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

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Introduction

- Excess bradykinin is the cause of signs and symptoms of swelling during 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 currently approved on-demand medications[8-12] leads to treatment of a number of HAE attacks being delayed or forgone[12-15]
- An unmet need exists for on-demand oral therapies that are effective and well-tolerated and may reduce the treatment burden enabling prompt administration

Methods

- RAPIDe-1* (NCT0461821116) was a Phase 2, double-blind, placebo-controlled, randomized, crossover, dose-ranging trial of deucrictibant immediate-release (IR) capsule (PHVS416) for treatment of angioedema attacks in patients with HAE-1/2.
- 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-enrolment use of: C1-inhibitor (C1-INH) for acute use or short-term prophylaxis (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 patient's safety/ability to participate in the study.
- A primary analysis included 147 qualifying HAE attacks treated by 62 patients with double-blinded placebo or deucrictibant IR capsule 10, 20, or 30 mg (modified intent-to-treat analysis, mITT = all randomized patients with ≥1 treated HAE attack and non-missing VAS results at both pre-treatment and ≥1 post-treatment time point of that attack).

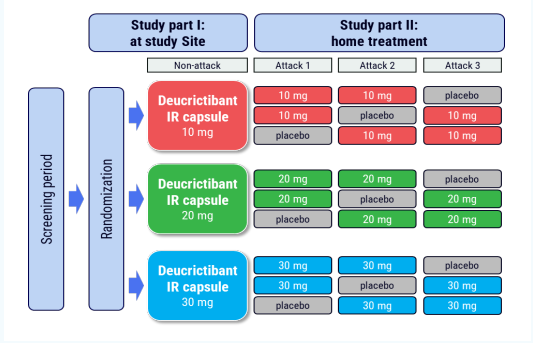


Figure 1. RAPIDe-1 trial design schematic

Results

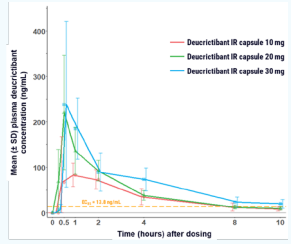
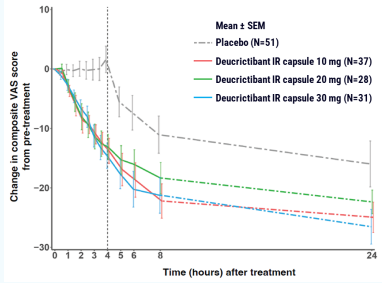


Figure 2. Pharmacokinetic profile of single dose of deucrictibant IR capsule 10, 20 or 30 mg in HAE patients



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[f]
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

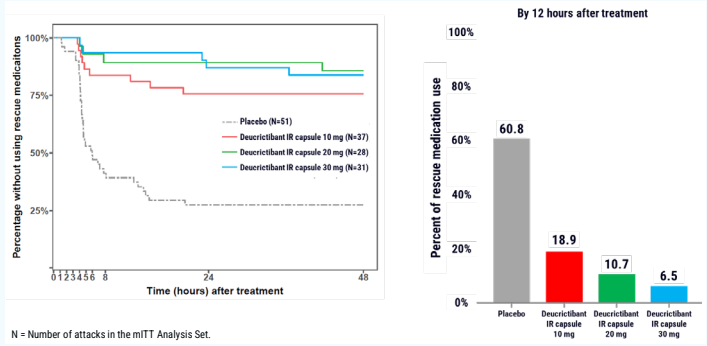
Median VAS-3 at baseline ranged from 24.33 to 27.00 across deucrictibant IR capsule doses (10, 20, and 30 mg).
[f]Nominal p-value; N = The number of attacks in the mITT Analysis Set. Figure is based on descriptive summary of mean and SEM (standard error of the mean). Least-squares mean differences, CIs, and p-values come from a mixed-effects model with repeated measures (MMRM). Data after rescue medication use not included.

Figure 3 and Table 1. Results of primary endpoint (reduction of attack symptoms by VAS-3)

	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 in 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 in 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[a]				
Median time in 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: PHVS416 – placebo		-0.79	-0.61	-0.39
p-value		<0.0001	0.0008	0.0291
TOS[d] at 4 hours[d]				
Least-squares mean difference: PHVS416 – placebo		64.13	62.69	71.06
p-value		<0.0001	<0.0001	<0.0001

N = Number of attacks included in the mITT Analysis Set. p-values for deucrictibant IR capsule 20mg and 30mg are based on statistical tests in the pre-specified 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.

Table 2. Results of key secondary efficacy endpoints



N = Number of attacks in the mITT Analysis Set.

Figure 4. Additional secondary endpoint: use of rescue medication

	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%)	-	-	-

N = Number of patients (Part I) and number of attacks (Part II) in the Safety Analysis Set. The Safety Analysis Set includes all randomized patients who received ≥1 dose of study drug between Part I and Part II.

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

Conclusions

The Phase 2 RAPIDe-1 trial for treatment of attacks in patients with HAE-1/2 met primary and all key secondary endpoints, providing evidence on the efficacy and safety of deucrictibant IR capsule in treating HAE attacks and supporting its further development as a potential on-demand therapy for HAE.

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