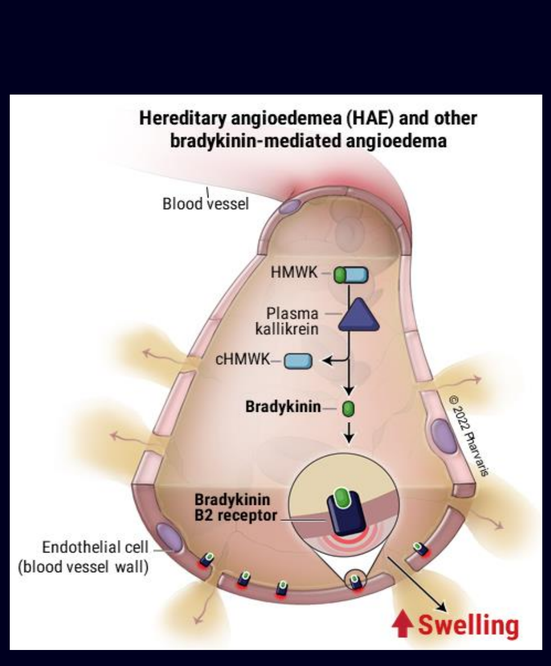
Development of two novel oral formulations of a first-in-class bradykinin B2 receptor antagonist for on-demand and prophylactic treatment of hereditary angioedema

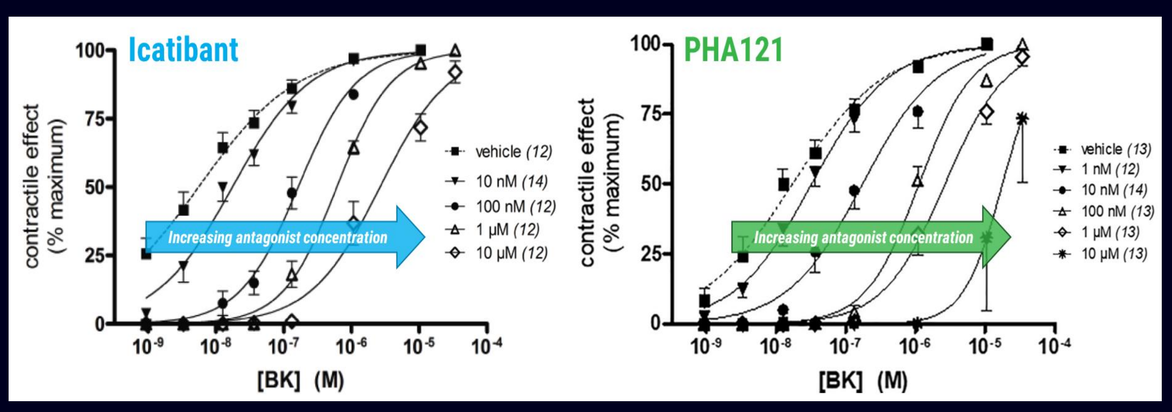
Maurer M.[1,2], Lesage A.[3], Gibson C.[4], Knolle J.[3], Groen K.[5], Crabbé R.[6], Lu P.[7]

[1]Institute of Allergology, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany, [2]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany, [3]Pharvaris GmbH, Zug, Switzerland, [4]AnalytiCon Discovery GmbH, Postdam, Germany, [5]DGr Pharma, Oudenbosch, The Netherlands, [6]RC Consultancy, Bassins, Switzerland, [7]Pharvaris Inc., Lexington, MA, United States of America

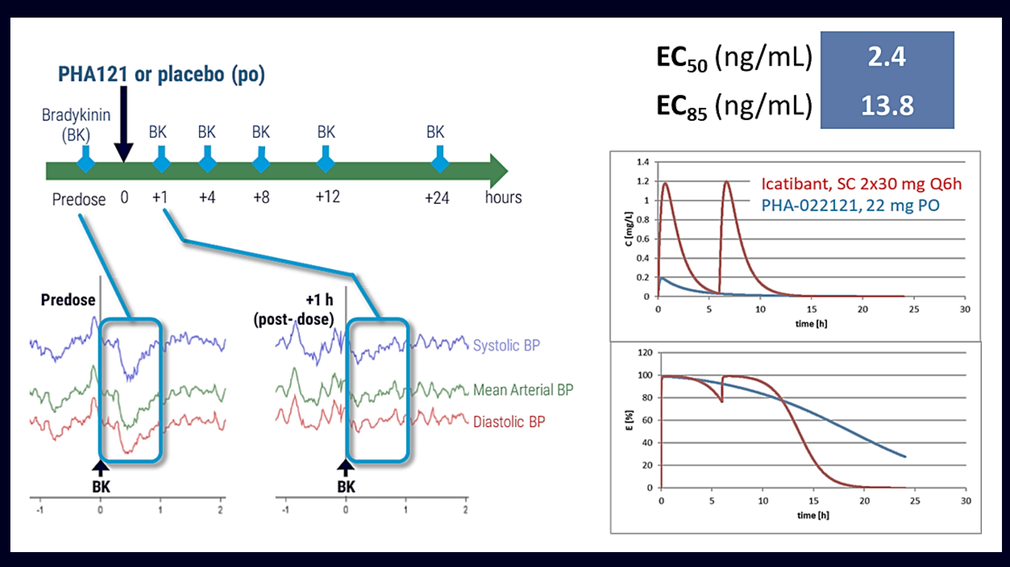
Rationale

Hereditary angioedema (HAE) is a rare and potentially life-threatening condition occurring in approximately 1 in 50,000 people globally[1]. Excess of bradykinin is the cause of clinical signs and symptoms of HAE attacks[2]. The efficacy and tolerability of bradykinin-B2-receptor antagonism for treatment of HAE attacks has been proven in clinical studies and >10 years of experience in real-world practice[3-5]. Despite availability of various options for treatment and prevention of HAE attacks, there are people living with HAE experiencing unmet needs related to treatment efficacy, tolerability, and administration preferences[6-8].





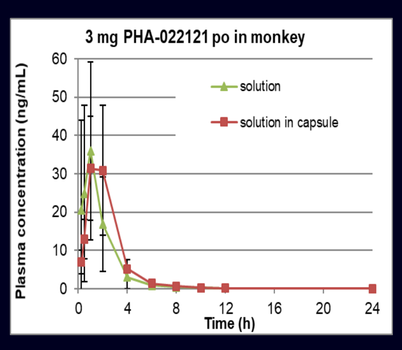
- Preclinical *in-vitro* and *ex-vivo* studies demonstrate that, on a molar basis and considering free plasmatic fraction, PHA121, oral inhibitor of bradykinin B2 receptor and active ingredient in PHVS416 and PHVS719, is 20-25-fold more potent than icatibant at competing with the endogenous human B2 receptor[9,10].
- PHA121 inhibited effects of increasing concentrations of bradykinin with higher potency than icatibant in an *ex-vivo* model of a human umbilical vein preparation, measured as vein contraction in a dose-concentration manner[9,10].

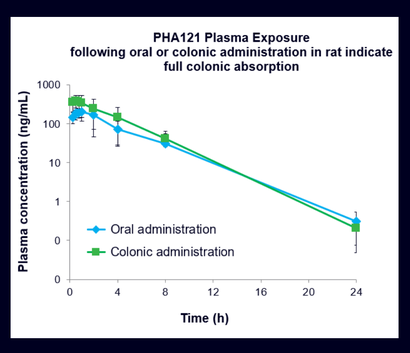


- In an *in vivo* bradykinin challenge study in humans oral PHA121 effectively inhibited effects of bradykinin with higher potency and longer estimated duration than subcutaneous icatibant[11-12].
- Healthy volunteers received intravenous bradykinin before and at different time points after treatment with oral PHA121 or placebo. PHA121 inhibited bradykinin-mediated drop (~20 mmHg) in blood pressure, with ~4-fold higher potency than icatibant[13] (estimated EC_{85}: 13.8 ng/ml).
- Effects of 1 dose of oral PHA121 were predicted to have a duration comparable to that of 2 sequential doses of subcutaneous icatibant[13].

Methods

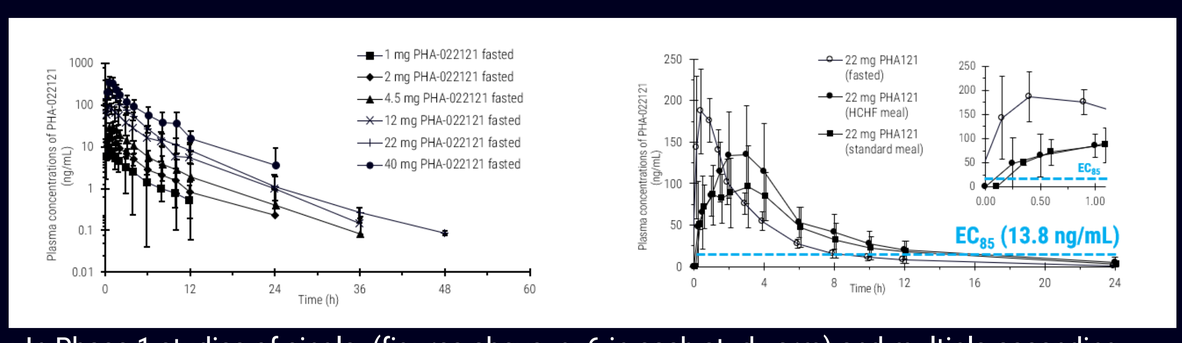
Oral bioavailability (extent of absorption) of PHA121 in oral solution was evaluated in a Phase 1 study and equivalence with PHVS416 exposure was assessed in preclinical and clinical studies. PHVS719 exposure was assessed in a Phase 1 study.



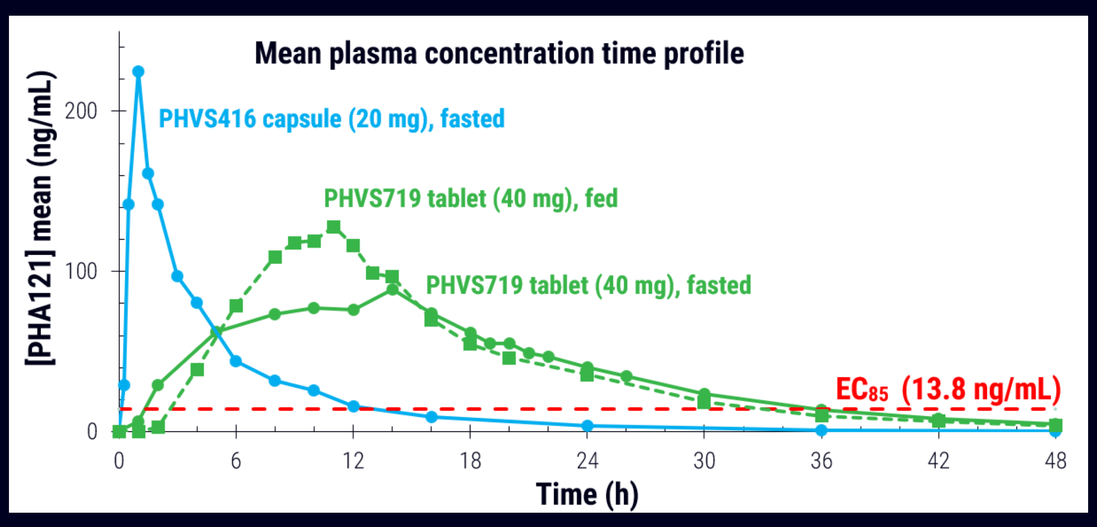


- Preclinical data showed that exposure of PHA121 in oral solution or in capsule formulation are comparable.
- Moreover, additional studies showed that exposures after oral or intracolonic administration of PHA121 are comparable demonstrating that PHA121 is highly absorbed in the gut.

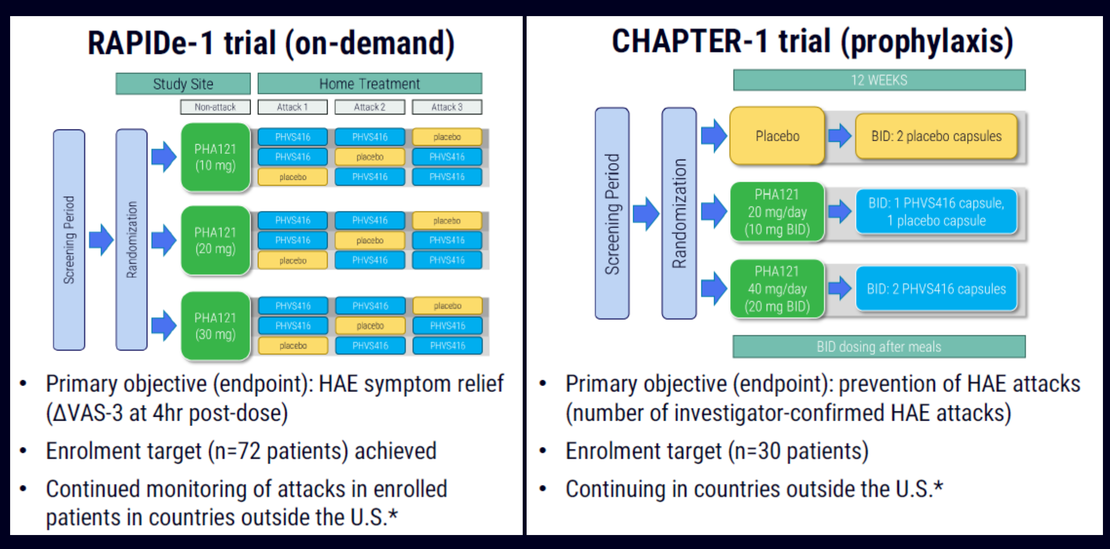
Results



- In Phase 1 studies of single- (figures above, n=6 in each study arm) and multiple-ascending doses of PHA121 in healthy volunteers, therapeutic exposure (EC_{85}) was reached within 30 minutes after dosing, in both fast and fed conditions.
- A single dose of PHA121 had a plasma half-life of ~3.4 to 5.6 hours, which is about 3-fold longer than the plasma half-life of icatibant[14].
- In Phase 1 studies of PHA121, no clinically significant changes were observed for physical exams, vital signs, electrocardiogram (ECG), and safety laboratory assessments. Most adverse events (AEs) reported were of mild severity and no severe AEs, serious AEs, or treatment discontinuations were reported. Total incidence and patterns of AEs were similar between groups of participants treated with PHA121 or placebo.



- Two formulations of PHA121 are under development for HAE: PHVS416 is PHA121 in softgel capsule and PHVS719 is PHA121 in extended-release tablet.
- PHVS416 meets intended attributes for oral on-demand treatment of HAE attacks with fast absorption: upon administration of a single dose of PHVS416 softgel capsule 20mg, therapeutic exposure (EC_{85}) is reached within 30 minutes and remains above therapeutic exposure for ~12 hours.
- PHVS719 meets intended attributes for prophylactic treatment to prevent HAE attacks: upon administration of a single dose of PHVS719 extended release tablet 40 mg, therapeutic exposure is reached within few hours and is sustained for >24 hours.



- 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.*

- 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.*

Efficacy and safety of PHA121 for treatment and prevention of HAE attacks are currently being explored in the RAPIDe-1 and CHAPTER-1 clinical trials*, respectively[15-16].

Conclusions

- In clinical trials, PHA121 is a potent orally available bradykinin B2 receptor antagonist.
- At the dose administered, PHVS416 has shown a rapid onset of action and a duration of exposure predicted to be comparable to two icatibant doses. PHVS719 has shown full coverage of the anticipated therapeutic exposure for 24h, supporting once-daily dosing for prophylaxis.
- Efficacy and safety of PHA121 for treatment of HAE, respectively, are being explored in ongoing clinical trials*.
- Pharvaris thanks all people with HAE who have participated in ongoing clinical trials* of PHA121 as well as all study Sites' Investigators and Staff.

*The FDA has placed a clinical hold on the clinical trials of PHA121 in the U.S. Regulators in ex-U.S. countries have been notified of U.S. clinical hold. Visit https://ir.pharvaris.com/ for the latest information and updates.

Disclosures

In relation to this presentation, the authors declare the following conflicts of interest:
MM: received research grant support and/or speaker/consultancy fees from Adverum, Attune, BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, and Takeda/Shire. AL: consultant to Pharvaris, holds stocks/stock options in Pharvaris. Advisor to Kosa Pharma, holds stocks in Kosa Pharma. CG: employee of AnalytiCon Discovery GmbH and consultant to Pharvaris, holds stock options in Pharvaris. JK:consultant to Pharvaris, holds stocks/stock options in Pharvaris. KG: employee of DGr Pharma and consultant to Pharvaris. RC: employee of CG Consultancy and consultant to Pharvaris, holds stocks in Pharvaris. PL: employee of Pharvaris, holds stock options in Pharvaris.

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