Efficacy and Safety of Bradykinin B2 Receptor Antagonism With Deucrictibant Immediate-Release Capsule for Treatment of Hereditary Angioedema Attacks: Results of RAPIDe-1 Phase 2 Trial

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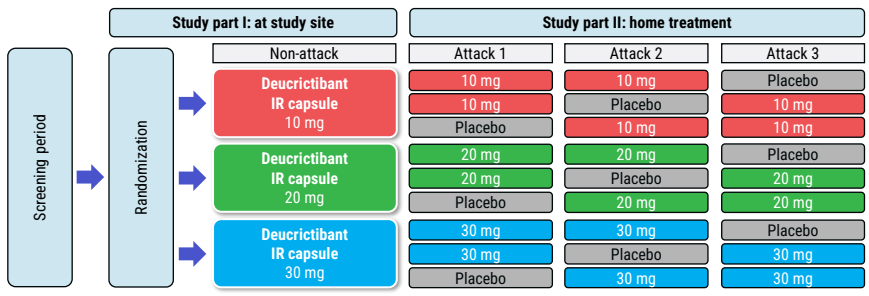
Introduction

- Excess bradykinin is the cause of signs and symptoms of swelling during hereditary angioedema (HAE) attacks,[1] and efficacy and tolerability of bradykinin B2 receptor antagonism for treatment of HAE attacks has been proven in clinical trials and ~15 years of post-marketing experience.[2-4]
- International guidelines for management of HAE in clinical practice recommend that attacks are treated as early as possible.[5-7]
- Burden associated with parenteral administration of approved on-demand medications[8-12] leads to treatment of many HAE attacks being delayed or forgone.[12-16]
- An unmet need exists for on-demand oral therapies that are effective and well tolerated to reduce the treatment burden and enable prompt administration.[12-16]

Methods

- RAPIDe-1 (NCT04618211)[17,*] was a Phase 2, double-blind, placebo-controlled, randomized, crossover, dose-ranging trial of deucrictibant immediate-release (IR) capsule for on-demand treatment of angioedema attacks in patients with HAE type 1 or type 2 (HAE-1/2) (**Figure 1**).

Figure 1. Study design



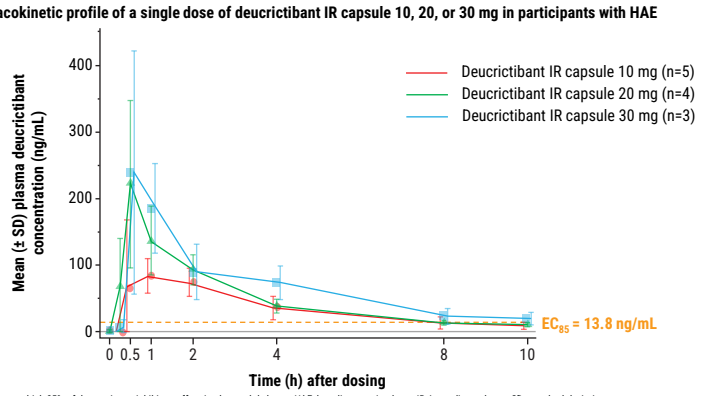
IR, immediate-release.

- Key inclusion criteria: diagnosis of HAE-1/2; ≥3 attacks in the last 4 months or ≥2 attacks in the last 2 months prior to screening; access to and experience with use of on-demand medications.
- Key exclusion criteria: pre-enrollment use of C1-inhibitor (C1-INH) for acute use or short-term prophylaxis (last 7 days); C1-INH for long-term prophylaxis, oral kallikrein inhibitors, attenuated androgens, anti-fibrinolytics (2 weeks); monoclonal antibodies for HAE (12 weeks); pregnancy or breast-feeding; conditions interfering with participant's safety/ability to participate in the study.
- The primary analysis included 147 qualifying HAE attacks in 62 participants treated with double-blinded placebo or deucrictibant IR capsule 10, 20, or 30 mg (modified intent-to-treat [mITT] analysis = all randomized participants with ≥1 treated HAE attack and non-missing Visual Analogue Scale [VAS] results at both pre-treatment and ≥1 post-treatment timepoint of that attack).

Results

- All three doses of deucrictibant IR capsule resulted in rapid absorption and achievement of therapeutic levels (≥EC_{85}) within 15–30 minutes, which were maintained for approximately 8 to >10 hours, depending on dose (**Figure 2**).

Figure 2. Pharmacokinetic profile of a single dose of deucrictibant IR capsule 10, 20, or 30 mg in participants with HAE



EC_{85}, plasma concentration at which 85% of the maximum inhibitory effect is observed; h, hours; HAE, hereditary angioedema; IR, immediate-release; SD, standard deviation.

- The primary endpoint was met, with deucrictibant IR capsule treatment showing a statistically significant and clinically meaningful reduction in attack symptoms by VAS-3 at 4 hours of −15.02 to −16.75 (*P*<0.0001 for all doses; nominal for 10 mg dose) compared with placebo (**Figure 3** and **Table 1**).

Figure 3. Results of primary endpoint: reduction in HAE attack symptoms by VAS-3

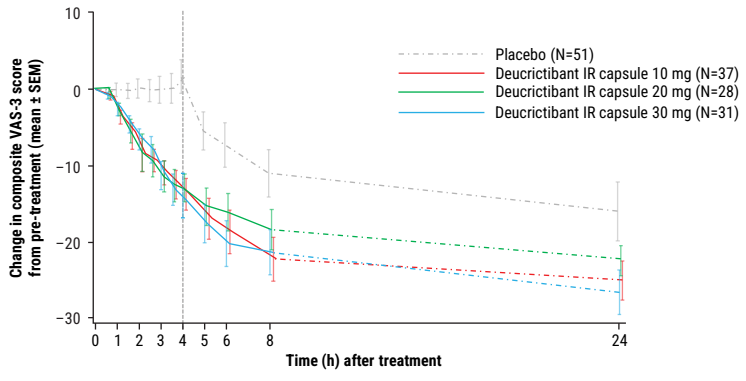


Table 1. Results of primary endpoint: reduction in HAE attack symptoms by VAS-3

Difference from placebo in change from pre-treatment to 4 hours post-treatment	Deucrictibant IR capsule		
	10 mg (n=33)	20 mg (n=27)	30 mg (n=30)
Least-squares mean (95% CI)	−16.75 (−21.52, −11.97)	−15.02 (−20.22, −9.81)	−16.28 (−21.27, −11.29)
***P* value**	*P*<0.0001[a]	*P*<0.0001	*P*<0.0001

CI, confidence interval; h, hours; HAE, hereditary angioedema; IR, immediate-release; mITT, modified intent-to-treat; MMRM, mixed-effects model with repeated measures; SEM, standard error of the mean; VAS, Visual Analogue Scale; VAS-3, 3-symptom composite VAS. VAS-3: evaluates patient-reported severity of skin pain, skin swelling, and abdominal pain. Median VAS-3 at baseline ranged from 24.3 to 27.0 across deucrictibant IR capsule doses (10, 20, and 30 mg). N = number of attacks in the mITT analysis set. Figure is based on descriptive summary of mean and SEM. n = number of treated attacks with non-missing VAS scores at 4 h and no rescue medication use. Least-squares mean differences, CIs, and *P* values come from MMRM. Data after rescue medication use not included. [a]Nominal *P* value.

Results (continued)

- All key secondary endpoints were met, demonstrating that deucrictibant IR capsule significantly:
  - Shortened time to onset of symptom relief (≥30% reduction in VAS-3) from pre-treatment score, with a median time of 2.1–2.7 hours vs 8.0 hours with placebo (**Table 2**).
  - Decreased time to a ≥50% reduction in VAS-3 score from the pre-treatment score of 3.3–4.0 hours vs 22.8 hours with placebo (**Table 2**).
  - Reduced time to almost complete or complete symptom relief (all individual VAS ≤10) (**Table 2**).
  - Improved MSCS and TOS scores at 4 hours post-treatment (**Table 2**).

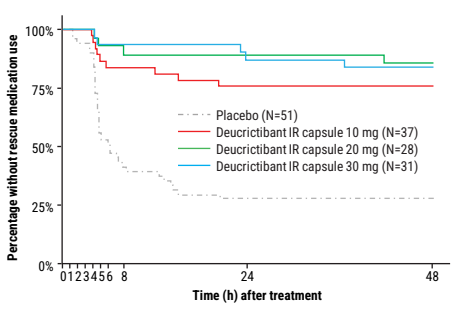
Table 2. Results of key secondary endpoints

	Placebo (N=51)	Deucrictibant IR capsule 10 mg (N=37)	Deucrictibant IR capsule 20 mg (N=28)	Deucrictibant IR capsule 30 mg (N=31)
Time to onset of symptom relief by VAS-3 ≥30% reduction[a]				
Median time, hours (95% CI)	8.0 (7.6, 46.9)	2.1 (1.5, 2.9)	2.7 (1.9, 3.5)	2.5 (1.9, 3.8)
Hazard ratio		3.81	3.08	3.61
P value		<0.0001	0.0021	<0.0001
Time to VAS-3 ≥50% reduction[a]				
Median time, hours (95% CI)	22.8 (20.0, 24.1)	3.3 (2.4, 3.9)	4.0 (2.9, 6.0)	4.0 (3.3, 5.8)
Hazard ratio		4.55	3.65	3.87
P value		<0.0001	0.0003	<0.0001
Time to almost complete or complete symptom relief by VAS-3[b]				
Median time, hours (95% CI)	42.0 (22.0, 48.1)	5.8 (3.6, 7.5)	20.0 (4.5, 20.0)	20.0 (6.0, 20.1)
Hazard ratio		5.09	2.25	2.65
P value		<0.0001	0.0127	0.0001
Change in MSCS[c] score at 4 hours[d]				
Least-squares mean difference: deucrictibant IR capsule − placebo		−0.79	−0.61	−0.39
P value		<0.0001	0.0008	0.0291
TOS[e] at 4 hours[d]				
Least-squares mean difference: deucrictibant IR capsule − placebo		64.13	62.69	71.06
P value		<0.0001	<0.0001	<0.0001

CI, confidence interval; IR, immediate-release; mITT, modified intent-to-treat; MSCS, Mean Symptom Complex Severity; TOS, Treatment Outcome Score; VAS, Visual Analogue Scale; VAS-3, 3-symptom composite VAS. VAS-3: evaluates patient-reported severity of skin pain, skin swelling, and abdominal pain. MSCS: evaluates global symptom severity at a point in time. TOS: evaluates patient-reported response to treatment of attack symptoms. N = number of attacks included in the mITT analysis set. *P* values for deucrictibant IR capsule 20 mg and 30 mg are based on statistical tests in the prespecified multiple comparison procedure, other *P* values are nominal. [a]Hazard ratios and *P* values are based on marginal Cox proportional hazards models. [b]Time when all 3 VAS scores have values ≤10 for ≥2 consecutive timepoints. [c]Minimal clinically important difference for MSCS = −0.30. [d]*P* values are based on mixed-effects models for repeated measures. [e]Minimal clinically important difference for TOS = 30.

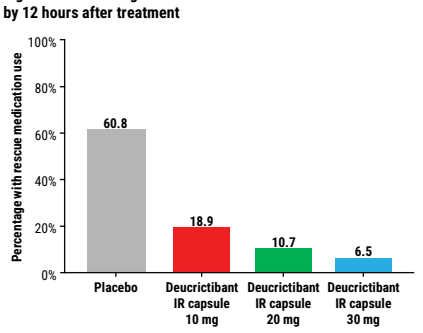
- Substantially less rescue medication was used for attacks treated with deucrictibant IR capsule compared to attacks treated with placebo (**Figure 4**).

Figure 4a. Kaplan-Meier plot of rescue medication use



h, hours; IR, immediate-release; mITT, modified intent-to-treat. N = number of attacks in the mITT analysis set.

Figure 4b. Percentage of attacks treated with rescue medication by 12 hours after treatment



- Deucrictibant IR capsule was generally well tolerated across all doses.
- In the non-attack phase, 2 participants experienced a treatment-related treatment-emergent adverse event (TEAE); in the attack treatment phase, 3 treatment-related TEAEs were reported for 1 attack treated with deucrictibant IR capsule 30 mg (2.8%), and 1 treatment-related TEAE was reported for 1 attack treated with placebo (1.9%) (**Table 3**).
- No serious treatment-related TEAEs, no severe treatment-related TEAEs, no TEAEs leading to treatment discontinuation, and no treatment-related TEAEs in laboratory parameters, vital signs, or ECG findings were reported.

Table 3. Treatment-related TEAEs within 48 hours after administration of study drug

	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)
Participants (part I) or attacks (part II) with any treatment-related TEAEs, n (%)	**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)	–	–	

IR, immediate-release; TEAE, treatment-emergent adverse event. N = number of participants (part I) and number of attacks (part II) in the safety analysis set. Safety analysis set includes all randomized participants who received ≥1 dose of study drug between part I and part II.

Conclusions

- **The Phase 2 RAPIDe-1 trial of deucrictibant IR capsule for treatment of attacks in patients with HAE-1/2 met the primary and all key secondary endpoints.**
- **Deucrictibant IR capsule treatment resulted in rapid onset of action, symptom relief, and resolution of HAE attacks, in addition to a substantial reduction in use of rescue medication, and was well tolerated at all dose levels.**
- **RAPIDe-1 trial results support further development of deucrictibant IR capsule as a potential on-demand treatment for HAE attacks.**

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

COI: Grants/research support, honoraria or consultation fees, sponsored speaker bureau − **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.**: Astria, BioCryst, Biomarin, Centogene, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Shire/Takeda; **M.L.B.**: BioCryst, CSL Behring, Shire HGT; **L.B.**: BioCryst, Blueprint, CSL Behring, Novartis, Shire/Takeda; **H.Cha.**: AstraZeneca (Alexion), CSL Behring, KalVista, Merck, Novartis, Pharming, Pharvaris, Roche, Sanofi, Sobi, Takeda; **D.M.C.**: Astria, BioCryst, CSL Behring, Ionis Pharmaceuticals, KalVista, Pharming, Pharvaris, Takeda; **A.D-T.**: BioCryst, Takeda; **O.F.**: BioCryst, CSL Behring, Takeda; **H.F.**: BioCryst, CSL Behring, Intellia, KalVista, ONO Pharmaceutical, Pharming, Pharvaris, Takeda; **J.G.**: CSL Behring, Shire/Takeda; **M.G.**: 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; **H.H.L.**: BioCryst, BioMarin, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Takeda; **R.L.**: BioCryst, CSL Behring, 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, Stallergenes, Teva; **M.A.R.**: Astria, BioCryst, Biomarin, CSL Behring, Cycle Pharma, Fresenius-Kabi, Grifols, Ionis, Ipsen, KalVista, Ono Pharma, Pfizer, Pharming, Pharvaris, RegenxBio, 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.**: AstraZeneca, Berlin-Chemie/Menarini Group, CSL Behring, Novartis, Pharming, Pharvaris, Shire/Takeda, Sobi, Teva; **W.H.Y.**: Aimmune, ALK, Amgen, AnaptysBio, Aslan Therapeutics, AstraZeneca, BioCryst, Celgene, CSL Behring, DBV Technologies, Dermira, Eli Lilly, Galderma, Genentech/Roche, Glenmark, GSK, Haleon, Incyte Biosciences, Ionis, Merck, Novartis, Novavax, Pharming, Pharvaris, Providence, Regeneron, Sanofi Genzyme, Shire/Takeda, VBI; medical advisor (volunteer) for Hereditary Angioedema Canada, a patient organization; member of Angioedema Centers of Reference and Excellence; **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.Che.**: 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 GrayMatters Consulting and consultant to Pharvaris, holds stocks/stock options in Pharvaris, and advisor to Kosa Pharma; **P.L.**: employee of Pharvaris, holds stocks/stock options in Pharvaris; **M.Mau.**: Adverum, Attune, BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, Takeda/Shire. **Acknowledgments:** Medical writing services were provided by Cara Bertozzi, PhD, and Holly Richendrfer, PhD, of Two Labs Pharma Services.

*RAPIDe-1 was a Pharvaris-sponsored clinical trial. ClinicalTrials.gov Identifier: NCT04618211.