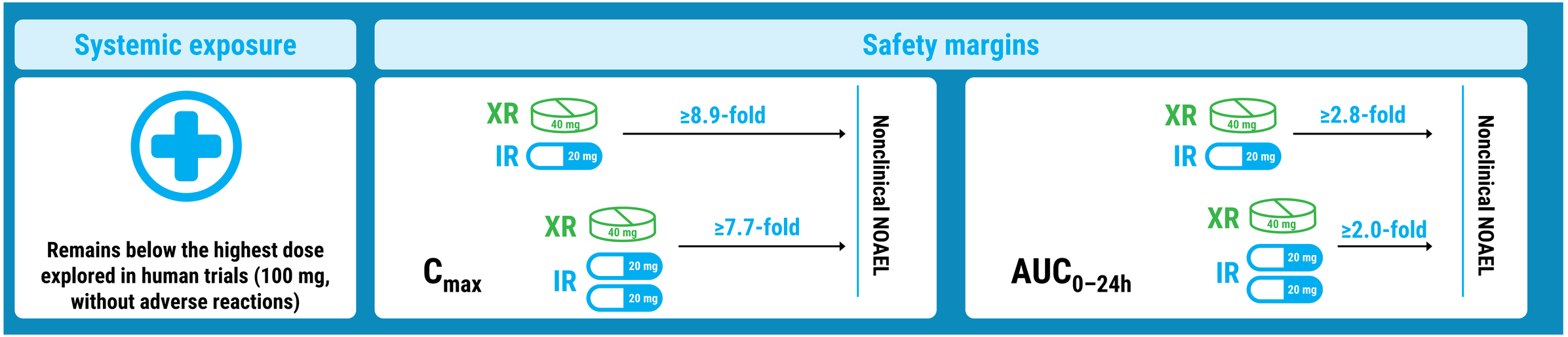
- In both combined scenarios, the estimated systemic exposure remains below the highest exposure explored in humans following clinical administration of deucrictibant 100 mg (as 50 mg BID) (**Table 4, Figure 2A and B**), a dose that was not associated with adverse reactions.
- In CHAPTER-1, bradykinin B2 receptor antagonist icatibant as on-demand treatment of breakthrough attacks while on prophylactic treatment with deucrictibant still showed evidence of efficacy, since mean breakthrough attack duration was comparable for the placebo-icatibant (1.12 days, n=25) and the deucrictibant-icatibant (1.05 days, n=20) groups.

Exposure	Clinical study	Combination of deucrictibant XR with IR[a]		Safety margin[a]	
	Deucrictibant 50 mg BID	XR + 1 IR	XR + 1 IR + 1 IR	XR + 1 IR	XR + 1 IR + 1 IR
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; h, hours; IR, immediate-release; T_{max}, time to maximum plasma concentration; XR, extended-release. [a]For the combined use of XR and IR it is assumed that the first IR dose is taken at the time where both T_{max} values are expected to coincide, providing a maximum peak of exposure. [b]In BID regimen, $AUC_{0-24} = 2*AUC_{0-12}$

Key takeaways

The combined use of deucrictibant extended-release (XR) 40 mg tablet and immediate-release (IR) 20 mg capsule(s) 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.



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