PHARVARIS

Development of PHA121 for On-Demand and Prophylactic Treatment of HAE

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Conflict of interest

C. Gibson: employee of AnalytiCon Discovery GmbH and consultant to Pharvaris, holds stock options in Pharvaris

A. Lesage: consultant to Pharvaris, holds stocks/stock options in Pharvaris

J. Knolle: consultant to Pharvaris, holds stocks/stock options in Pharvaris

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R. Crabbé: employee of RC Consultancy and consultant to Pharvaris, holds stocks in Pharvaris

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

G. Giannattasio (presenter): employee of Pharvaris, holds stocks in Pharvaris

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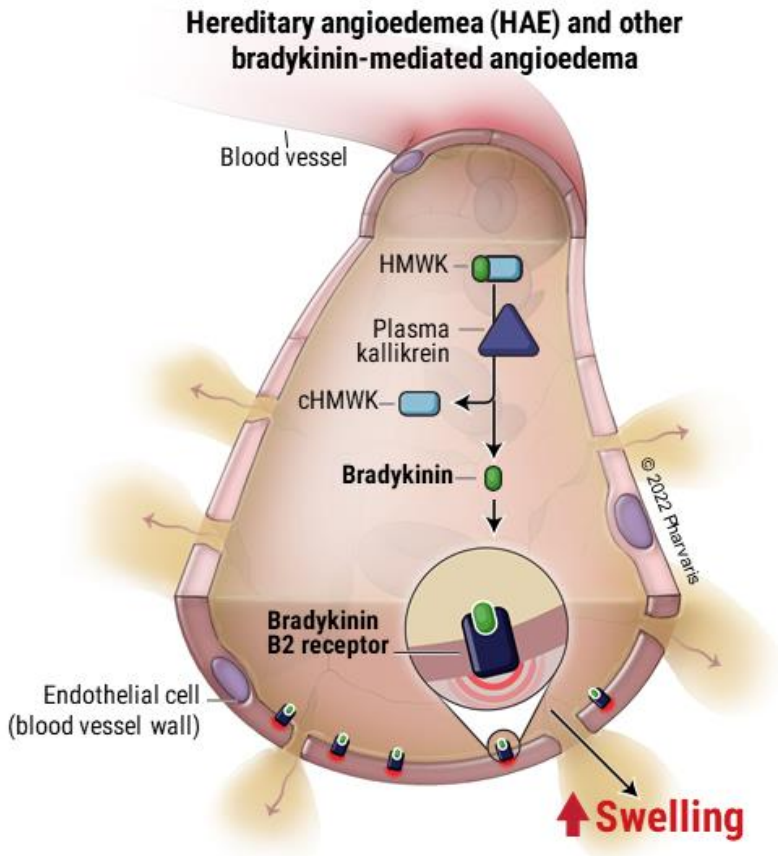
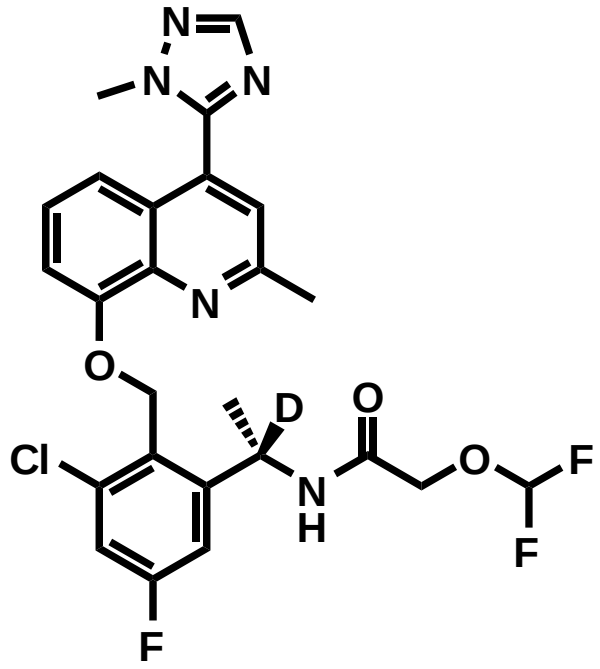
Hereditary angioedema (HAE) is a bradykinin-mediated condition with unmet medical needs



- Excess bradykinin is the cause of signs and symptoms of swelling during HAE attacks[1]
- Efficacy and tolerability of bradykinin B2 receptor antagonism for treatment of HAE attacks has been proven in clinical trials and >10 years of post-marketing experience[2-4]
- Despite availability of various options for treatment and prevention of HAE attacks, there are people with HAE continuing to have unmet needs with regards to efficacy, tolerability, and administration preferences[5-7]

[1]Busse PJ et al. N Engl J Med 2020; [2]Cicardi M et al. N Engl J Med 2010; [3]Lumry WR et al. Ann Allergy Asthma Immunol 2011; [4]Maurer M et al. Clin Exp Allergy 2022; [5]The Voice of the Patient – Hereditary Angioedema, FDA, Report May 2018; [6]Geba D et al. J Drug Assess 2021; [7]Bouillet L et al. Allergy Asthma Proc 2022.

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

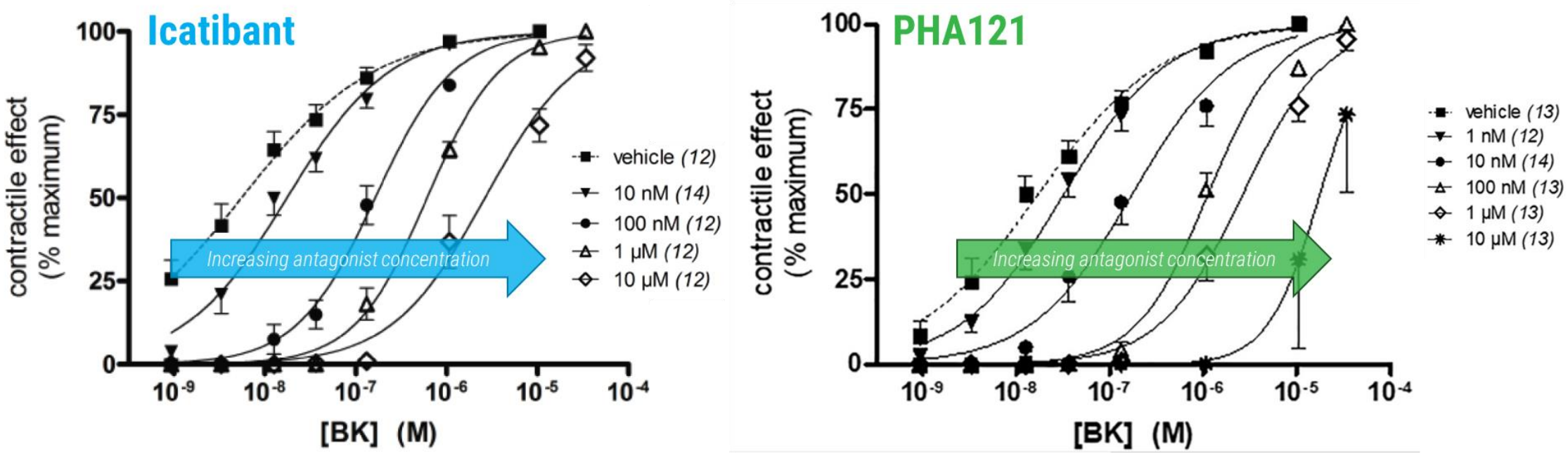


- First orally bioavailable bradykinin B2 receptor antagonist
- Highly potent and selective B2 receptor antagonist
- 2.4-fold lower molecular weight than icatibant
- Metabolic soft spot has been stabilized by the introduction of a deuterium atom
- Optimized for metabolic stability and exposure in humans

Lesage A et al. Front Pharmacol 2020; Lesage A et al. Int Immunopharmacol 2022.

PHA121 is a potent, competitive inhibitor of human bradykinin B2 receptor

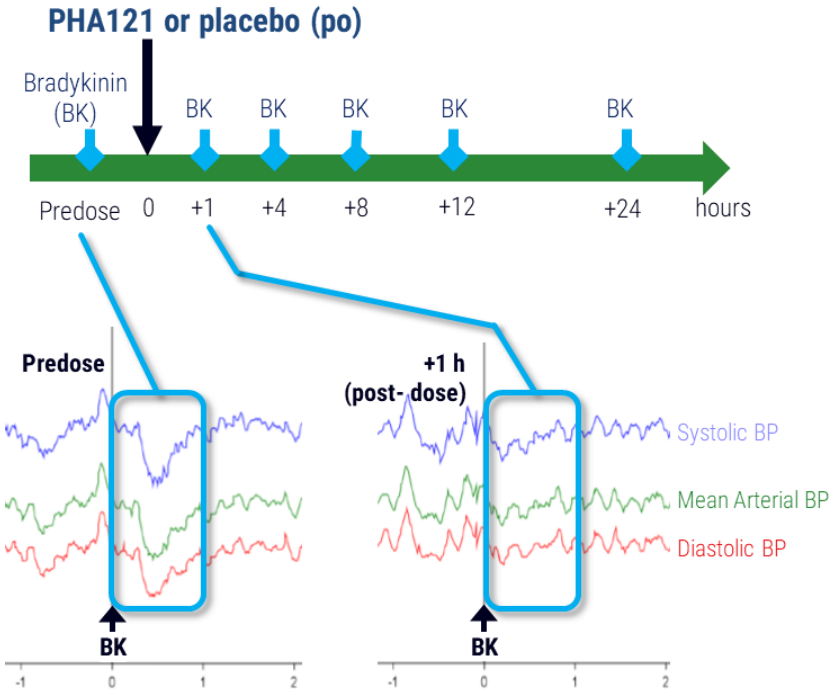
Competitive antagonism of bradykinin-induced contraction
(*ex-vivo* human umbilical vein preparation)



PHA121 is 25-fold more potent than icatibant at the endogenous human B2 receptor

Lesage A et al. Front Pharmacol 2020; Lesage A et al. Int Immunopharmacol 2022.

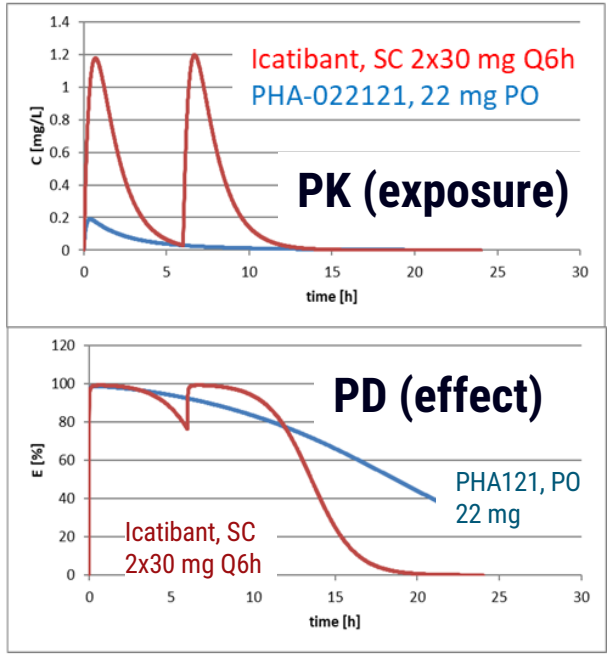
In healthy volunteers, oral pre-treatment with PHA121 inhibits bradykinin-induced hemodynamic changes



PK/PD modeled using a nonlinear mixed-effect E_{max} model comparing effect (inhibition of the baseline, average-to-peak) to PK (two-compartment model, first-order oral absorption)

EC_{50} (ng/mL)	2.4
EC_{85} (ng/mL)	13.8

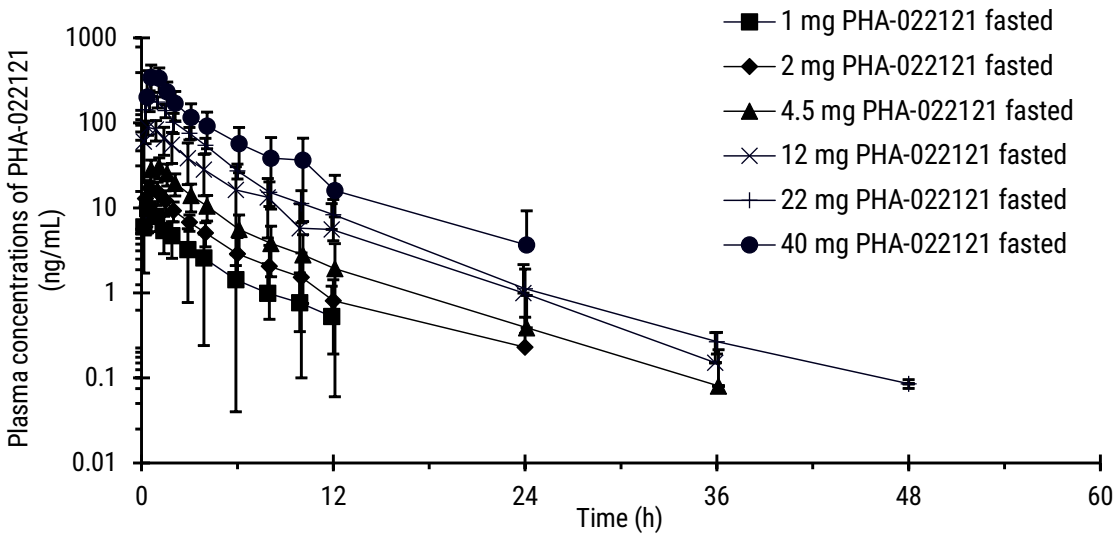
Potency ~4x higher than icatibant (published data)



A single PHA121 dose is predicted to provide similar PD effect as two sequential injections of icatibant

Lesage A et al. AAAAI 2020; Derendorf H et al. ACAAI 2020; Center for Drug Evaluation and Research, Application number: 022150Orig1s000 (NDA: 22-150, product: icatibant) accessed at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022150Orig1s000ClinPharmR.pdf.

PHA121 was well tolerated in Phase 1 SAD and MAD trials



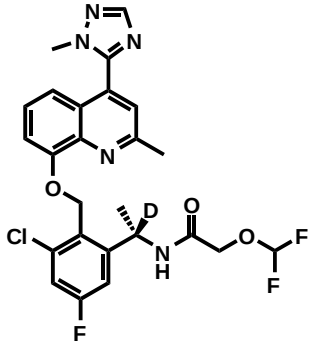
- **Approximately dose-proportional PK** with single and multiple oral doses
- **Half-life approximately 3.4-5.6 hours** (approximately three-fold longer than icatibant)

PHA121 (oral solution)

- No clinically significant changes were observed for physical exams, vitals, ECG, and safety lab assessments
- No SAEs or severe AEs were reported with no treatment discontinuations
- Most AEs observed were of mild severity
- Total incidence of AEs was similar between active and placebo groups
- No clear differences for AE patterns between different dosing regimens vs. placebo

MAD, multiple ascending dose; SAD, single ascending dose.
Lu P et al. ACAAI 2020; Crabbé R et al. AAAAI 2021.

Development of two oral products utilizing PHA121 as active ingredient for on-demand and prophylactic treatment of HAE attacks

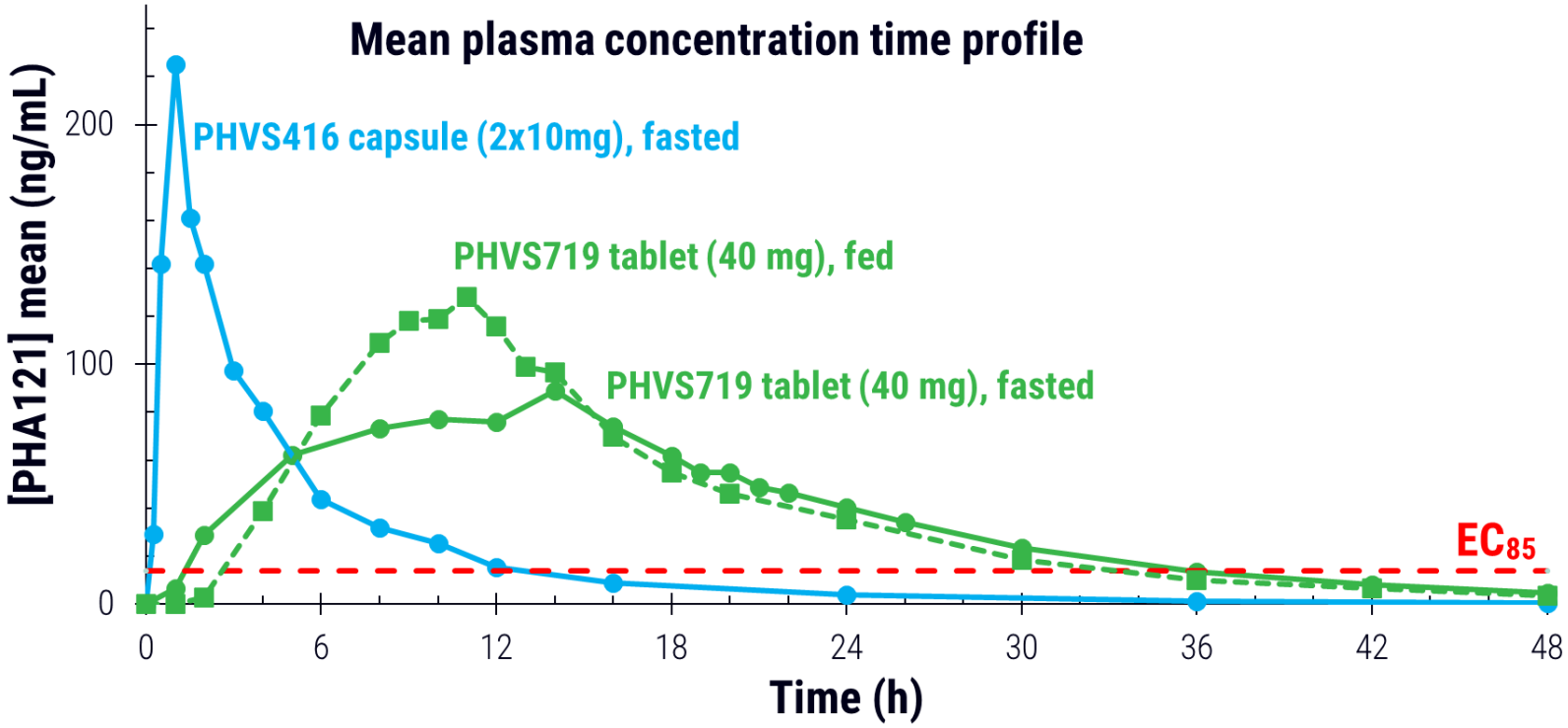


PHVS416

Softgel capsule formulation
(rapid absorption in the stomach)

PHVS719

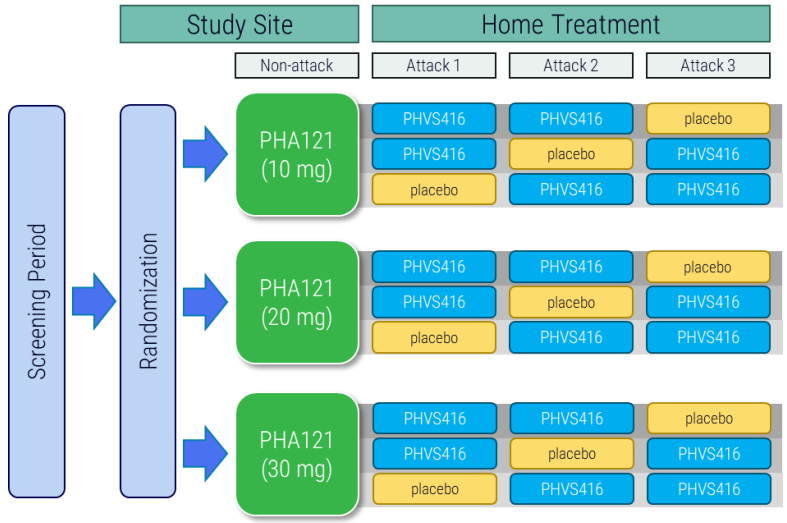
Extended-release tablet formulation
(colonic absorption)



Lesage A et al. KININ 2022.

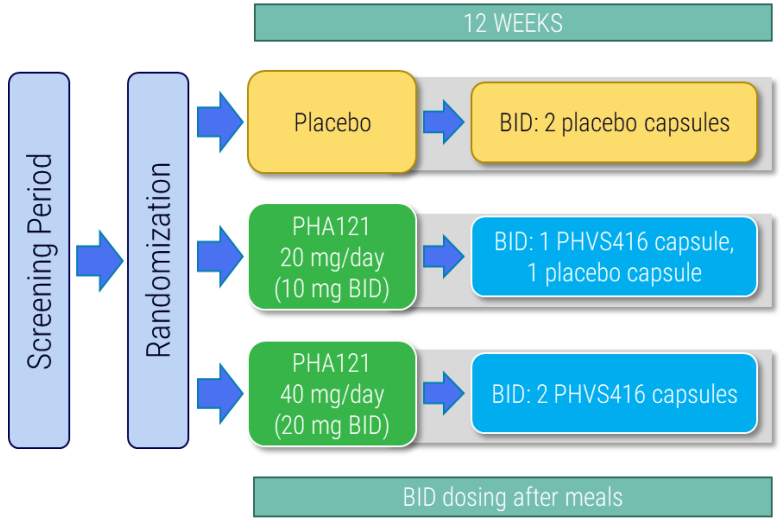
Ongoing* Phase 2 trials of PHA121 (PHVS416) for on-demand and prophylaxis treatment of type I and II HAE attacks

RAPIDe-1 trial (on-demand)



- Primary objective (endpoint): HAE symptom relief (ΔVAS-3 at 4hr post-dose)
- Enrolment target (n=72 patients) achieved
- Continued monitoring of attacks in enrolled patients in countries outside the U.S.*

CHAPTER-1 trial (prophylaxis)



- Primary objective (endpoint): prevention of HAE attacks (number of investigator-confirmed HAE attacks)
- Enrolment target (n=30 patients)
- Continuing in countries outside the U.S.*

*The FDA has placed a clinical hold on the clinical trials of PHA121 in the U.S. Regulators in ex-US countries have been notified of U.S. clinical hold. https://clinicaltrials.gov/ct2/show/NCT04618211; https://clinicaltrials.gov/ct2/show/NCT05047185.

Summary

- PHA121 is an investigational orally bioavailable bradykinin B2 receptor antagonist shown to be more potent, and is predicted to have longer pharmacodynamic effects, than approved icatibant
- In our clinical studies to date, single and multiple doses of PHA121 were well tolerated in humans
- Two formulations of PHA121, designed to provide specific pharmacological characteristics suitable for on-demand and prophylactic use, are currently being investigated* for hereditary angioedema
- Two Phase 2 trials of PHA121 (PHVS416 formulation) for treatment and prevention of type I and II HAE attacks are currently ongoing*

Pharvaris thanks all people with HAE
who have participated in ongoing clinical trials* of PHA121
as well as all study Sites' Investigators and Staff

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