Efficacy and Safety of the Oral Bradykinin B2 Receptor Antagonist Deucrictibant Immediate-Release Capsule (PHVS416) in Treatment of Hereditary Angioedema Attacks: Topline Results of RAPIDe-1 Phase 2 Trial

H Farkas, *J Anderson, E Aygören-Pürsün, ML Baeza, L Bouillet, H Chapdelaine, DM Cohn, A Du-Thanh, O Fain, J Greve, M Guilarte, D Hagin, R Hakl, JS Jacobs, A Kessel, S Kiani-Alikhan, P Králícková, HH Li, R Lleonart, M Magerl, ME Manning, A Reshef, MA Riedl, B Ritchie, G Spadaro, M Staevska, P Staubach, M Stobiecki, GL Sussman, MD Tarzi, A Valerieva, WH Yang, MH Jouvin, R Crabbé, S van Leeuwen, H Chen, L Zhu, J Knolle, A Lesage, P Lu, M Maurer*

13th C1-Inhibitor Deficiency and Angioedema Workshop
Budapest, Hungary– 4-7 May 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

H.F.: BioCryst, CSL Behring, KalVista, ONO Pharmaceutical, Pharming, Pharvaris, Takeda.

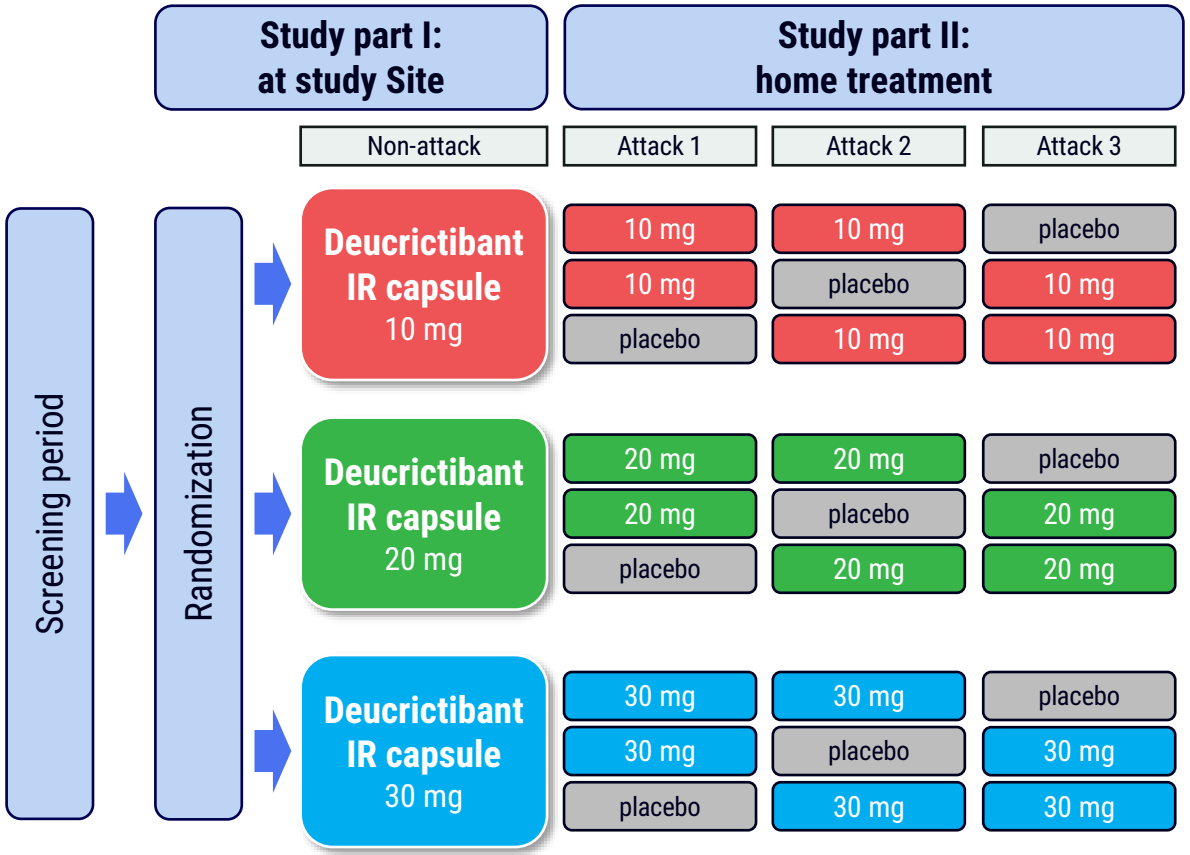
J.A.: BioCryst, BioMarin, CSL Behring, Cycle Pharmaceuticals, KalVista, Pharming, Pharvaris, Takeda. E.A.P.: BioCryst, Biomarin, Centogene, CSL Behring, KalVista; Pharming, Pharvaris, Shire/Takeda. M.L.B.: BioCryst, CSL Behring, Shire HGT. L.B.: BioCryst, Blueprint, CSL Behring, Novartis, Shire/Takeda. 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. 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.Mag.: BioCryst, CSL Behring, KalVista, Novartis, Octapharma, Pharming, Shire/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, 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

RAPIDe-1: phase 2 trial of deucrictibant immediate-release (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; VAS: visual analogue score.
ClinicalTrials.gov Identifier: NCT04618211, https://clinicaltrials.gov/ct2/show/NCT04618211; EudraCT Number: 2020-003445-11 (both accessed 27 April 2023).

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 27 April 2023). EudraCT Number: 2020-003445-11 (accessed 27 April 2023). Maurer M et al. AAAAI 2023.

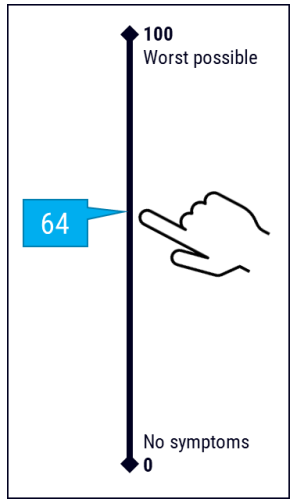
Demographics and baseline characteristics were generally balanced between deucrictibant IR capsule dose groups (mITT Analysis Set)

- 156 attacks from 73 patients included in the Safety Analysis Set
- 147 attacks from 62 patients included in the mITT Analysis Set for efficacy

	Deucrictibant IR capsule 10 mg	Deucrictibant IR capsule 20 mg	Deucrictibant IR capsule 30 mg	Total
N	22	18	22	62
Age in yrs (mean)	42.5	44.5	41.9	42.9
Sex - M/F	7/15	5/13	8/14	20/42
Race - White/Other	20/2	18/0	22/0	60/2
Height in cm (mean)	169	167	170	169
BMI (mean)	27.5	27.6	27.9	27.7
Years since HAE diagnosis (mean)	21.11	21.64	23.98	22.28
HAE type				
HAE-1	18	15	22	55
HAE-2	4	2	0	6
HAE-1 or HAE-2	0	1	0	1

BMI: body mass index; HAE: hereditary angioedema; mITT: modified intent-to-treat; 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.

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

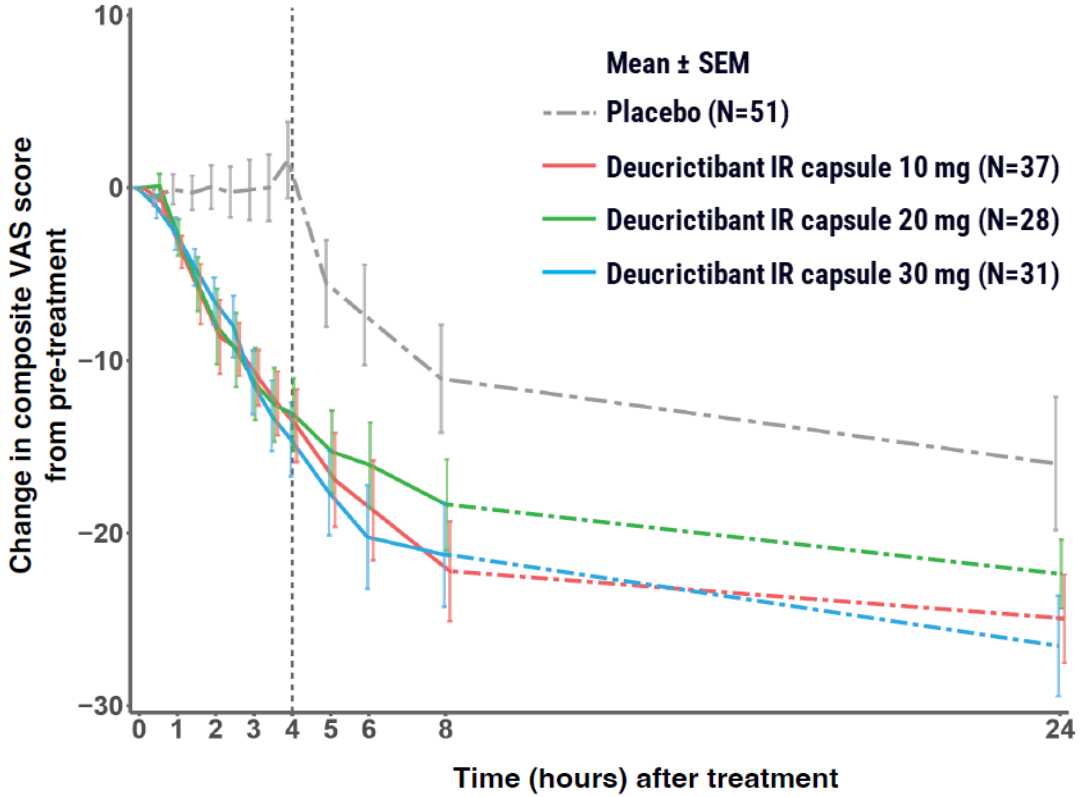
Presented in poster P-25
Riedl MA et al.

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.

Qualification ensured treatment and assessment of effects in confirmed attacks

- In RAPIDe-1 clinical trial setting, attacks were qualified for treatment with study drug by Investigators:
  - ≥1 symptom (skin pain, skin swelling, or abdominal pain) reached a VAS score of 30
  - study drug had to be administered as early as possible after attack qualification (<6 hrs from symptom onset and <3 hrs from ≥1 VAS score reaching score of 30)
    - **25% of the attacks treated in <1 hour and 50% in ~1.5 hours since onset of symptoms (mITT Analysis Set)**
  - ≥5 days since previous administration of study drug or standard-of-care medication
  - no vomiting or intolerable pain
  - no treatment with rescue medication for the first 4 hours after study drug unless intolerable symptoms

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



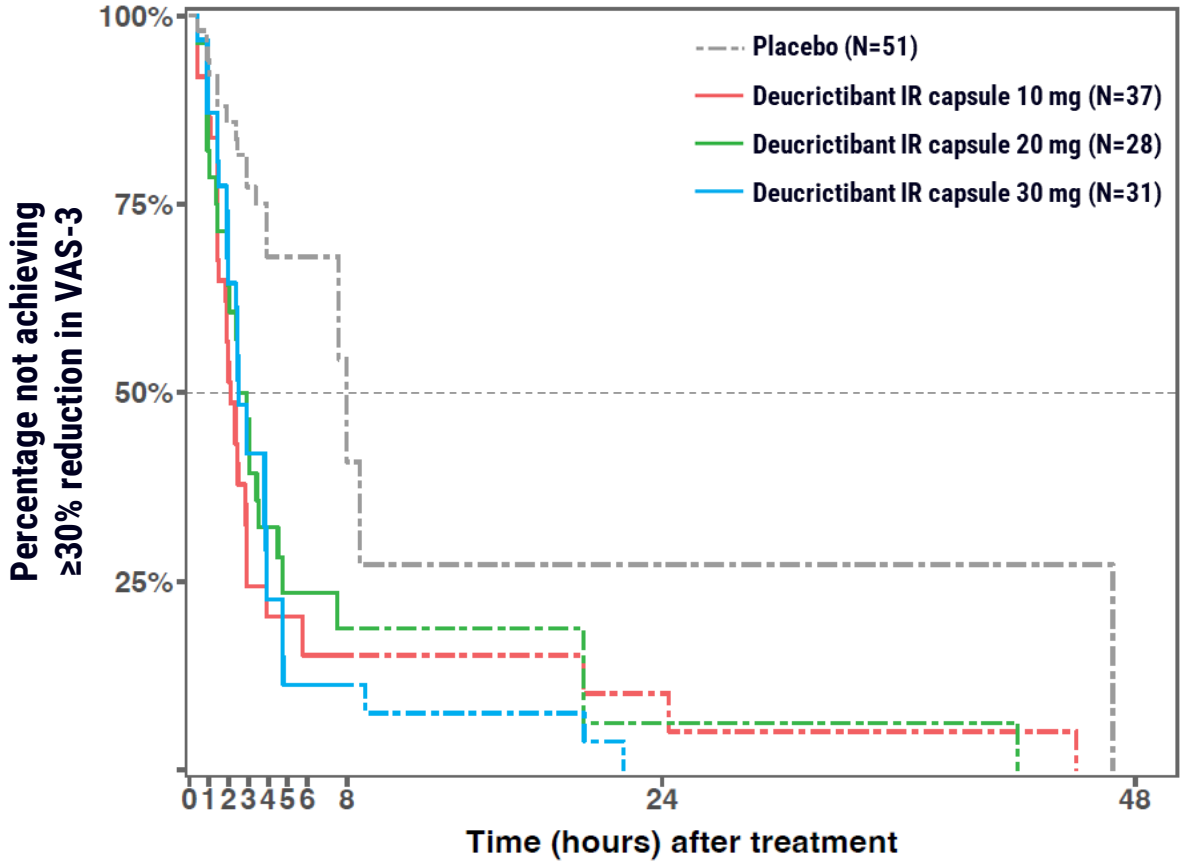
Difference from placebo in change from pre-treatment to 4 h post-treatment, least-squares mean (95% CI)

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
Combined deucrictibant IR capsule	-16.08 (-19.87, -12.29)	

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

CI: Confidence interval; IR: immediate-release; 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 = The 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. The combined PHVS416 result is based on post-hoc analysis using a similar MMRM with all three active doses combined vs placebo.

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
Combined deucrictibant IR capsule	2.4 (2.0, 2.9)	

Consistent with results of TOS analyses

Time to "a little better" for all involved body sites

Presented in poster P-25 – Riedl MA et al.

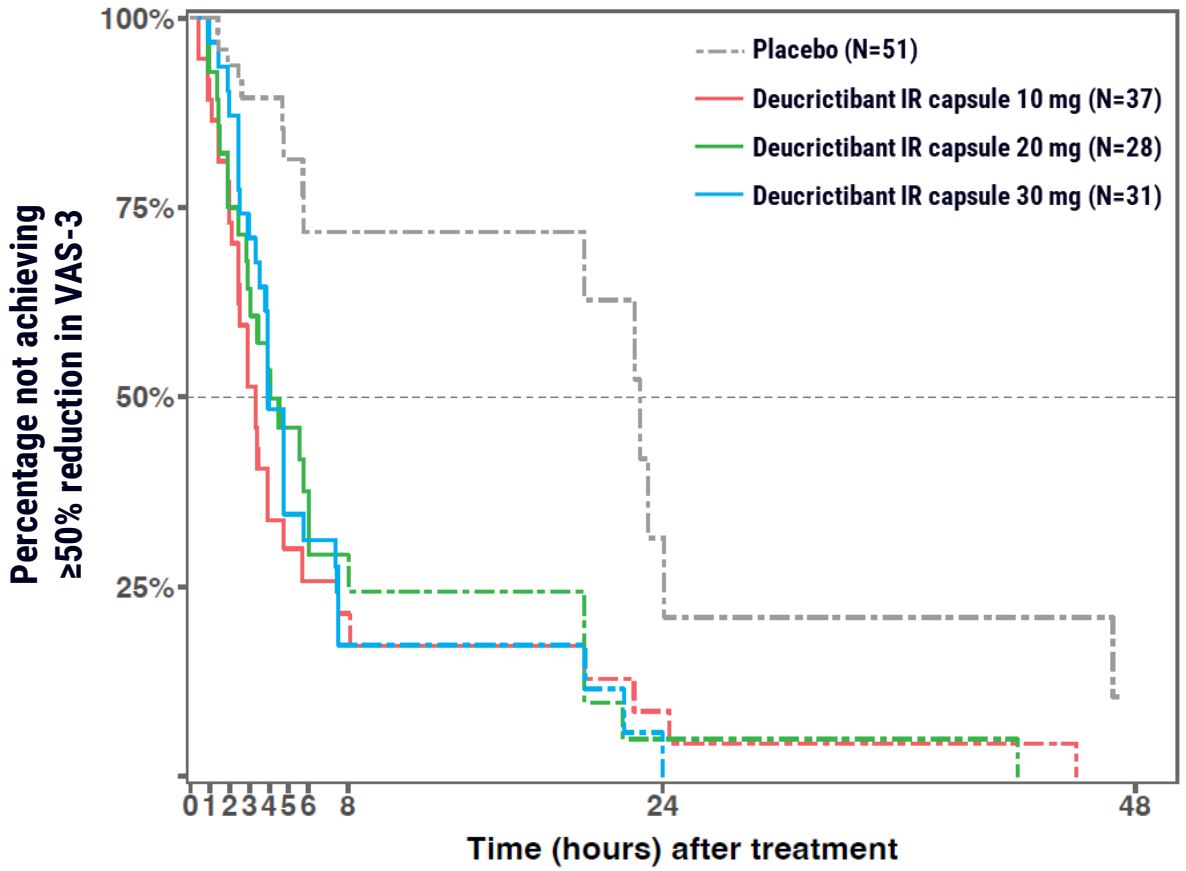
Consistent results across attacks by body location

Presented in poster P-38 – Valerieva A et al.

CI: Confidence interval; IR: immediate-release; 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. The combined deucrictibant IR capsule results are based on post-hoc analyses to provide a reference of the result by pooling all three active doses.

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
Combined deucrictibant IR capsule	3.9 (3.0, 4.8)	

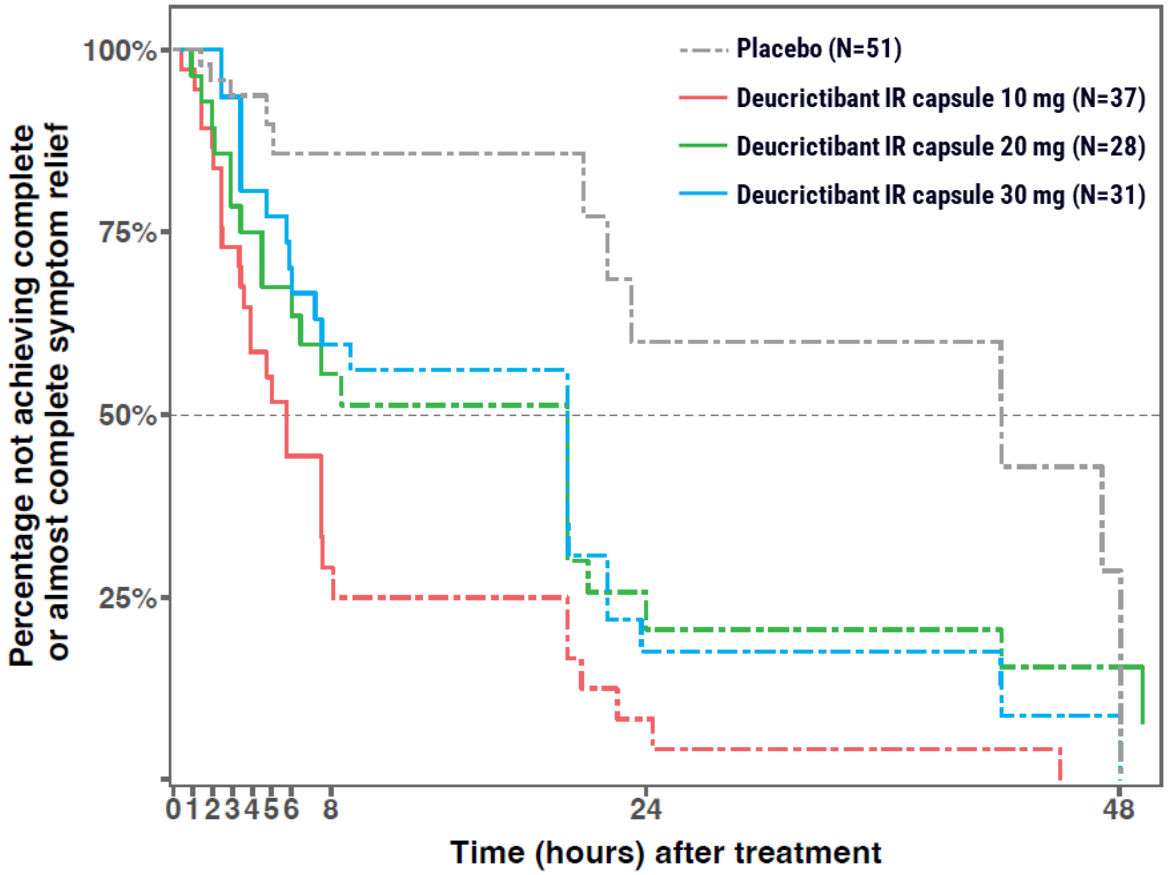
Consistent results across attacks by body location

Presented in poster P-38 – Valerieva A et al.

CI: Confidence interval; IR: immediate-release; 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. The combined deucrictibant IR capsule results are based on post-hoc analyses to provide a reference of the result by pooling all three active doses.

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
Combined deucrictibant IR capsule	7.5 (5.9, 20.0)	

Consistent with results of TOS analyses

Time to "a lot better or resolved" for all involved body sites

Presented in poster P-25 – Riedl MA et al.

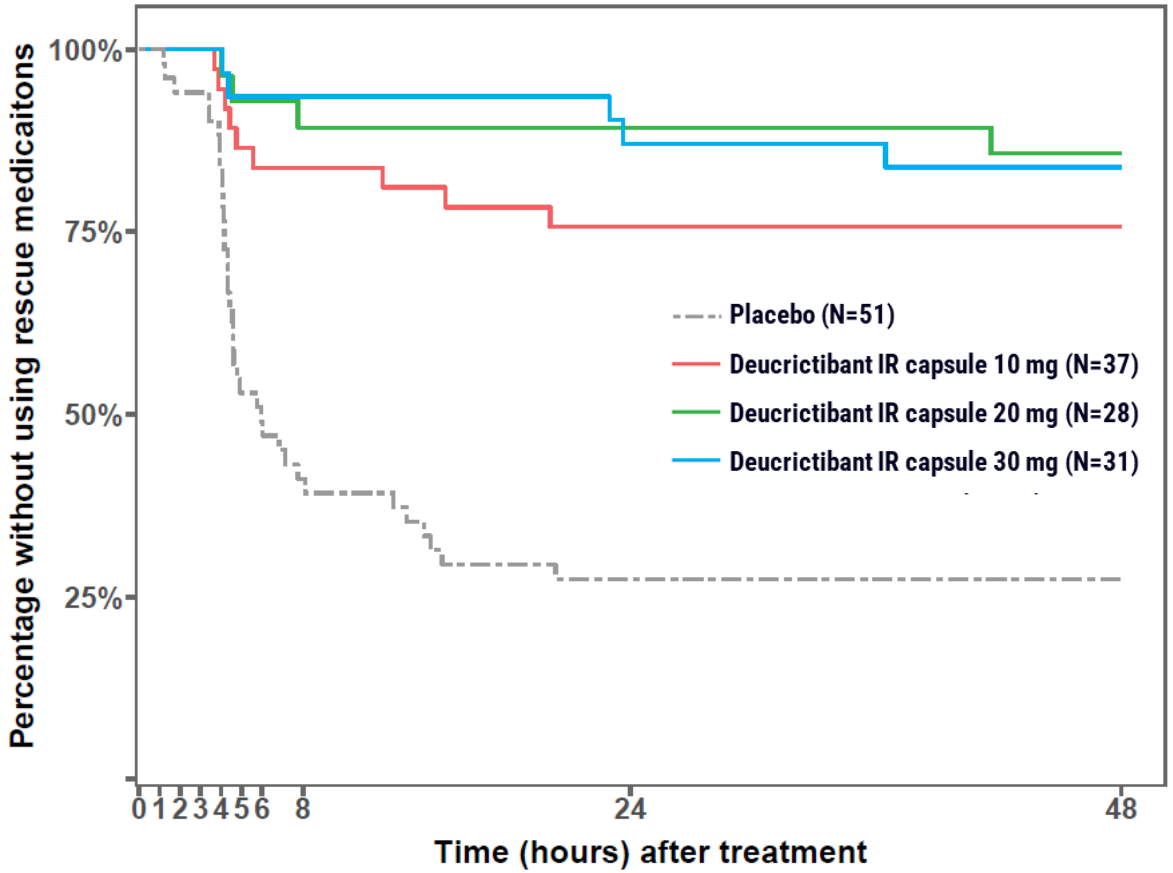
Consistent results across attacks by body location

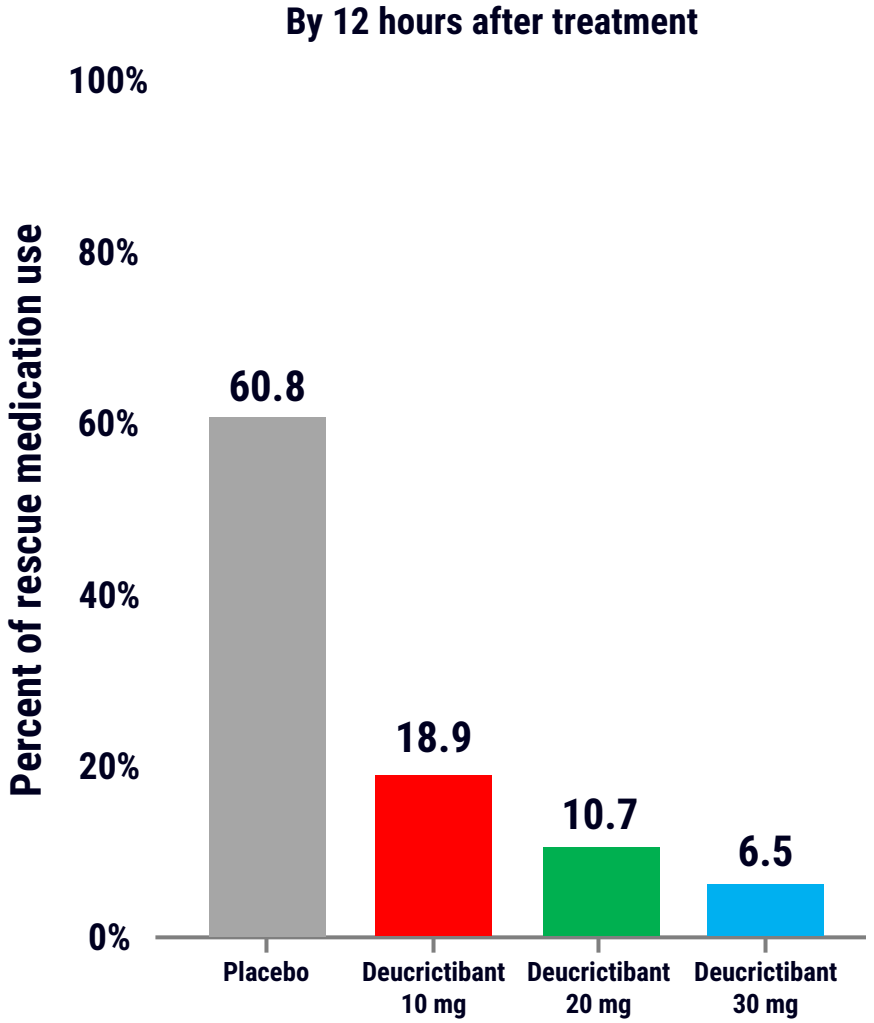
Presented in poster P-38 – Valerieva A et al.

CI: Confidence interval; IR: immediate-release; 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. The combined deucrictibant IR capsule results are based on post-hoc analyses to provide a reference of the result by pooling all three active doses.

Deucrictibant IR capsule substantially reduced use of rescue medication





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

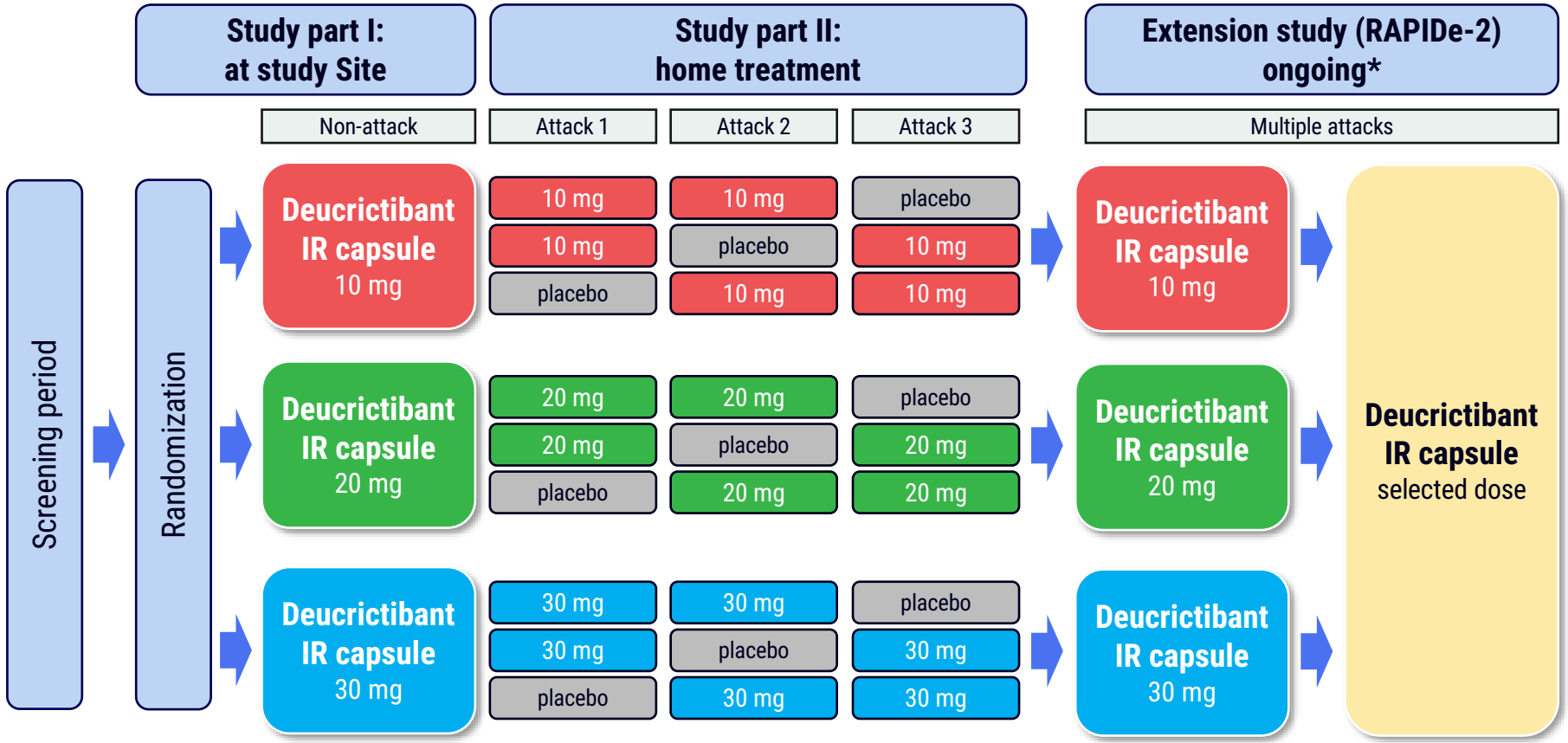
Deucrictibant IR capsule was generally well-tolerated at all doses

	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.

Ongoing RAPIDe-2 extension study will provide additional evidence from long-term treatment of attacks with deucrictibant IR capsule



- Long-term safety & efficacy
- VAS, TOS, MSCS, PGI-C, PGI-S
- Non-laryngeal & laryngeal attacks
- Attacks presenting with vomiting
- Use of second dose, if needed

IR: immediate-release; MSCS: Mean Symptom Complex Severity; PGI-C: Patient Global Impression of Change; PGI-S: Patient Global Impression of Severity; TOS: Treatment Outcome Score; VAS: visual analogue scale.
*The study is planned to continue until the availability of commercial supply, or another means of continued treatment can be provided. ClinicalTrials.gov Identifier: NCT05396105, https://clinicaltrials.gov/ct2/show/NCT05396105; EudraCT Number: 2021-006906-58 (both accessed 27 April 2023). RAPIDe-2 trial is currently on hold in the U.S.. Regulators in ex U.S. countries have been notified of the U.S. clinical hold. For the latest information and updates visit: https://ir.pharvaris.com/.

Conclusions

- 74 patients from 13 countries were enrolled into RAPIDe-1 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.