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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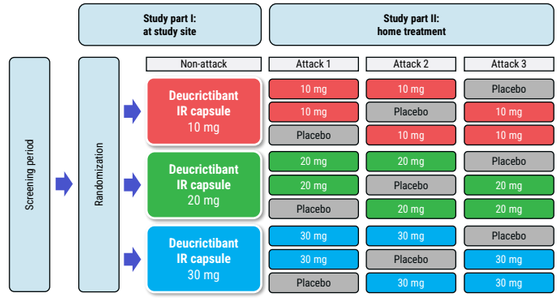
Introduction

- 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 recommend that HAE 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 and may reduce the treatment burden enabling prompt administration.[12,15,16]

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 the on-demand treatment of angioedema attacks in patients with HAE type 1 or type 2 (HAE-1/2) (**Figure 1**).
- 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 treated by 62 participants 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 VAS results at both pre-treatment and ≥1 post-treatment time point of that attack).

Figure 1. Study design

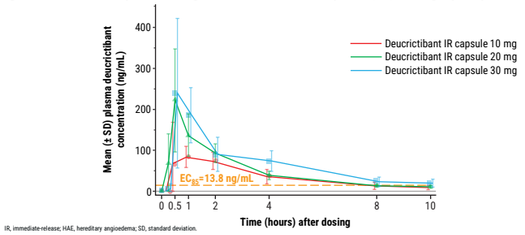


IR, immediate-release.

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



IR, immediate-release; HAE, hereditary angioedema; 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 attack symptoms by VAS-3

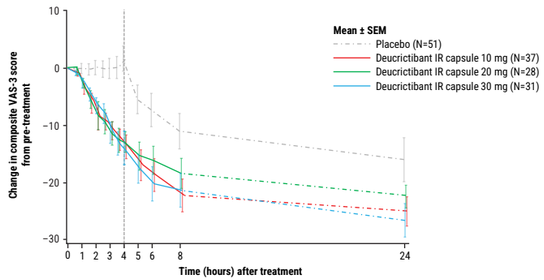


Table 1. Results of primary endpoint: reduction in attack symptoms by VAS-3

Difference from placebo in change from pre-treatment to 4 hours post-treatment	Deucrictibant IR capsule		
	10 mg	20 mg	30 mg
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; 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. 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. Least-squares mean differences, CIs, and P values come from MMRM. Data after rescue medication use not included. [a]Nominal P value.

- 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				
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[b] score at 4 hours[c]				
Least-squares mean difference: deucrictibant IR capsule – placebo		−0.79	−0.61	−0.39
P value		<0.0001	0.0008	0.0291
TOS[d] at 4 hours[c]				
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. 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]Minimal clinically important difference for MSCS = −0.30. [c]P values are based on mixed-effects models for repeated measures. [d]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

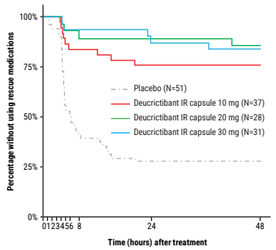
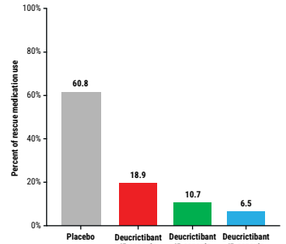


Figure 4b. Percentage of attacks treated with rescue medication by 12 hours after treatment



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

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

Table 3. Treatment-related AEs 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 AEs, 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)	–	–	–

AE, adverse event; IR, immediate-release. 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 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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