Efficacy and safety of the oral bradykinin B2 receptor antagonist deucrictibant immediate-release capsule (PHVS416) in treatment of hereditary angioedema attacks: results of RAPIDe-1 phase 2 trial

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2023 HAEi Regional Conference EMEA
Munich, Germany – 1-3 September 2023

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

Conflicts of interest disclosure

Consultancy fees, research grant support, speaker fees, and/or clinical trial fees

M.Mag.: BioCryst, CSL Behring, KalVista, Novartis, Octapharma, Pharming, Shire/Takeda.

J.A.: BioCryst, BioMarin, CSL Behring, Cycle Pharmaceuticals, KalVista, Pharming, Pharvaris, Takeda. E.A.P.: BioCryst, Biomarin, Centogene, CSL Behring, KalVista; Pharming, Pharvaris, Shire/Takeda. M.L.B.: BioCryst, CSL Behring, Shire HGT. L.B.: BioCryst, Blueprint, CSL Behring, Novartis, Shire/Takeda. H.C.: CSL Behring, Dyax, Green Cross, Merck, Novartis, Pharvaris, Sanofi, Sobi, Takeda. D.M.C.: BioCryst, CSL Behring, Pharming, Pharvaris, Shire/Takeda. A.D-T.: BioCryst, Takeda. O.F.: BioCryst, CSL Behring, Takeda. H.F.: BioCryst, CSL Behring, KalVista, ONO Pharmaceutical, Pharming, Pharvaris, Takeda. J.G.: CSL Behring, Shire/Takeda. M.G.: CSL Behring, Novartis, Takeda; participated in advisory boards organized by BioCryst, CSL Behring, Novartis, Pharming, Pharvaris, Takeda. D.H.: none. R.H.: BioCryst, CSL Behring, KalVista, Pharming Pharvaris, Shire/Takeda. J.S.J.: BioCryst, CSL Behring, Cycle pharmaceuticals, Oasis pharmaceuticals, Pharming, Pharvaris, Takeda. A.K.: CSL Behring, Pharming, Takeda. S.K.-A.: BioCryst, Biotest, CSL Behring, Ionis Pharmaceuticals, KalVista, Pharvaris, Shire/Takeda, X4 Pharmaceuticals. P.K.: none. R.L.: BioCryst, CSL Behring, Takeda. H.H.L.: BioCryst, BioMarin, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Takeda. M.E.M.: Allakos, Amgen, AstraZeneca, BioCryst, Blueprint, CSL Behring, Cycle, Genentech, GSK, KalVista, Merck, Novartis, Pharming, Pharvaris, Sanofi/Regeneron, Takeda. A.R.: BioCryst, CSL Behring, Pharming, Pharvaris, Shire/Takeda, Stallergens, Teva. M.A.R.: Astria, BioCryst, Biomarin, CSL Behring, Cycle Pharma, Fresenius-Kabi, Grifols, Ionis, Ipsen, KalVista, Ono Pharma, Pfizer, Pharming, Pharvaris, RegenexBio, Sanofi-Regeneron, Takeda. B.R.: BioCryst, CSL-Behring, Ionis, KalVista, Pharvaris, Takeda. G.S.: Pharvaris, Takeda. M.Sta.: Pharming, Pharvaris, Sobi. P.S.: CSL Behring, Novartis, Pfleger, Shire/Takeda. M.Sto.: BioCryst, CSL Behring, KalVista, Pharming, Shire/Takeda. G.L.S.: Aimmune, Amgen, CSL Behring, DBV, Genentech, Green Cross, Kedrion, Leo, Novartis, Novo, Pediapharm, Sanofi. M.D.T.: none. A.V.: Astra Zeneca, Berlin-Chemie/MenariniGroup, CSL Behring, Novartis, Pharming, Pharvaris, Shire/Takeda, Sobi, Teva. W.H.Y.: Aimmune, ALK, AnaptysBio, AstraZeneca, BioCryst, CSL Behring, DBV Technologies, Dermira, Genentech, GlaxoSmithKline, Glenmark, Merck, Novartis, Pharming, Regeneron, Roche, Sanofi, Shire/Takeda. M.Mau.: Adverum, Attune, BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, Takeda/Shire.

M.-H.J.: employee of Pharvaris at the time the analyses were conducted, holds stocks in Pharvaris. R.C.: employee of CG Consultancy and consultant to Pharvaris, holds stocks in Pharvaris. S.v.L.: employee of SLC Consultancy and consultant to Pharvaris, holds stocks in Pharvaris. H.C.: employee of Pharvaris at the time the analyses were conducted, holds stocks in Pharvaris. L.Z.: employee of Pharvaris, holds stocks in Pharvaris. J.K.: employee of JCK Consult and consultant to Pharvaris, holds stocks/stock options in Pharvaris. A.L.: employee of GrayMattersConsulting and consultant to Pharvaris, holds stocks/stock options in Pharvaris. Advisor to KosaPharma, holds stocks in KosaPharma. P.L.: employee of Pharvaris, holds stocks/stock options in Pharvaris.

RAPIDe-1 was a Pharvaris-sponsored clinical trial. ClinicalTrials.gov Identifier: NCT04618211. EudraCT Number: 2020-003445-11.

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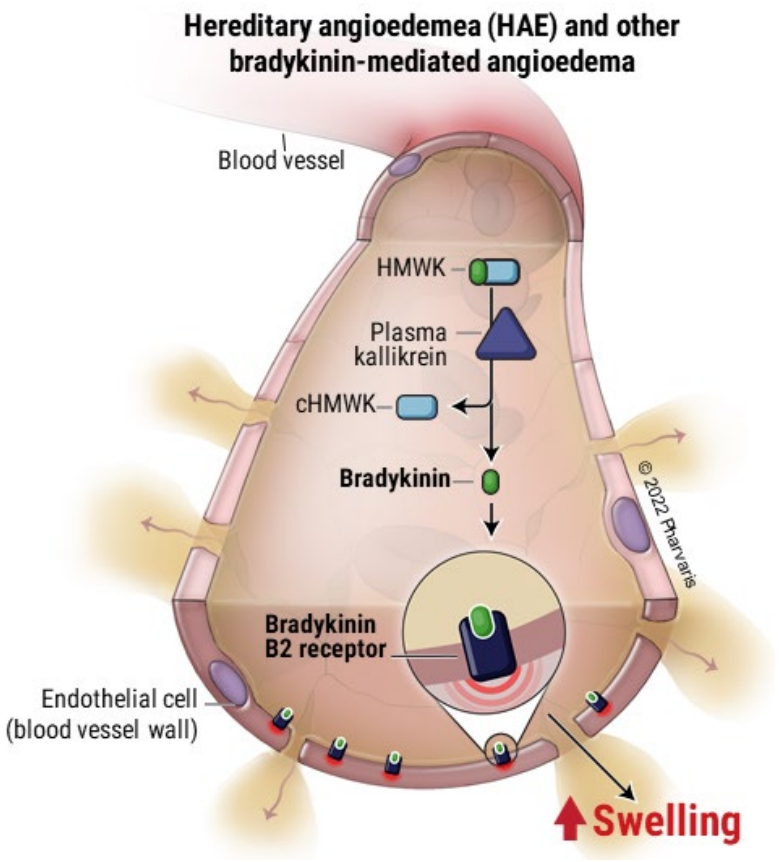
Hereditary angioedema (HAE) is a bradykinin-mediated condition with unmet medical needs



- International guidelines recommend that HAE attacks are **treated as early as possible**[5-7]
- Burden associated with **parenteral administration** of currently approved on-demand medications[8-13] leads to treatment of a number of HAE attacks being **delayed or forgone**[13-16]
- An unmet need exists for **on-demand oral** therapies that are effective and well-tolerated and may reduce the treatment burden enabling prompt administration

[1]Busse PJ et al. N Engl J Med 2020;382:1136-48. [2]Cicardi M et al. N Engl J Med 2010;363:532-41. [3]Lumry WR et al. Ann Allergy Asthma Immunol 2011;107:529-37. [4]Maurer M et al. Clin Exp Allergy 2022;52:1048-58. [5]Betschel S et al. Allergy Asthma Clin Immunol 2019;15:72. [6]Busse PJ et al. J Allergy Clin Immunol Pract 2021;9:132-50. [7]Maurer M et al. Allergy 2022;77:1961-90. [8]Berinert® [package insert], https://labeling.cslbehring.com/pi/us/berinert/en/berinert-prescribing-information.pdf (accessed 15 August 2023). [9]Cinryze® [summary of product characteristics], https://www.ema.europa.eu/en/documents/product-information/cinryze-epar-product-information_en.pdf (accessed 15 August 2023). [10]Firazyr® [package insert], https://www.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf (accessed 15 August 2023). [11]Kalbitor® [package insert], https://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf (accessed 15 August 2023). [12]Ruconest® [package insert], https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf (accessed 15 August 2023). [13]Burnette A et al. AAAAI 2023. [14]Tuong LA et al. Allergy Asthma Proc 2014;35:250-4. [15]US Food and Drug Administration, Center for Biologics Evaluation and Research. The voice of the patient–Hereditary angioedema. May 2018. https://www.fda.gov/media/113509/download (accessed 15 August 2023). [16]Radojicic C et al. AAAAI 2023.

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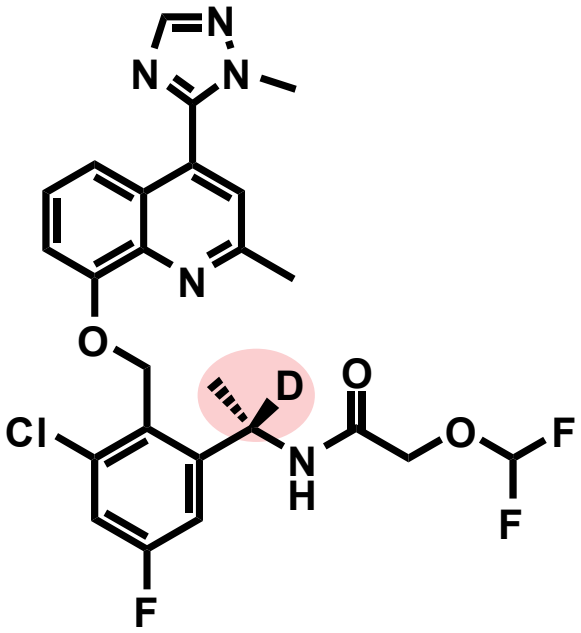
Deucrictibant (formerly PHA121, PHA-022121) is an orally bioavailable, selective, highly potent, competitive antagonist of bradykinin B2 receptor



- Antagonist of bradykinin B2 receptor (-*tibant* stem[1])
- 2.4-fold lower molecular weight than icatibant
- Metabolic soft spot stabilized by introduction of a *deu*terium atom
  - Optimized for metabolic stability and exposure in humans
- Pure antagonistic activity at bradykinin B2 receptor (no partial agonistic activity as icatibant was found to exert at high concentrations, as reached locally at site of injection[2])

Lesage A et al. Front Pharmacol 2020;11:916. Lesage A et al. Int Immunopharmacol 2022;105:108523.
[1]https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/who-pharm-s-nom-1570.pdf (accessed 15 August 2023). [2]https://www.ema.europa.eu/en/documents/assessment-report/firazyr-epar-public-assessment-report_en.pdf (accessed 15 August 2023).

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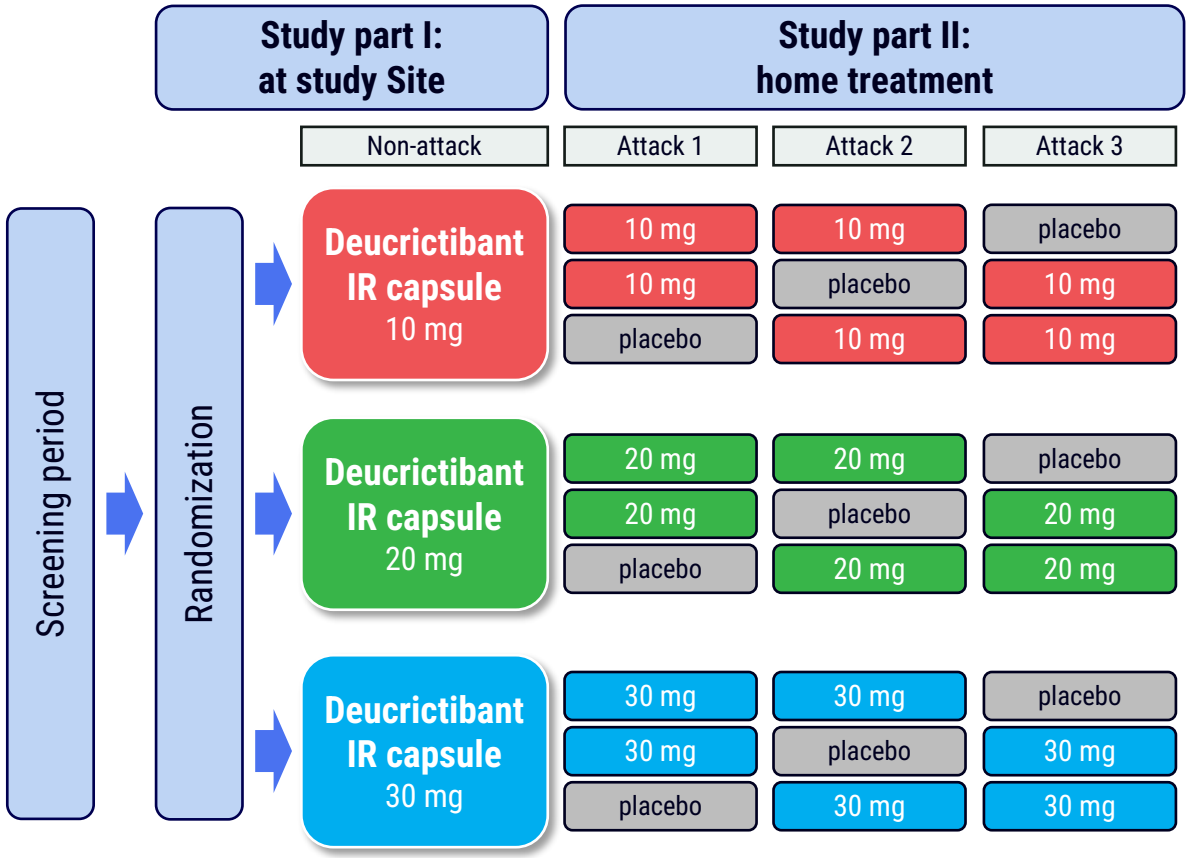
RAPIDe-1: phase 2 trial of deucrictibant IR capsule as on-demand treatment for HAE-1/2 attacks

- **Double-blind, placebo-controlled, cross-over trial with 3-dose levels**
  - **Study part I** – randomized patients received a single dose of deucrictibant IR capsule at study Site for PK and safety assessment
  - **Study part II** – randomized patients treated up to 3 qualifying HAE attacks: 2 attack with deucrictibant IR capsule and 1 attack with placebo
- **74 HAE patients enrolled from 31 Sites**



HAE: hereditary angioedema. IR: immediate-release. PK: pharmacokinetic.
ClinicalTrials.gov Identifier: NCT04618211, https://clinicaltrials.gov/ct2/show/NCT04618211 (accessed 15 August 2023). EudraCT Number: 2020-003445-11, https://www.clinicaltrialsregister.eu/ctr-search/search?query=2020-003445-11 (accessed 15 August 2023).

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RAPIDe-1: eligibility criteria

Key inclusion criteria

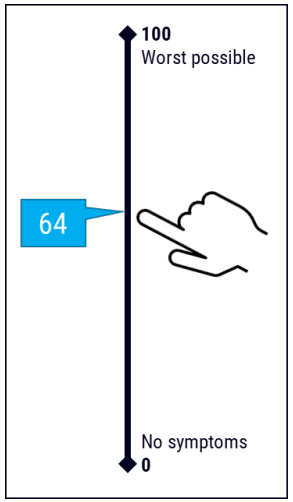
- Age 18-75
- Diagnosis of HAE-1/2
- Documented history of HAE attacks: ≥3 attacks in the last 4 months, or ≥2 in the last 2 months
- Reliable access and experience to use standard of care acute attack medications

Key exclusion criteria

- Pregnancy or breast-feeding;
- Diseases interfering with patient's safety or ability to participate in the study;
- Use of HAE therapies prior to enrolment:
  - C1-INH for acute use or short-term prophylaxis (7 days)
  - C1-INH for prophylaxis, oral kallikrein inhibitors, attenuated androgens, anti-fibrinolytics (2 weeks)
  - monoclonal antibodies for HAE therapy (12 weeks)

C1-INH: C1-inhibitor. HAE: hereditary angioedema.
ClinicalTrials.gov Identifier: NCT04618211 (https://clinicaltrials.gov/ct2/show/NCT04618211; accessed 15 August 2023). EudraCT Number: 2020-003445-11, https://www.clinicaltrialsregister.eu/ctr-search/search?query=2020-003445-11 (accessed 15 August 2023). Maurer M et al. AAAAI 2023.

RAPIDe-1: primary, key secondary and other endpoints



Primary endpoint

- Change in VAS-3 (abdominal pain, skin swelling, skin pain) score from pre- to 4h post-treatment

Key secondary endpoints

- Time to onset of symptom relief (VAS-3; ≥30% reduction from the pre-treatment score)
- Time to almost complete and complete symptom relief (VAS; all 3 items ≤10)
- Time to a ≥50% reduction in VAS-3 score from the pre-treatment score
- Change of MSCS (Mean Symptom Complex Severity) score from pre-treatment to 4h post-treatment
- TOS (Treatment Outcome Score) at 4h post-treatment

Other endpoints included in the topline outputs

- Proportion of attacks treated with study drug requiring use of rescue medication
- Time to the first use of HAE rescue medication
- Safety and PK assessments

HAE: hereditary angioedema. PK: pharmacokinetics. VAS: visual analogue scale.
The mITT Analysis Set includes all randomized patients who had ≥1 treated HAE attack and who had non-missing VAS results at both pre-treatment and ≥1 post-treatment time point of that attack.

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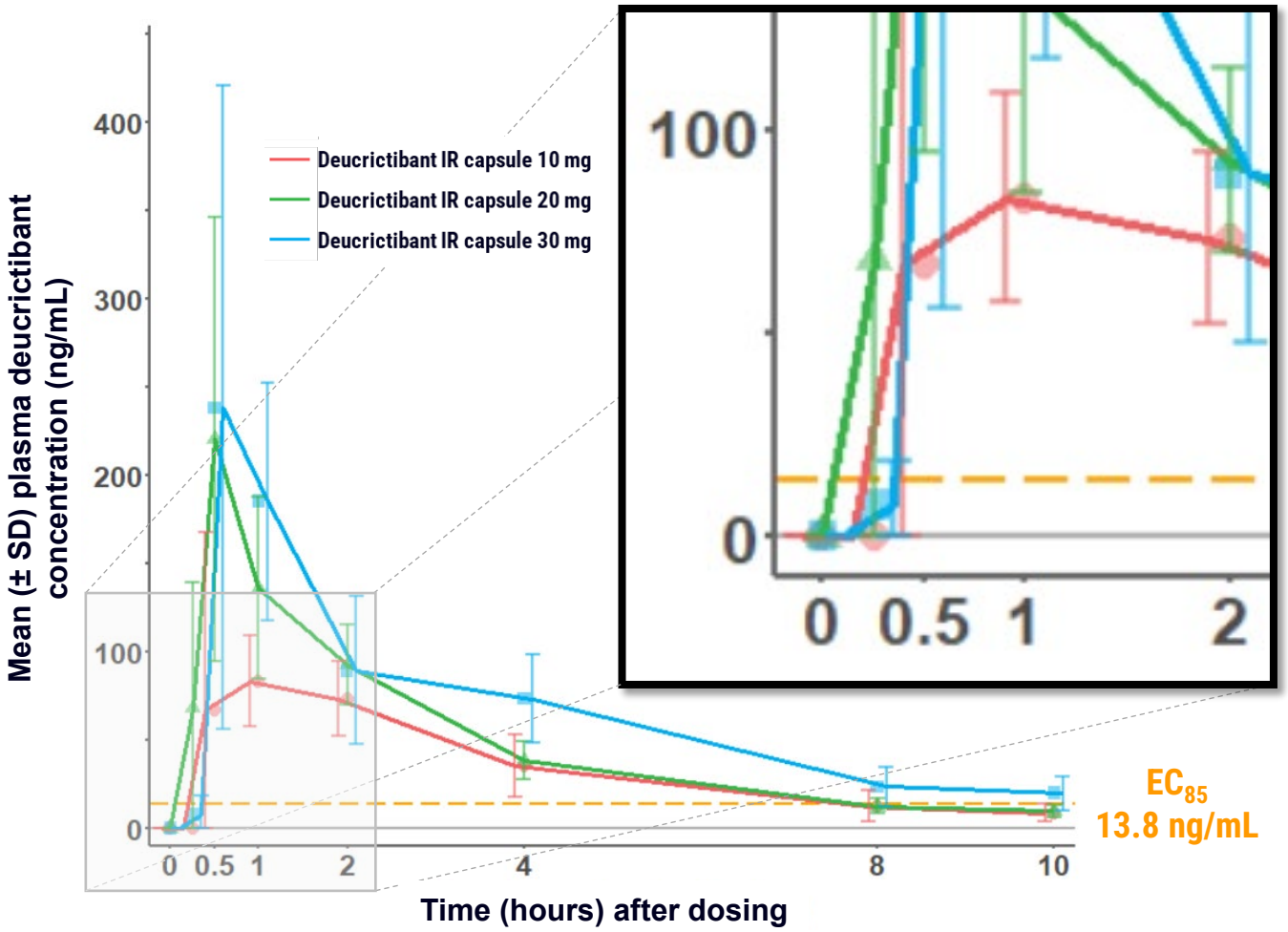
Pharmacokinetics of deucrictibant IR capsule in RAPIDe-1 confirmed rapid achievement of therapeutic levels for all doses assessed



- Rapid absorption with mean plasma levels >EC_{85} reached within 15-30 minutes for all doses of deucrictibant IR capsule
- Mean plasma levels of deucrictibant maintained >EC_{85} for approx. 8 to >10 hours (10 to 30 mg deucrictibant IR capsule doses)

IR: immediate-release.
Maurer M et al. AAAAI 2023.

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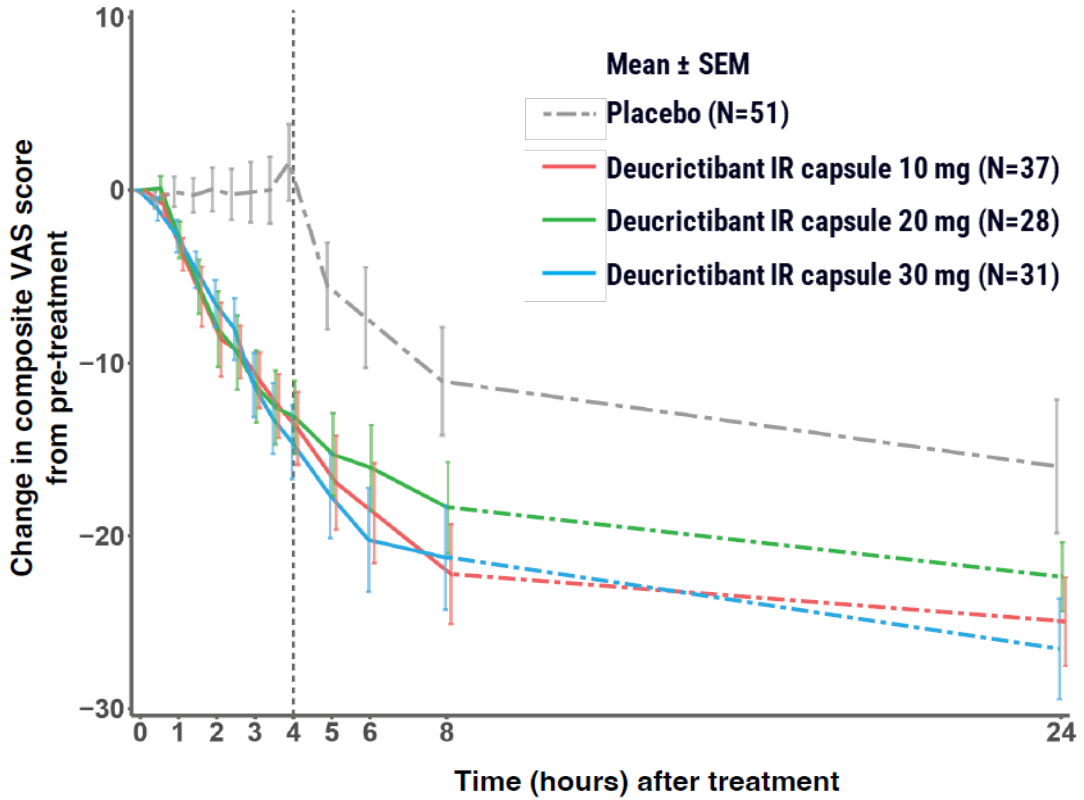
Primary endpoint: deucrictibant IR capsule significantly reduced attack symptoms by VAS-3 at 4 hours



Difference from placebo in change from pre-treatment to 4 h post-treatment, least-squares mean (95% CI)

Deucrictibant IR capsule 10 mg	-16.75 (-21.52, -11.97)	p < 0.0001†
Deucrictibant IR capsule 20 mg	-15.02 (-20.22, -9.81)	p < 0.0001
Deucrictibant IR capsule 30 mg	-16.28 (-21.27, -11.29)	p < 0.0001

Median VAS-3 at pre-treatment ranged from 24.33 to 27.00 across different dose levels

CI: Confidence interval. IR: immediate-release. mITT: modified intent-to-treat. SEM: standard error of the mean. VAS: visual analogue scale.
†Nominal p-value; VAS assessed every 30 minutes up to 4 hours post-treatment, then at 5, 6, 8, 24, 48 hours; N = number of attacks in the mITT Analysis Set. Attacks in mITT Analysis Set refer to attacks treated with blinded study drug that had non-missing VAS result at pre-treatment and at least one non-missing VAS result post-treatment. VAS-3 = electronically captured, numerically assisted visual analogue scale. Figure is based on descriptive summary of mean and SEM (standard error of the mean). Least-squares mean differences, CIs, and p-values come from a mixed-effects model with repeated measures (MMRM). Data after rescue medication use is not included.

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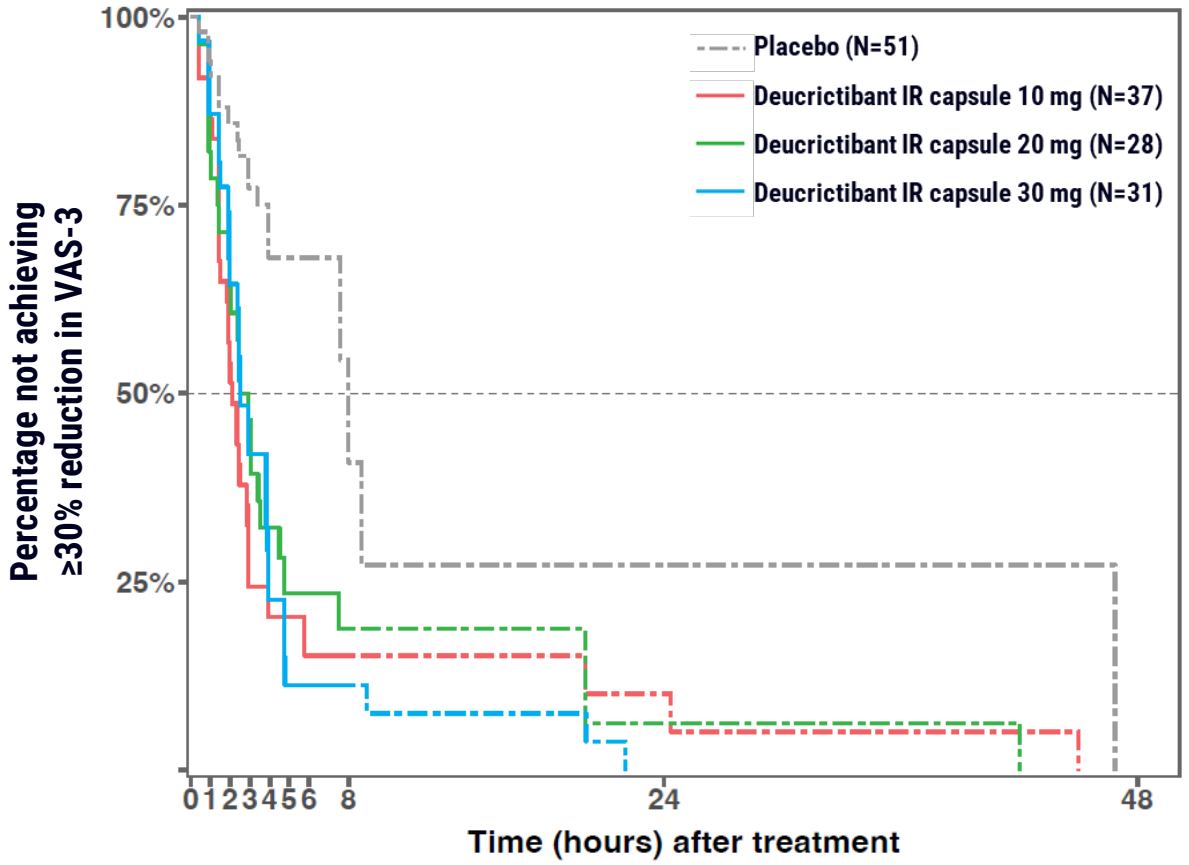
Deucrictibant IR capsule significantly shortened time to onset of symptom relief (≥30% reduction in VAS-3)



Median time in hours (95% CI)		
Placebo	8.0 (7.6, 46.9)	
Deucrictibant IR capsule 10 mg	2.1 (1.5, 2.9)	p < 0.0001†
Deucrictibant IR capsule 20 mg	2.7 (1.9, 3.5)	p = 0.0021
Deucrictibant IR capsule 30 mg	2.5 (1.9, 3.8)	p < 0.0001

CI: Confidence interval. IR: immediate-release. mITT: modified intent-to-treat. VAS: visual analogue scale.
†Nominal p-value; VAS assessed every 30 minutes up to 4 hours post-treatment, then at 5, 6, 8, 24, 48 hours. N = number of attacks in the mITT Analysis Set. Median time based on Kaplan-Meier estimates. p-values based on a marginal Cox proportional hazards model.

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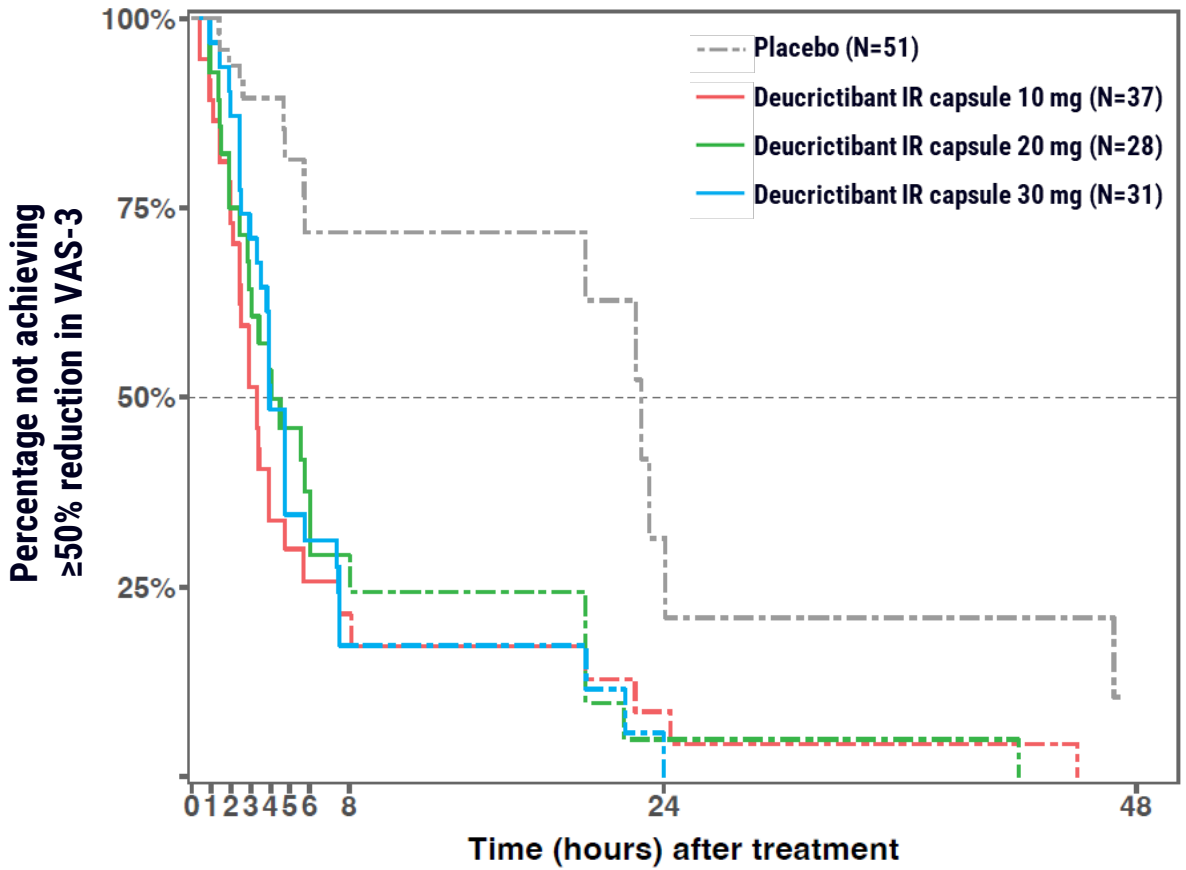
Deucrictibant IR capsule significantly reduced time to ≥50% reduction in VAS-3



Median time in hours (95% CI)		
Placebo	22.8 (20.0, 24.1)	
Deucrictibant IR capsule 10 mg	3.3 (2.4, 3.9)	p < 0.0001†
Deucrictibant IR capsule 20 mg	4.0 (2.9, 6.0)	p = 0.0003
Deucrictibant IR capsule 30 mg	4.0 (3.3, 5.8)	p < 0.0001

CI: Confidence interval. IR: immediate-release. mITT: modified intent-to-treat. VAS: visual analogue scale.
†Nominal p-value; VAS assessed every 30 minutes up to 4 hours post-treatment, then at 5, 6, 8, 24, 48 hours. N = number of attacks in the mITT Analysis Set. Median time based on Kaplan-Meier estimates. p-values based on a marginal Cox proportional hazards model.

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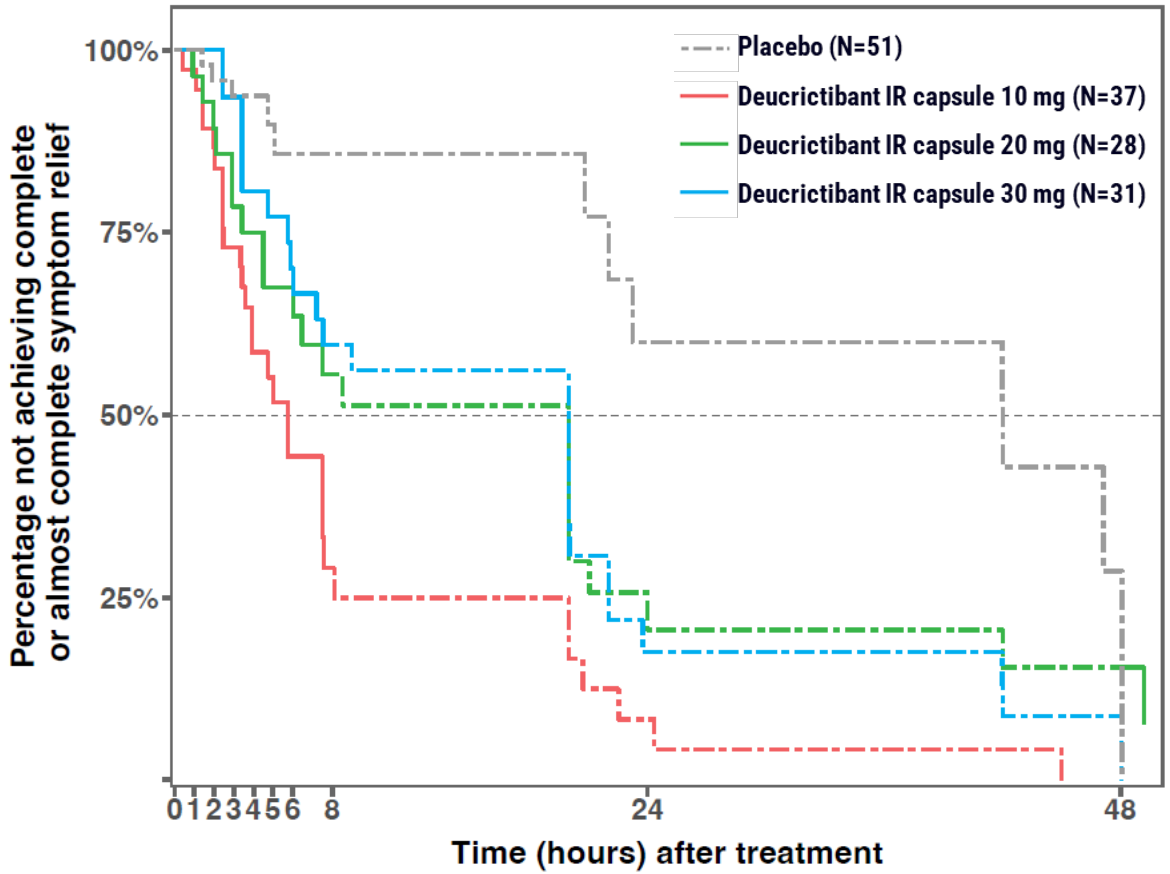
Deucrictibant IR capsule significantly reduced time to almost complete or complete symptom relief (all individual VAS ≤10)



Median time in hours (95% CI)		
Placebo	42.0 (22.0, 48.1)	
Deucrictibant IR capsule 10 mg	5.8 (3.6, 7.5)	p < 0.0001†
Deucrictibant IR capsule 20 mg	20.0 (4.5, 20.0)	p = 0.0127
Deucrictibant IR capsule 30 mg	20.0 (6.0, 20.1)	p = 0.0001

CI: Confidence interval; IR: immediate-release; mITT: modified intent-to-treat. VAS: visual analogue scale.
†Nominal p-value; VAS assessed every 30 minutes up to 4 hours post-treatment, then at 5, 6, 8, 24, 48 hours. N = number of attacks in the mITT Analysis Set. Median time based on Kaplan-Meier estimates. p-values based on a marginal Cox proportional hazards model.

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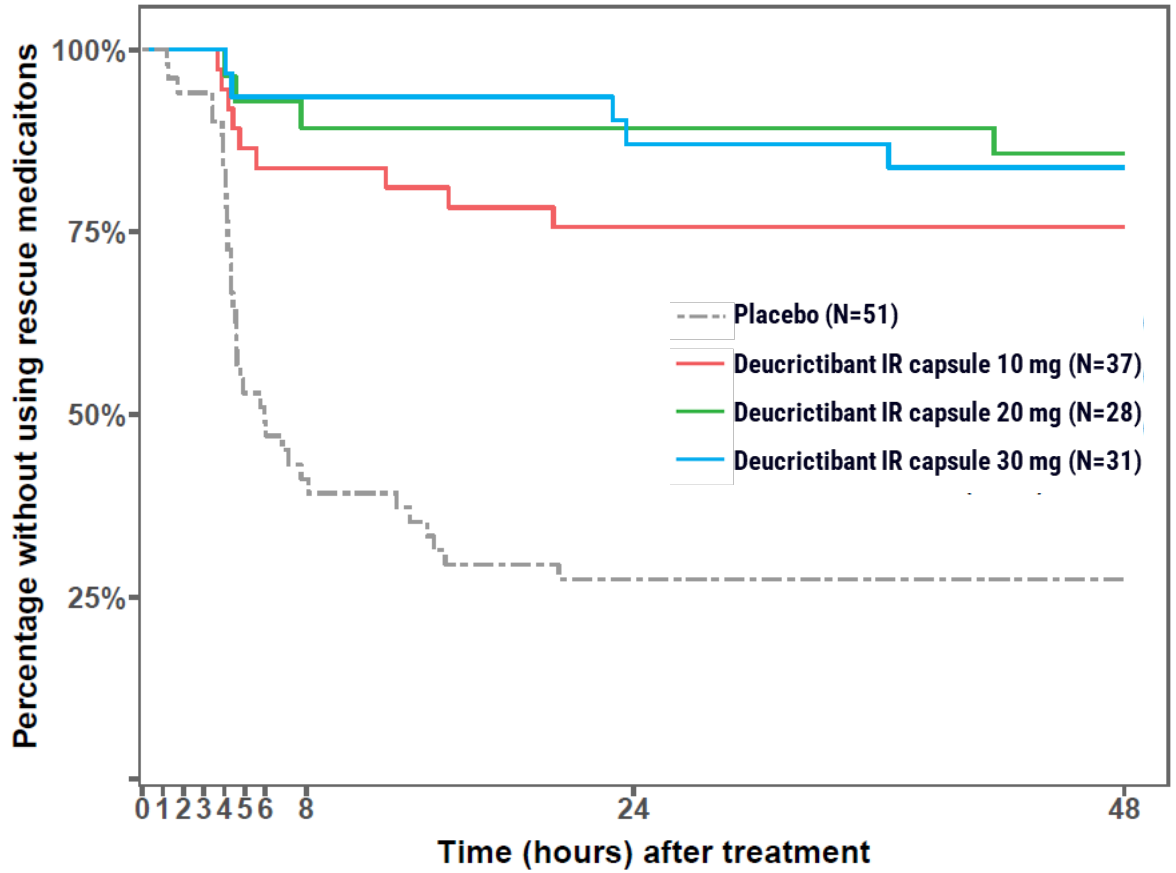
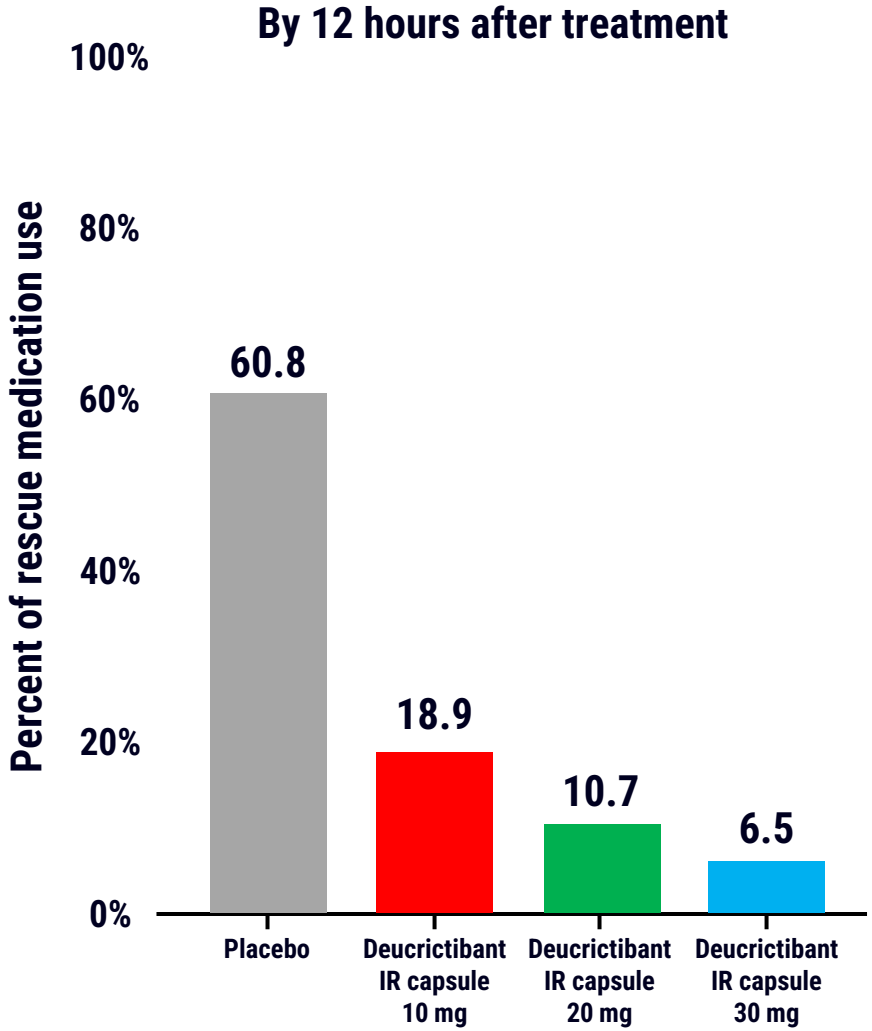
Deucrictibant IR capsule substantially reduced use of rescue medication





IR: immediate-release. mITT: modified intent-to-treat.
N = number of attacks in the mITT Analysis Set.

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Deucrictibant IR capsule was generally well-tolerated at all doses

	Study part I (non-attack)			Study part II (attacks 1, 2, 3)			
	Deucrictibant IR capsule				Deucrictibant IR capsule		
	10 mg N=23	20 mg N=24	30 mg N=25	Placebo N=53	10 mg N=38	20 mg N=29	30 mg N=36
Subjects (study part I) or attacks (study part II) with any treatment-related AEs	**1 (4.3%)**	**1 (4.2%)**	**-**	**1 (1.9%)**	**-**	**-**	**1 (2.8%)**
Headache	-	1 (4.2%)	-	-	-	-	-
Nausea	1 (4.3%)	-	-	-	-	-	1 (2.8%)
Vomiting	-	-	-	-	-	-	1 (2.8%)
Fatigue	-	-	-	-	-	-	1 (2.8%)
Blister	-	-	-	1 (1.9%)	-	-	-

- No treatment-related SAEs or severe AEs
- No AEs leading to treatment discontinuation
- No treatment-related AEs of laboratory parameters, vital signs, or ECG parameters

AE: adverse event. ECG: electrocardiogram. IR: immediate-release. SAE: serious adverse event.
N = number of subjects (study part I) or number of attacks (study part II) in the Safety Analysis Set. The Safety Analysis Set includes all randomized patients who received any dose of study drug. Treatment-related AEs within 48 h post-treatment are included.

Conclusions

- Deucrictibant is an orally bioavailable antagonist of bradykinin B2 receptor under development for on-demand (immediate-release capsule) and prophylaxis (extended-release tablet) of HAE attacks
- 74 patients from 13 countries were enrolled into RAPIDe-1 Phase 2 on-demand trial and 62 of them had 147 attacks that were treated with blinded study drug and were included in efficacy evaluation
  - The primary endpoint and all key secondary endpoints were met
  - Deucrictibant IR capsule demonstrated rapid onset of action, symptom relief, resolution of HAE attacks
  - Deucrictibant IR capsule substantially reduced the use of rescue medication
  - Deucrictibant IR capsule was well-tolerated at all dose levels
- **RAPIDe-1 trial results support further development of deucrictibant immediate-release capsule as a potential on-demand treatment for HAE attacks**

The Authors and the Sponsor thank all people with HAE as well as all study Sites' Staff who participated in the RAPIDe-1 trial

HAE: hereditary angioedema. IR: immediate-release.

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