

Treatment of HAE Attacks with Deucrictibant: RAPIDe-1 Phase 2 Trial Results

M. Magerl, J. Anderson, E. Aygören-Pürsün, M.L. Baeza, L. Bouillet, H. Chapdelaine, D.M. Cohn, A. Du-Thanh, O. Fain, H. Farkas, J. Greve, M. Guilarte, D. Hagin, R. Hakl, J.S. Jacobs, A. Kessel, S. Kiani-Alikhan, P. Králíčková, H.H. Li, R. Leonart, M.E. Manning, A. Reshef, M.A. Riedl, B. Ritchie, G. Spadaro, M. Staevska, P. Staubach, M. Stobiecki, G. L.Sussman, M.D. Tarzi, A. Valerieva, W.H. Yang, M.H. Jouvin, R. Crabbé, S. van Leeuwen, H. Chen, L. Zhu, J. Knolle, A. Lesage, P. Lu, M. Maurer

*GA²LEN UCARE Conference 2023
São Paulo, Brazil – 7-9 December*

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, Pflieger, Shire/Takeda. M.Sto.: BioCryst, CSL Behring, KalVista, Pharming, Shire/Takeda. G.L.S.: Aimune, Amgen, CSL Behring, DBV, Genentech, Green Cross, Kedrion, Leo, Novartis, Novo, Pediapharm, Sanofi. M.D.T.: none. A.V.: AstraZeneca, Berlin-Chemie/MenariniGroup, CSL Behring, Novartis, Pharming, Pharvaris, Shire/Takeda, Sobi, Teva. W.H.Y.: Aimune, 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.

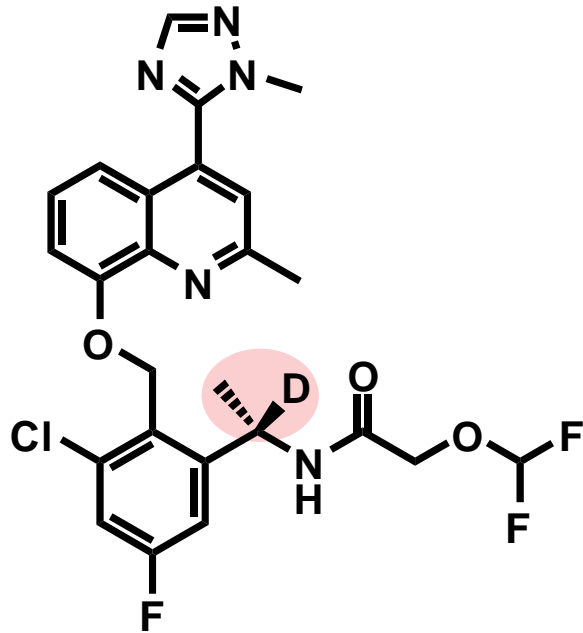
RAPIDe-1 was a Pharvaris-sponsored clinical trial. ClinicalTrials.gov Identifier: NCT04618211. EudraCT Number: 2020-003445-11.

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

- International guidelines recommend that HAE attacks are **treated as early as possible**¹⁻³
- Burden associated with **parenteral administration** of currently approved on-demand medications⁴⁻⁸ leads to treatment of a number of HAE attacks being **delayed or forgone**⁹⁻¹³
- An unmet need exists for **on-demand oral** therapies that are effective and well tolerated and may reduce the treatment burden enabling prompt administration

¹Betschel S et al. Allergy Asthma Clin Immunol 2019;15:72. ²Busse PJ et al. J Allergy Clin Immunol Pract 2021;9:132-50. ³Maurer M et al. Allergy 2022;77:1961-90. ⁴Beriner[®] [package insert], <https://labeling.cslbehring.com/pi/us/berinert/en/berinert-prescribing-information.pdf> (accessed 28 November 2023). ⁵Cinryze[®] [summary of product characteristics], https://www.ema.europa.eu/en/documents/product-information/cinryze-epar-product-information_en.pdf (accessed 28 November 2023). ⁶Firazyr[®] [package insert], https://www.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf (accessed 28 November 2023). ⁷Kalbitor[®] [package insert], https://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf (accessed 28 November 2023). ⁸Ruconest[®] [package insert], https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf (accessed 28 November 2023). ⁹Burnette A et al. AAAAI 2023. ¹⁰Tuong LA et al. Allergy Asthma Proc 2014;35:250-4. ¹¹US 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> (28 November 2023). ¹²Radojicic C et al. AAAAI 2023. ¹³Mendivil J et al. ACAA 2023.

Deucrictibant is an orally bioavailable, selective, highly potent, competitive antagonist of bradykinin B2 receptor

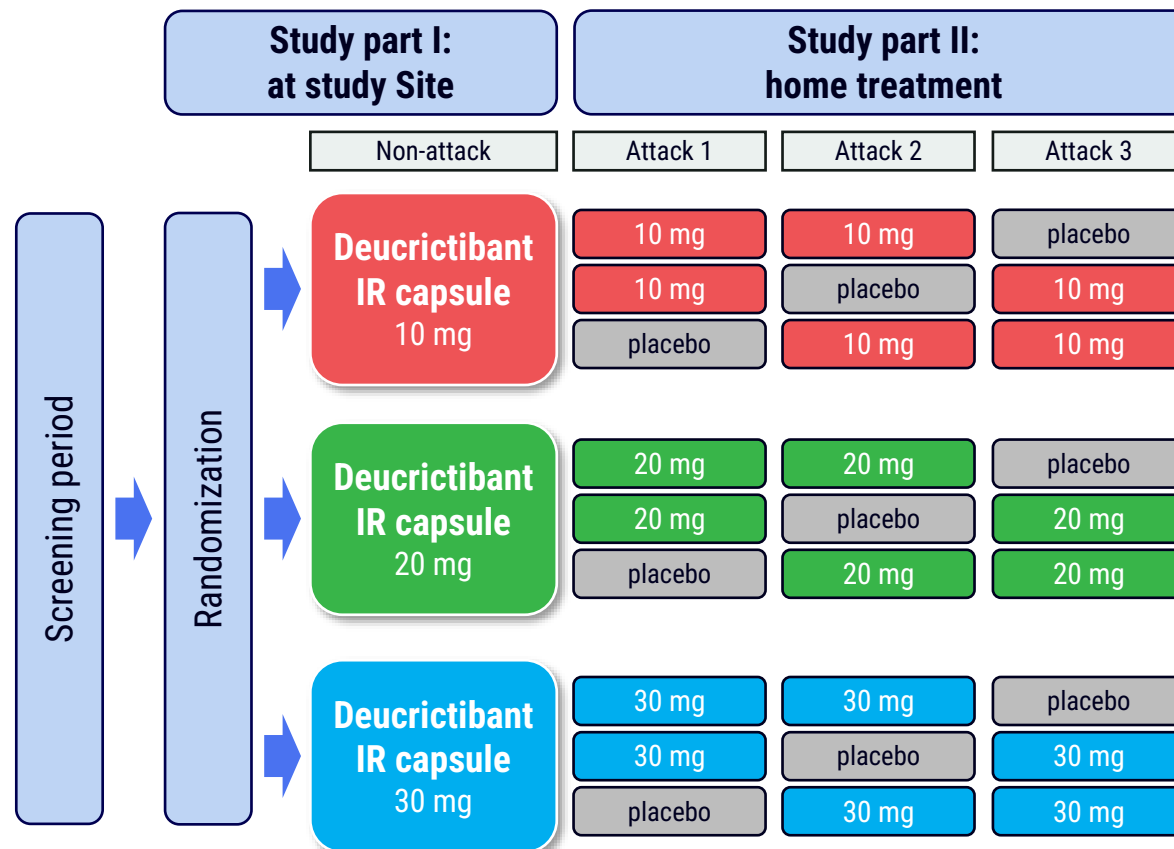


- Antagonist of bradykinin B2 receptor (*-tibant* stem¹)
- 2.4-fold lower molecular weight than icatibant
- Metabolic soft spot stabilized by introduction of a *deuterium* atom

RAPIDe-1: phase 2 trial of deucricitbant 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 deucricitbant IR capsule at study Site for PK and safety assessment
 - Study part II** – randomized patients treated up to 3 qualifying HAE attacks: 2 attacks with deucricitbant IR capsule and 1 attack with placebo

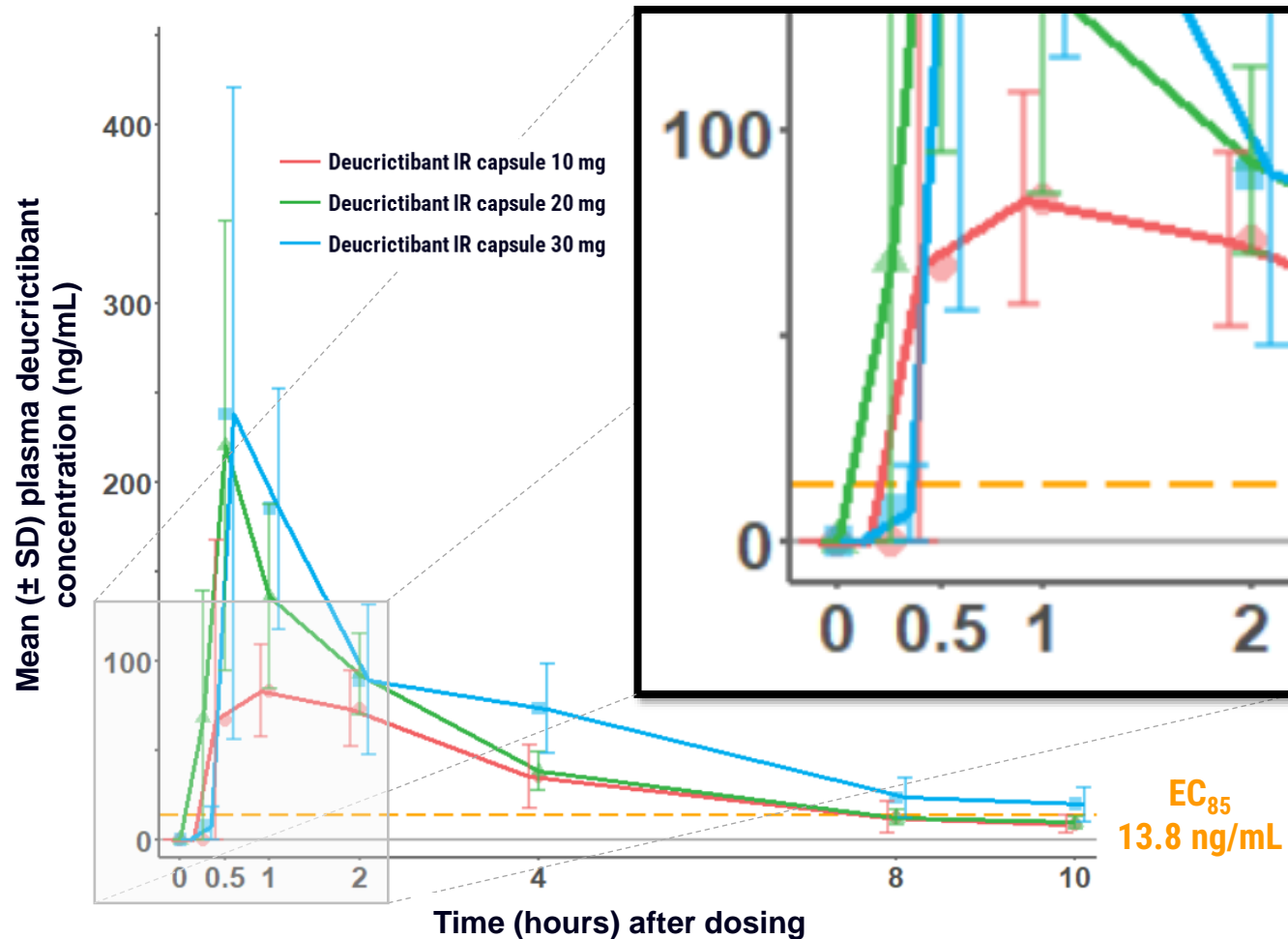
- 74 HAE patients enrolled from 31 Sites**



HAE: hereditary angioedema. IR: immediate-release. PK: pharmacokinetic.

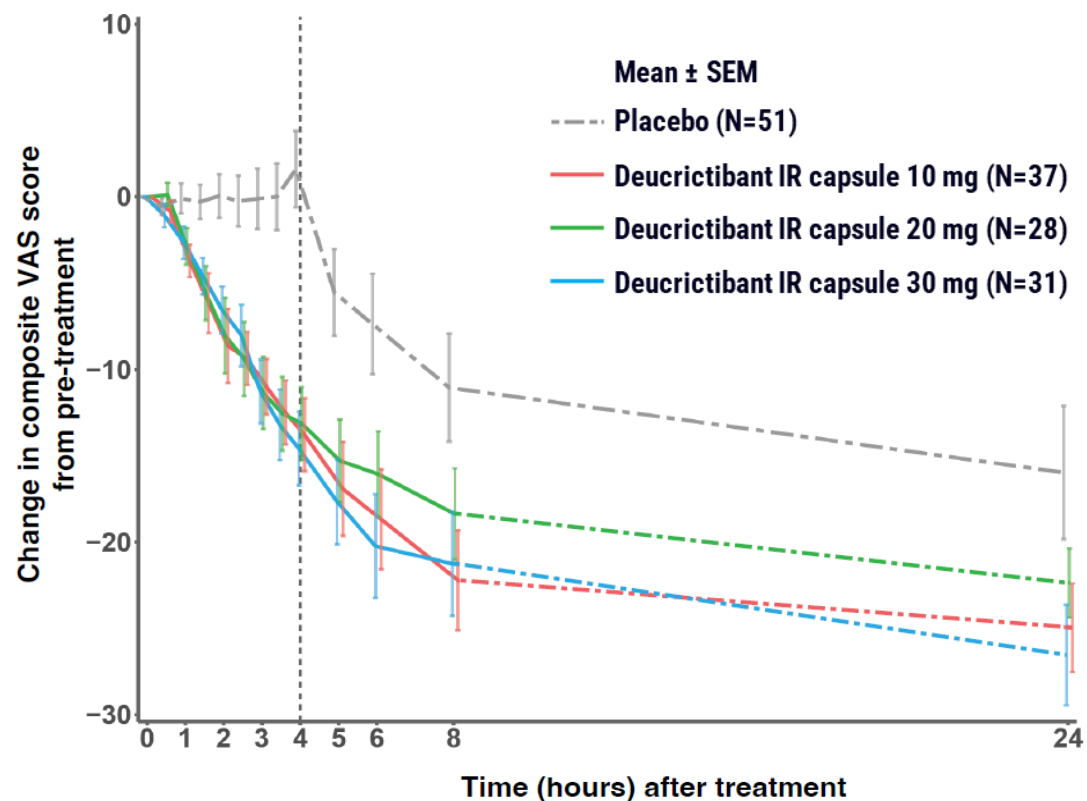
ClinicalTrials.gov Identifier: NCT04618211, <https://clinicaltrials.gov/ct2/show/NCT04618211> (accessed 28 November 2023). EudraCT Number: 2020-003445-11, <https://www.clinicaltrialsregister.eu/ctr-search/search?query=2020-003445-11> (accessed 28 November 2023).

Pharmacokinetics of deucricitabant 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 deucricitabant IR capsule
- Mean plasma levels of deucricitabant maintained $>EC_{85}$ for approx. 8 to >10 hours (10 to 30 mg deucricitabant IR capsule doses)

Primary endpoint: deucricitbant 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)

Deucricitbant IR capsule 10 mg	-16.75 (-21.52, -11.97)	$P < 0.0001^\dagger$
Deucricitbant IR capsule 20 mg	-15.02 (-20.22, -9.81)	$P < 0.0001$
Deucricitbant IR capsule 30 mg	-16.28 (-21.27, -11.29)	$P < 0.0001$

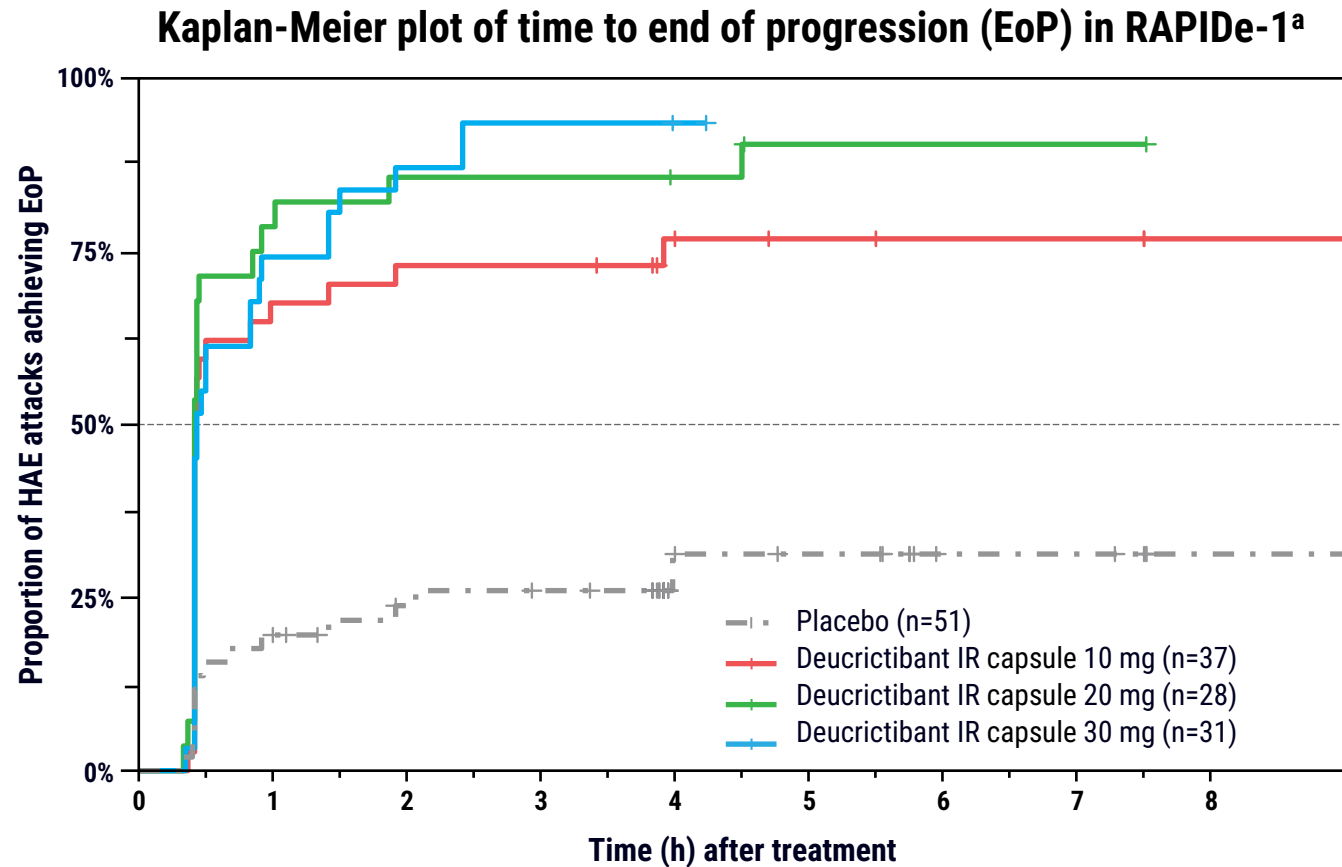
Median VAS-3 at pre-treatment ranged from 24.33 to 27.00 across different dose levels

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.

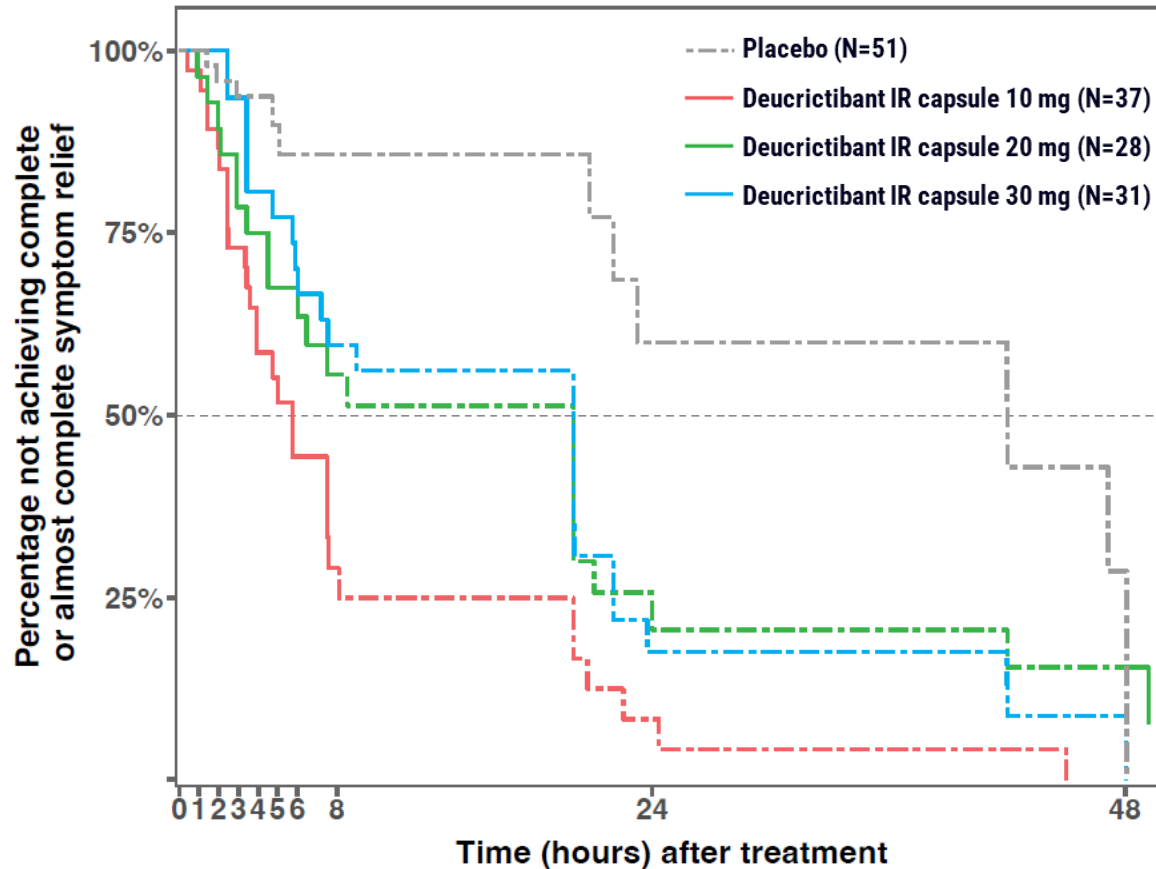
Early-onset response to treatment of hereditary angioedema attacks with deucrictibant (Maurer M. et al)

Happy Poster Hour, Friday, 8 December, 7:00 PM [P081]



End of progression was assessed in a post-hoc analysis of RAPIDe-1

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



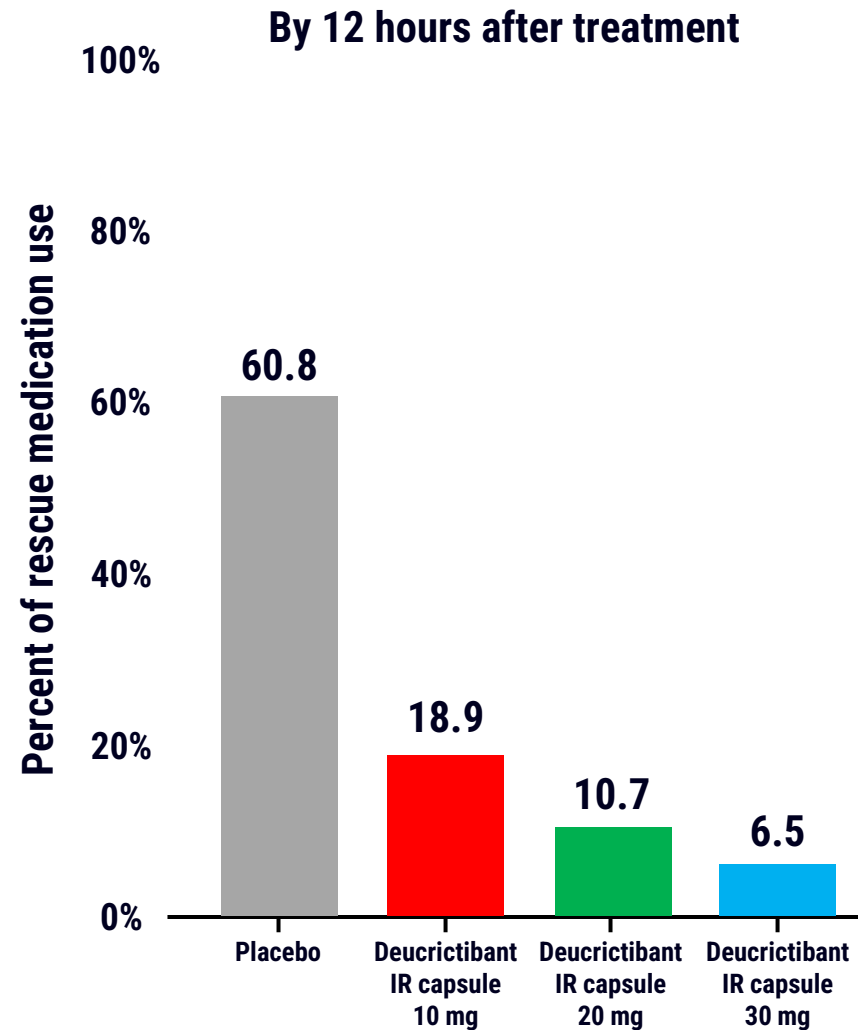
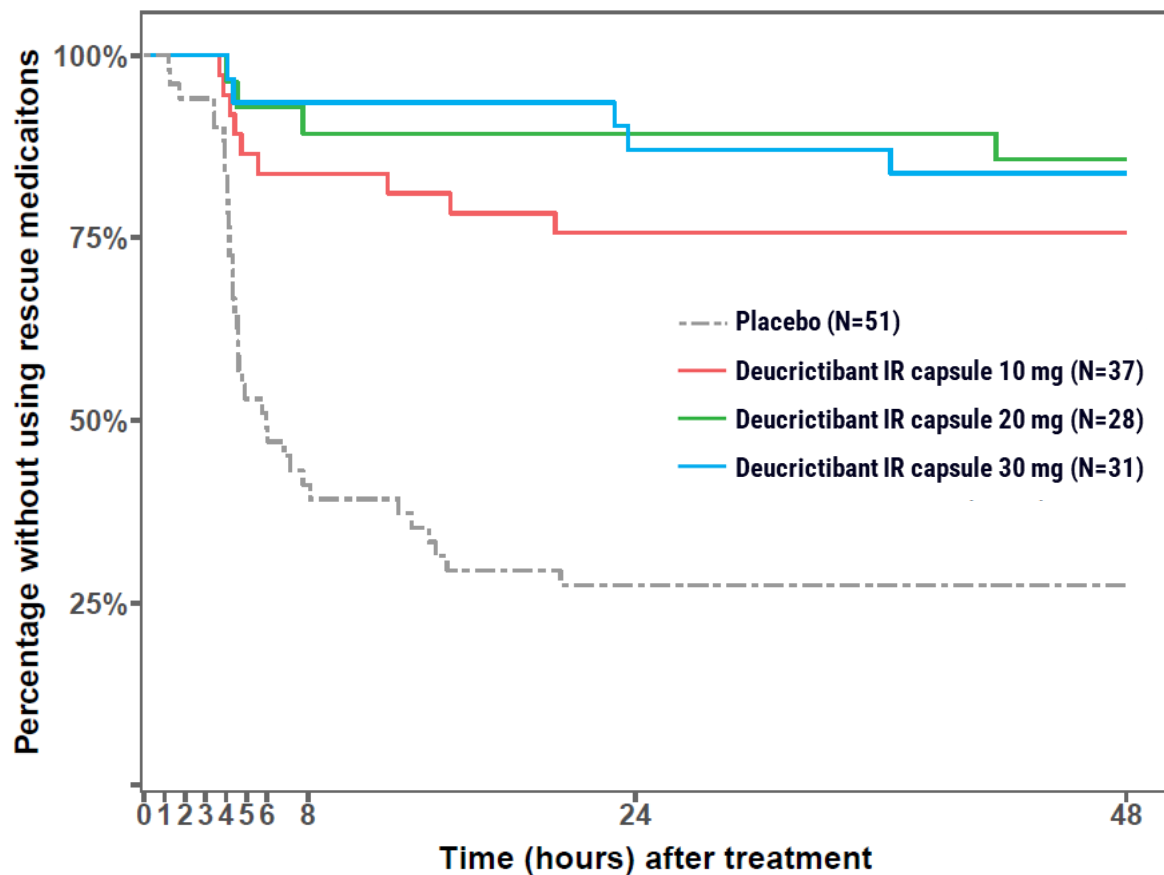
Median time in hours (95% CI)

Placebo	42.0 (22.0, 48.1)	
Deucrictibant IR capsule 10 mg	5.8 (3.6, 7.5)	$P < 0.0001^\dagger$
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.

Deucrichtibant 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.

Deucricitibant IR capsule was generally well tolerated at all doses

	Study part I (non-attack)			Study part II (attacks 1, 2, 3)			
	Deucricitibant IR capsule			Deucricitibant 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.

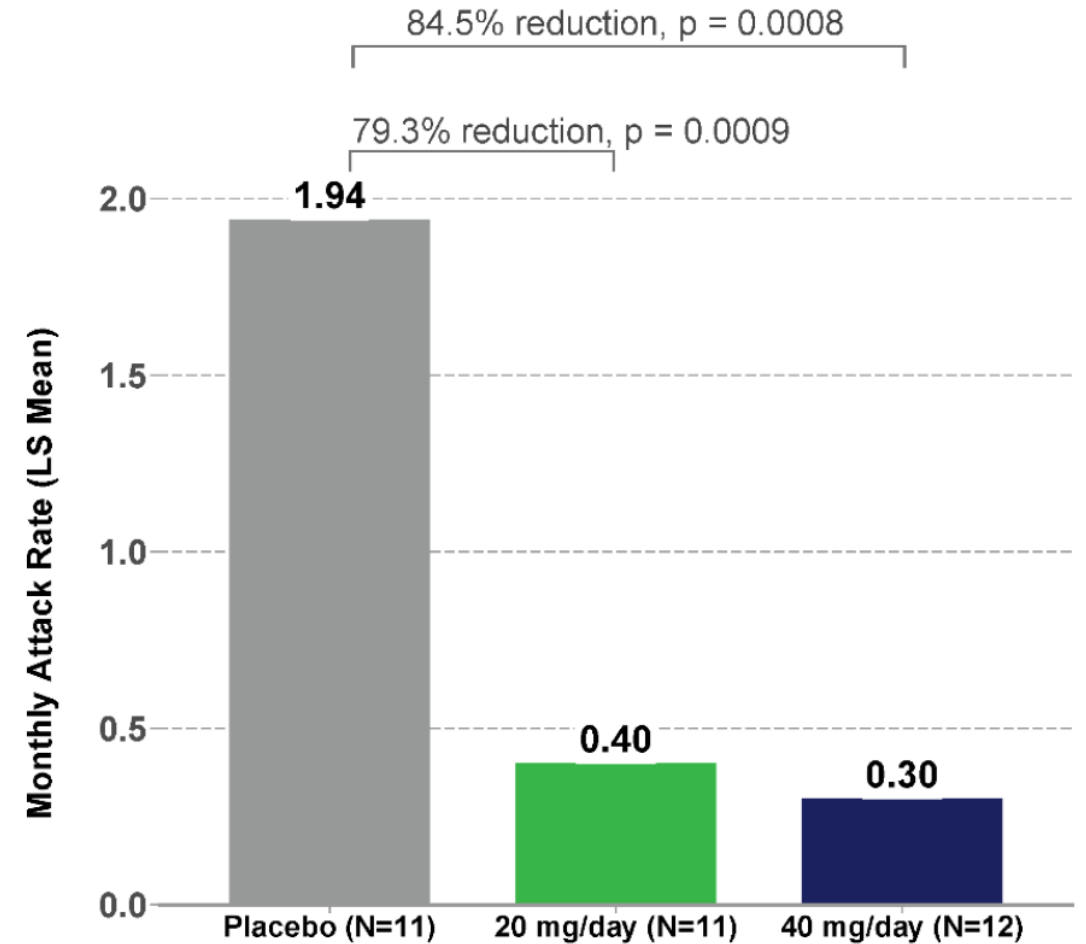
Conclusions

- Deucricitibant 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 the 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 the efficacy evaluation
 - The primary endpoint and all key secondary endpoints were met
 - Deucricitibant IR capsule demonstrated rapid onset of action, symptom relief, and resolution of HAE attacks
 - Deucricitibant IR capsule substantially reduced the use of rescue medication
 - Deucricitibant IR capsule was well tolerated at all dose levels
- **RAPIDe-1 trial results support further development of deucricitibant 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.

Oral deucricitbant for long-term prophylaxis – Phase 2 results

- 12-week placebo-controlled Phase 2 trial (CHAPTER-1)
- **Primary endpoint met: 84.5% (p=0.0008) reduction in monthly attack rate deucricitbant 40 mg/day vs. placebo**
- 92.3% reduction in occurrence of moderate and severe attacks
- 92.6% fewer attacks treated with on-demand medication
- Clinical meaningful improvement in health-related QoL
- Deucricitbant well-tolerated at both doses studied
 - no serious adverse events
 - no severe treatment-emergent adverse events
 - no adverse events leading to treatment discontinuation



LS Mean = least squares mean. Results based on a Poisson regression model adjusted for baseline attack rate and time on treatment.