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Efficacy and Safety of Bradykinin B2 Receptor Inhibition with Oral PHVS416 in Treating Hereditary Angioedema Attacks: Results of RAPIDe-1 Phase 2 Trial

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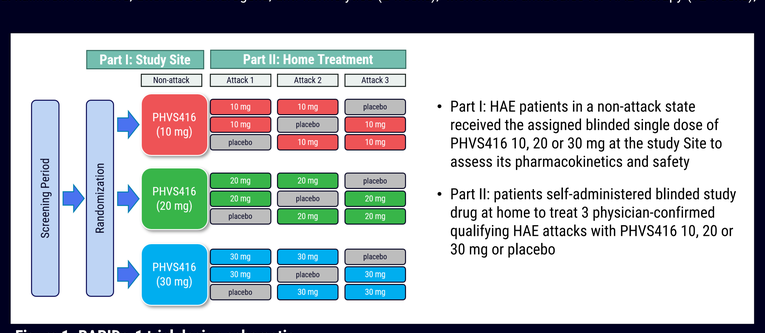
Introduction

- Hereditary angioedema (HAE) attacks are caused by excessive bradykinin and bradykinin B2 receptor antagonism was proven to be an effective and well-tolerated treatment approach in clinical trials and in >10 years of real-world clinical practice.[1-4]
- Currently approved on-demand therapies for HAE attacks are administered intravenously or subcutaneously with substantial treatment burden due to the time required for preparation and administration as well as potential occurrence of pain, discomfort or other injection site reactions,[5-8] leading to treatment of many attacks being delayed or forgone.[9-10]
- An unmet need exists for on-demand oral therapies that are effective and well-tolerated and may reduce the treatment burden enabling prompt administration as recommended by clinical guidelines.[11-13]
- PHVS416 is an investigational* softgel capsule formulation containing PHA-022121 (PHA121), a highly potent, specific, and orally bioavailable competitive antagonist of the bradykinin B2 receptor.[14-15]

Methods

- RAPIDe-1* (ClinicalTrials.gov Identifier: NCT04618211[16]) is a Phase 2, double-blind, placebo-controlled, randomized, crossover, dose-ranging trial of PHVS416 softgel capsule for the acute treatment of angioedema attacks in patients with type 1 and 2 HAE.
- Key Inclusion criteria:
  - Confirmed diagnosis of HAE type 1 or type 2;
  - History of HAE attacks: ≥3 HAE attacks in the last 4 months, or ≥2 in the last 2 months prior to screening;
  - Reliable access and experience to use standard of care on-demand 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-inhibitor (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);



- Part I: HAE patients in a non-attack state received the assigned blinded single dose of PHVS416 10, 20 or 30 mg at the study Site to assess its pharmacokinetics and safety
- Part II: patients self-administered blinded study drug at home to treat 3 physician-confirmed qualifying HAE attacks with PHVS416 10, 20 or 30 mg or placebo

Figure 1. RAPIDe-1 trial design schematic

- Primary endpoint
  - Change in VAS-3 (3-symptom composite [skin pain, skin swelling, abdominal pain] visual analogue scale) score from pre-treatment to 4 hours post-treatment
- Key secondary efficacy endpoints
  - Time to onset of symptom relief (VAS-3; ≥30% reduction from the pre-treatment score)
  - Time to a ≥50% reduction in VAS-3 score from the pre-treatment score
  - Time to almost complete and complete symptom relief (VAS; all 3 items ≤10)
  - Change of MSCS (mean symptom complex severity) score from pre-treatment to 4 hours post-treatment
  - TOS (treatment outcome score) at 4 hours post-treatment
- Other secondary endpoints
  - Proportion of study-drug-treated attacks requiring the use of HAE rescue medication
  - Time to the first use of HAE rescue medication
  - Safety and PK assessment
- A primary analysis was performed including 147 qualifying HAE attacks treated by 62 patients with double-blinded placebo or PHVS416 10, 20, or 30 mg (modified intent-to-treat analysis, mITT = 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 of attacks for treatment with study drug had to be confirmed the Investigator or designee before administration of study drug via a remote consultation. Study drug had to be taken within 3 hours after ≥1 attack symptom (skin pain, skin swelling, or abdominal pain) reached moderate intensity (VAS score ≥30) and within 6 hours after onset of symptoms at any location. Attacks occurring within 5 days from previously treated attacks treated (with study drug or standard HAE medication) or involving the internal head and neck, regardless of intensity did not qualify for treatment with study drug and had to be treated with patient's standard HAE medication.

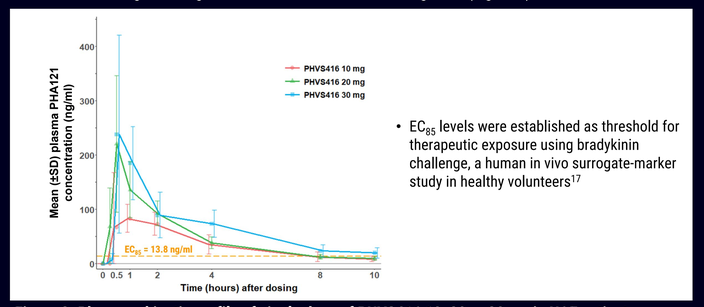
Results

- RAPIDe-1 enrolled 74 patients in Canada, Europe, Israel, the United Kingdom, and the United States*.
- Baseline characteristics of patients included in the mITT were generally balanced across treatment dose cohorts (Table 1).

	PHVS416 10 mg	PHVS416 20 mg	PHVS416 30 mg	Total
N	22	18	22	62
Age in years (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 1	18	15	22	55
Type 2	4	2	0	6
Type 1 or Type 2	0	1	0	1

Table 1. Baseline characteristics of patients included in the mITT Analysis Set

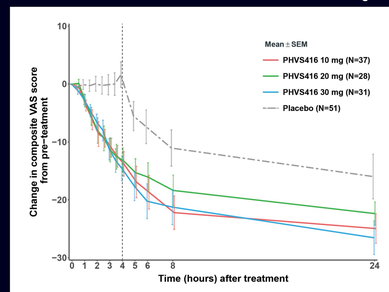
- PHA121 was absorbed with mean plasma levels reaching the threshold of therapeutic exposure >EC_{85} (13.8 ng/mL) within 15-30 minutes from PHVS416 administration. Mean plasma levels of PHA121 were maintained >EC_{85} for approx. 8 hours at 10 mg or 20 mg doses and for >10 hours at 30 mg dose (Figure 2).



- EC_{85} levels were established as threshold for therapeutic exposure using bradykinin challenge, a human in vivo surrogate-marker study in healthy volunteers[17]

Figure 2. Pharmacokinetic profile of single dose of PHVS416 10, 20 or 30 mg in HAE patients

- Primary endpoint was met. PHVS416 significantly reduced symptoms of HAE attacks measured as change in VAS-3 score from pre-treatment to 4 hours post-treatment (least squares mean difference of change in VAS-3: -16.75, -15.02, and -16.28 for PHVS416 10, 20 and 30 mg, respectively, vs. placebo).



Difference from placebo in change from pre-treatment to 4 h post-treatment, least-squares mean (95% CI)		
PHVS416 10 mg	-16.75 (-21.52, -11.97)	p < 0.0001†
PHVS416 20 mg	-15.02 (-20.22, -9.81)	p < 0.0001
PHVS416 30 mg	-16.28 (-21.27, -11.29)	p < 0.0001
Combined PHVS416	-16.08 (-19.87, -12.29)	

Figure 3 and Table 2. Results of primary endpoint (reduction of attack symptoms by VAS-3)

Median VAS-3 at baseline ranged from 24.33 to 27.00 across PHVS doses (10, 20, and 30 mg). †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. 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.

- All key secondary efficacy endpoints were also met. PHVS416 significantly reduced time to onset of symptom relief (VAS-3 reduction ≥30% from pre-treatment score), time to VAS-3 reduction ≥50% from pre-treatment score, and time to almost complete/complete symptom relief (all 3 VAS items ≤10) as well as to symptom relief and resolution of attacks assessed through the MSCS and TOS vs. placebo (Table 3).

	Placebo N=51	PHVS416 10 mg N=37	PHVS416 20 mg N=28	PHVS416 30 mg N=31	Combined PHVS416* N=96
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)	2.4 (2.0, 2.9)
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)	3.9 (3.0, 4.8)
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)	7.5 (5.9, 20.0)
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	-0.61
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	66.05
p-value		<0.0001	<0.0001	<0.0001	

Table 3. Results of key secondary efficacy endpoints

N = Number of attacks included in the mITT Analysis Set. p-values for PHVS416 20mg and PHVS416 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. *The combined PHVS416 results are based on post-hoc analyses to provide a reference of the result by pooling all three active doses.

- PHVS416 substantially reduced use of rescue medication to treat attacks vs. placebo (Figure 4).

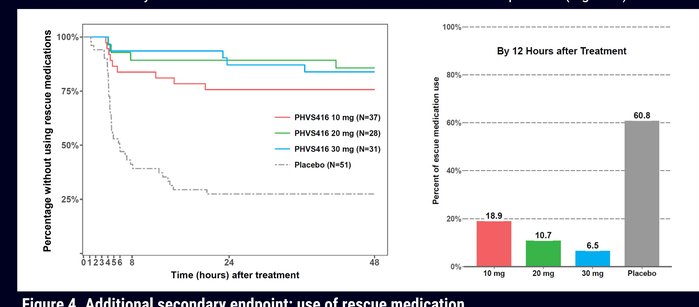


Figure 4. Additional secondary endpoint: use of rescue medication

N = Number of attacks in the mITT Analysis Set.

- PHVS416 was well-tolerated with 3 treatment-related adverse events (TRAEs) reported for 1 PHVS416 30mg-treated attack (2.8%) and 1 TRAE reported for 1 placebo-treated attack (1.9%), no serious TRAEs or AEs of severe severity, no AEs leading to treatment discontinuation, and no TRAEs of laboratory or ECG parameters, vital signs (Table 4).

	Part I (Non-Attack)			Part II (Attacks 1, 2, 3)			
	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
Patients (Part I) or attacks (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%)	-	-	-

Table 4. Treatment-related adverse events within 48 hours after administration of study drug

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.

Conclusions

The Phase 2 RAPIDe-1 trial* of PHVS416 for the treatment of attacks in patients with type 1 and 2 HAE met primary and all key secondary endpoints, providing evidence on the efficacy and safety of PHVS416 in treating HAE attacks and supporting its further development as a potential on-demand therapy for HAE.

*In August 2022, the U.S. Food & Drug Administration (FDA) placed a hold on the clinical trials of PHA121 in the U.S. based on its review of nonclinical data. FDA has subsequently agreed to partially lift the clinical hold on RAPIDe-1 trial[16] and allow 2 remaining U.S. participants in RAPIDe-1[16] to complete treatment of a final HAE attack per protocol. All other clinical studies[18-19] of PHA121 are 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/.

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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 Consulting 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. P.L.: employee of Pharvaris, holds stocks/stock options in Pharvaris.