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

MA Riedl, *J Anderson, E Aygören-Pürsün, ML Baeza, L Bouillet, H Chapdelaine, DM Cohn, A Du-Thanh, O Fain, H Farkas, 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, 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*

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

Conflicts of interest disclosure

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

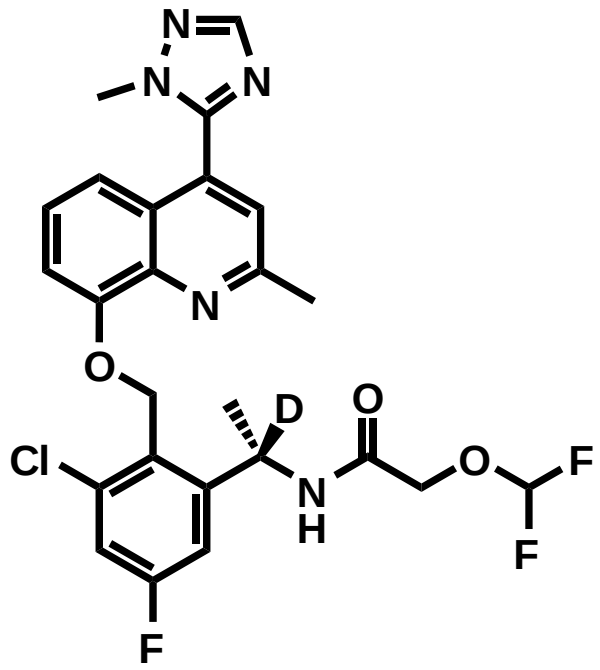
M.-H.J.: employee of Pharvaris at the time the analyses were conducted, holds stocks in Pharvaris. R.C.: employee of CG Consultancy and consultant to Pharvaris, holds stocks in Pharvaris. S.v.L.: employee of SLC Consultancy and consultant to Pharvaris, holds stocks in Pharvaris. H.C.: employee of Pharvaris, 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.

Unmet needs for additional treatment options for HAE

- 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]
- 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]

[1]Busse P J et al. N Engl J Med 2020;382:1136-48. [2]Cicardi M et al. N Engl J Med 2010;363:532-41. [3]Lumry WR et al. Ann Allergy Asthma Immunol 2011;107:529-37. [4]Maurer M et al. Clin Exp Allergy 2022;52:1048-58. [5]Berinert® [package insert], https://labeling.cslbehring.com/pi/us/berinert/en/berinert-prescribing information.pdf (accessed 15 January 2023). [6]Firazyr® [package insert], https://www.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf (accessed 15 January 2023). [7]Kalbitor® [package insert], https://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf (accessed 15 January 2023). [8]Ruconest® [package insert], https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf (accessed 15 January 2023). [9]Tuong LA et al. Allergy Asthma Proc 2014;35:250-4. [10]US Food and Drug Administration, Center for Biologics Evaluation and Research. The voice of the patient–Hereditary angioedema. May, 2018. https://www.fda.gov/media/113509/download (accessed 15 January 2023). [11]Betschel S et al. Allergy Asthma Clin Immunol 2019;15:72. [12]Busse PJ et al. J Allergy Clin Immunol Pract 2021;9:132-50. [13]Maurer M et al. Allergy 2022;77:196190.

PHA121 (PHA-022121) oral antagonist of bradykinin B2 receptor



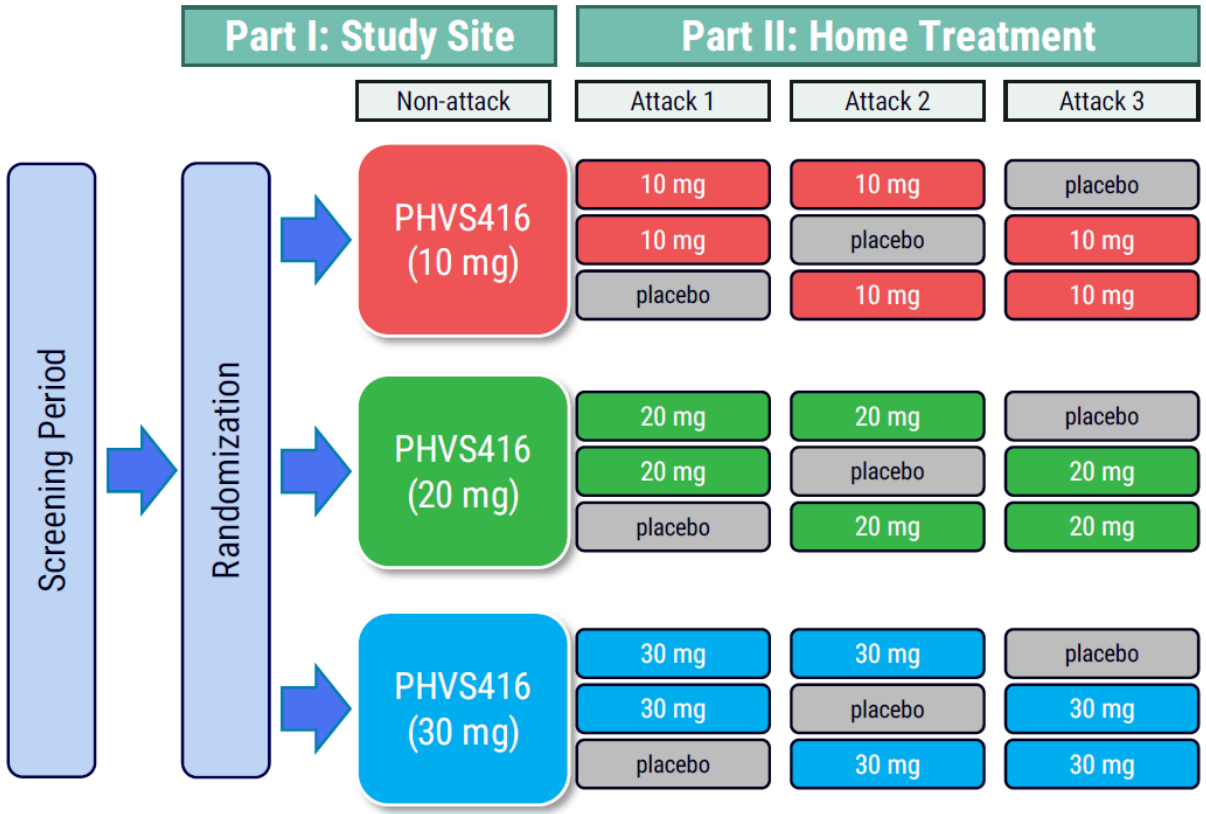
- First orally bioavailable bradykinin B2 receptor antagonist
- Highly potent and selective B2 receptor antagonist
- 2.4-fold lower molecular weight than icatibant
- Metabolic soft spot has been stabilized by the introduction of a deuterium atom
- Optimized for metabolic stability and exposure in humans

PHVS416 is an investigational* soft capsule formulation containing PHA121, not yet approved by regulatory authorities

Lesage A et al. Front Pharmacol 2020;11:916. Lesage A et al. Int Immunopharmacol 2022;105:108523.

*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 [https://clinicaltrials.gov/ct2/show/NCT04618211 (accessed 15 January 2023)] and allow 2 remaining U.S. participants in RAPIDe-1 to complete treatment of a final HAE attack per protocol. All other clinical studies [https://clinicaltrials.gov/ct2/show/NCT05047185 (accessed 15 January 2023), https://clinicaltrials.gov/ct2/show/NCT05396105 (accessed 15 January 2023)] 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/.

RAPIDe-1: PHVS416 phase 2 on-demand trial for HAE-1/2



- **Primary objective:** to evaluate angioedema symptom relief within 4 hours in acute attacks of patients with HAE-1/2
- **Study design:** Placebo-controlled, double-blinded 3-dose levels
  - Part I: all patients randomized and received a single dose of PHVS416 in clinic for PK and safety assessment
  - Part II: all patients treated up to 3 attacks with 2 PHVS416 vs. 1 placebo
- 74 HAE patients enrolled from ~30 Sites in Canada, Europe, Israel, UK, and US

VAS: visual analogue score. MCSC: mean symptom complex severity. TOS: treatment outcome score.
https://clinicaltrials.gov/ct2/show/NCT04618211 (accessed 15 January 2023). https://www.clinicaltrialsregister.eu/ctr-search/search?query=2020-003445-11 (accessed 15 January 2023).

Demographics and baseline characteristics were generally balanced (mITT Analysis Set)

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

	PHVS416 30 mg	PHVS416 20 mg	PHVS416 10 mg	Total
N	22	18	22	62
Age in yrs (mean)	41.9	44.5	42.5	42.9
Sex - M/F	8/14	5/13	7/15	20/42
Race - White/Other	22/0	18/0	20/2	60/2
Height in cm (mean)	170	167	169	169
BMI (mean)	27.9	27.6	27.5	27.7
Years since HAE diagnosis (mean)	23.98	21.64	21.11	22.28
HAE type				
HAE-1	22	15	18	55
HAE-2	0	2	4	6
HAE-1 or HAE-2	0	1	0	1

mITT: modified intent-to-treat. 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 score from pre-treatment 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

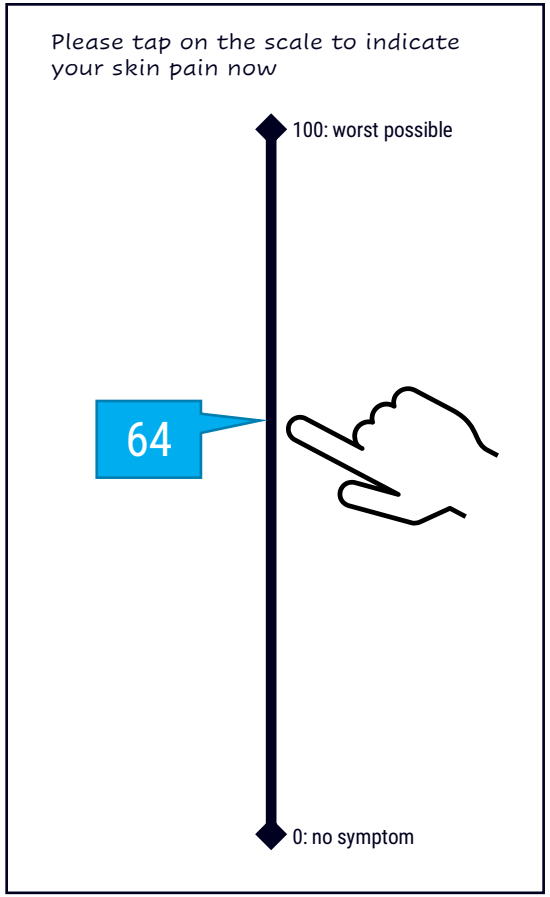
Other endpoints included in the topline outputs

- Proportion of IMP-treated attacks requiring the use of HAE rescue medication
- Time to the first use of HAE rescue medication
- Safety and PK assessments

VAS-3 is a measure of HAE attack severity based on electronically-captured numerically-assisted visual scale

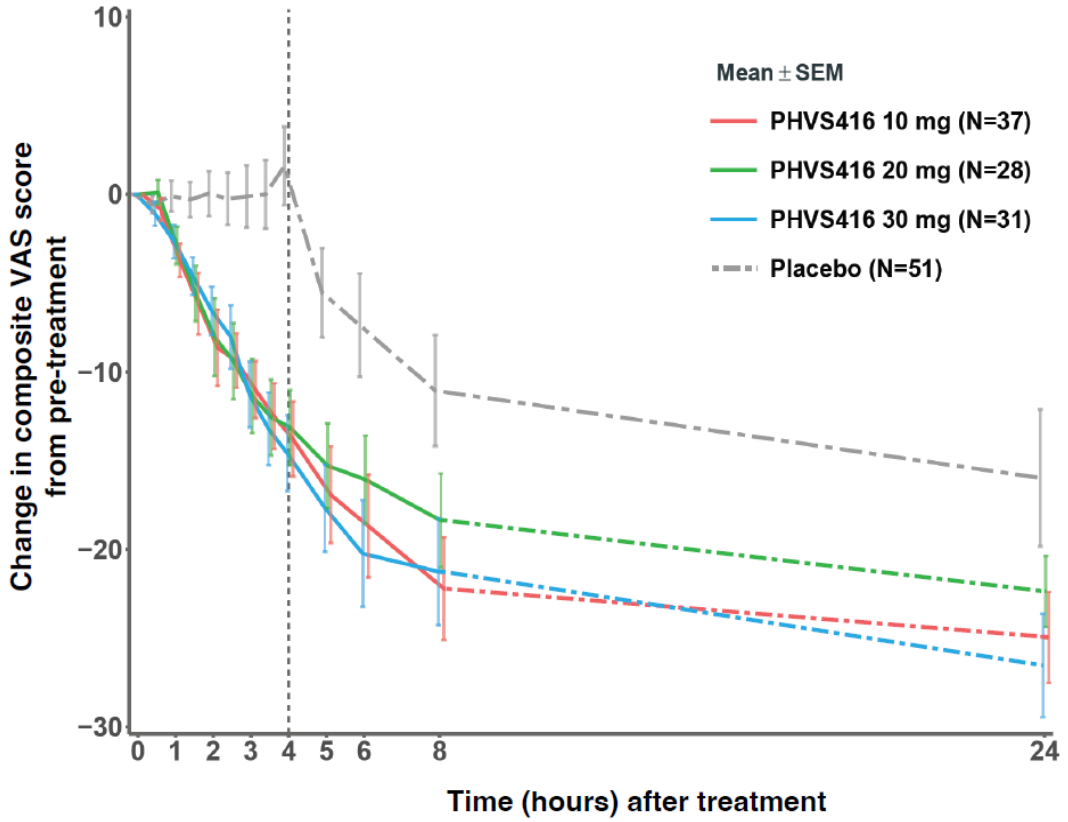
- Electronically captured patient-reported assessment of three symptoms
  - Skin pain, skin swelling, abdominal pain
- Patient indicates the severity of symptom on a sliding scale, from 0-100
- Once an attack qualifies and is treated, VAS-3 assessed every ~30 min until 4 hours post-treatment and then at 5, 6, 8, 24, 48 hours post-treatment

- Used in approval of two most recently approved on-demand therapies
  - Icatibant and recombinant C1 esterase inhibitor
- VAS, MSCS, TOS are only endpoints listed for attacks in FDA compendium of clinical outcome assessments (2021) as listed by Division of Pulmonology, Allergy and Critical Care



Firazyr® (icatibant) is a registered trademark of Shire and marketed by Takeda. Ruconest® (C1 esterase inhibitor [recombinant]) is a registered trademark of and marketed by Pharming.
FDA 2021 COA compendium: https://www.fda.gov/drugs/development-resources/clinical-outcome-assessment-compendium.

Primary endpoint
PHVS416 significantly reduced attack symptoms by VAS-3 at 4 hours

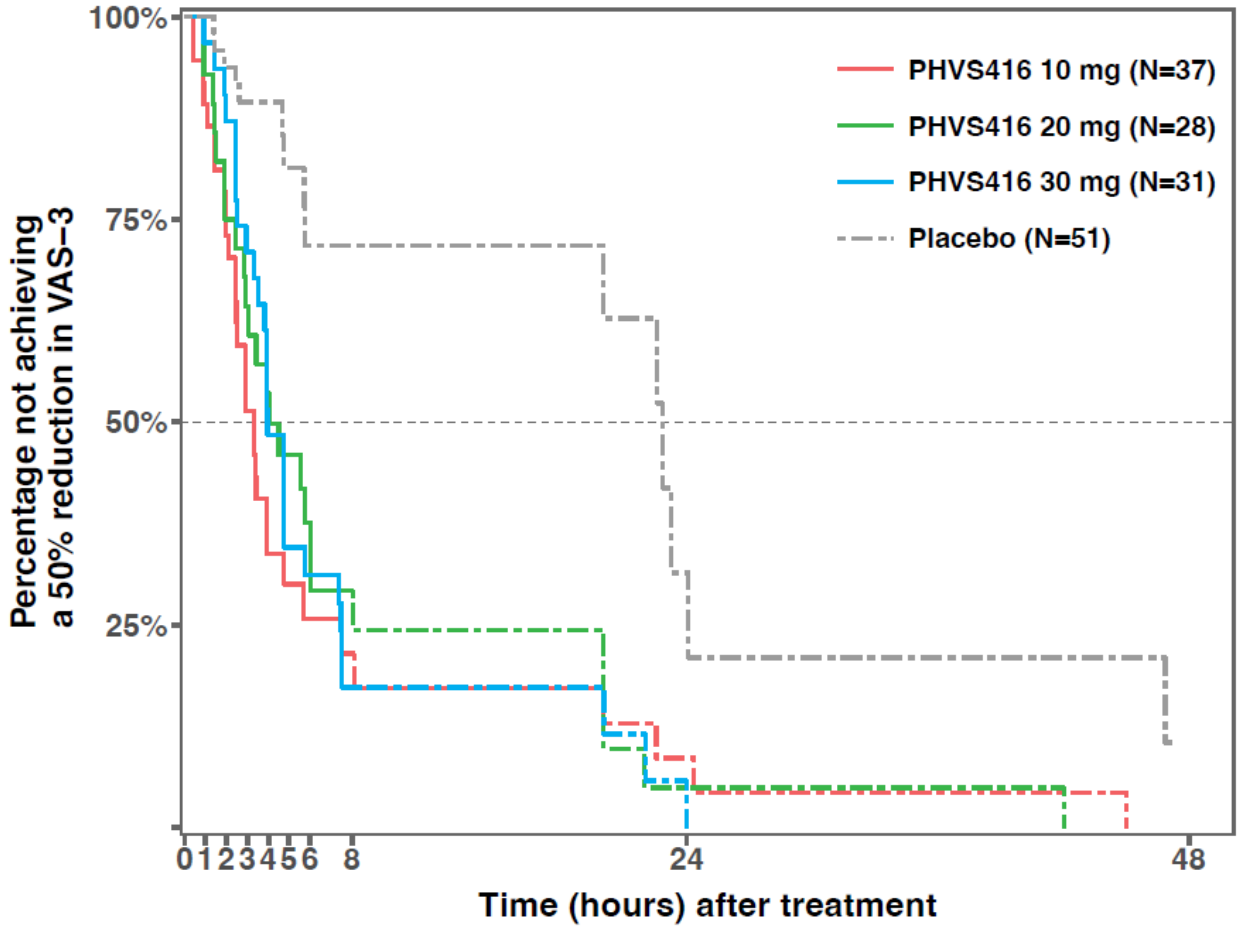


Difference from placebo in change from pre-treatment to 4 h post-treatment, least-squares mean (95% CI)		
PHVS416 10 mg	-16.75 (-21.52, -11.97)	p < 0.0001†
PHVS416 20 mg	-15.02 (-20.22, -9.81)	p < 0.0001
PHVS416 30 mg	-16.28 (-21.27, -11.29)	p < 0.0001
Combined PHVS416	-16.08 (-19.87, -12.29)	

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

†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. Attacks in mITT Analysis Set refer to attacks treated with blinded study drug that had non-missing VAS result at pre-treatment and ≥1 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 results are based on post-hoc analysis using a similar MMRM with all three active doses combined vs placebo.

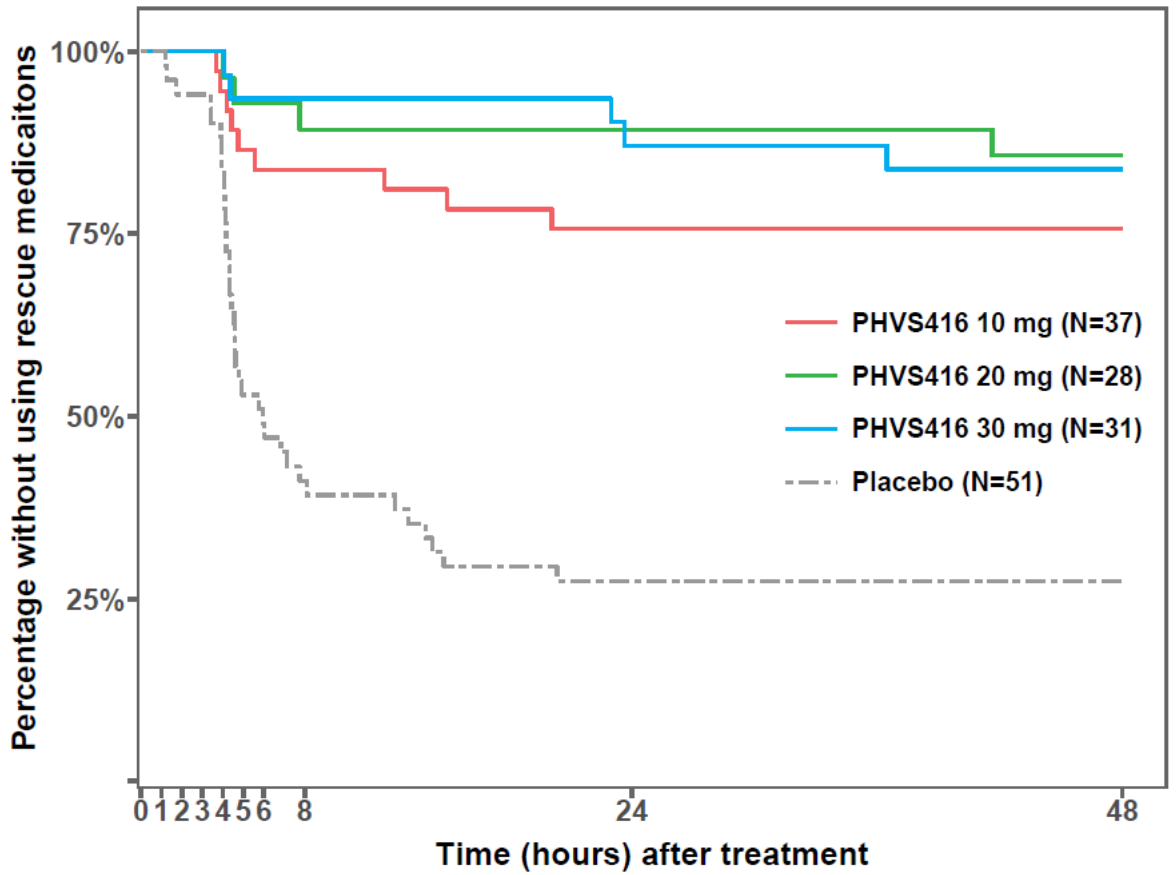
PHVS416 significantly reduced time to ≥50% reduction in VAS-3

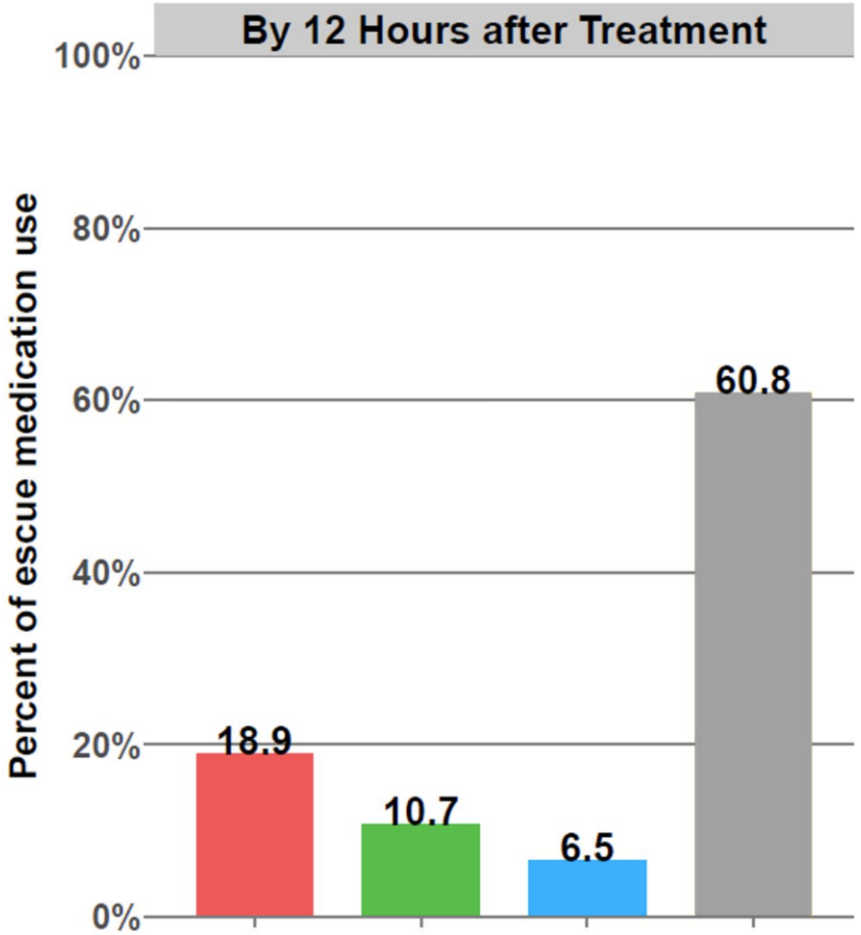


Median time in hours (95% CI)		
Placebo	22.8 (20.0, 24.1)	
PHVS416 10 mg	3.3 (2.4, 3.9)	p < 0.0001
PHVS416 20 mg	4.0 (2.9, 6.0)	p = 0.0003
PHVS416 30 mg	4.0 (3.3, 5.8)	p < 0.0001
Combined PHVS416	3.9 (3.0, 4.8)	

CI: Confidence interval. VAS: Visual Analogue Scale. Median time based on Kaplan-Meier estimates. p-values based on a marginal Cox proportional hazards model (CPHM) with a robust variance-covariance estimator to account for the within-patient correlation. The model includes treatment, attack, and pre-treatment VAS-3 score as independent variable. The Combined PHVS416 results are based on post-hoc analysis.

PHVS416-treated patients used substantially less rescue medication





PHVS416 was generally well-tolerated at all doses

- No treatment-related SAEs or AEs of severe severity
- No AEs leading to treatment discontinuation
- No treatment-related AEs of laboratory parameters, vital signs, or ECG parameters
- Few treatment-related AEs reported within 48 h after administration of study drug

	Part I (Non-Attack)			Part II (Attack 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
Subjects (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%)	-	-	-

AE: adverse event. ECG: electrocardiogram. SAE: serious adverse event.
N: number of subjects (Part I) or number of attacks (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.

Conclusions

- A total of 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 included in efficacy evaluation
- The primary endpoint and all key secondary endpoints were met
- PHVS416 demonstrated rapid onset of action, symptom relief, and resolution of HAE attacks
- PHVS416 substantially reduced the use of rescue medications
- PHVS416 was well-tolerated at all dose levels
  - There were no treatment-related SAEs, no treatment-related AEs of severe severity, and no AEs leading to treatment discontinuation

RAPIDe-1 trial results support further development of PHVS416 as a potential on-demand treatment for HAE attacks

AE: adverse event. HAE: hereditary angioedema. SAE: serious adverse event.