Development of PHVS719: an Oral Extended-Release Bradykinin B2 Receptor Antagonist to Prevent Hereditary Angioedema Attacks

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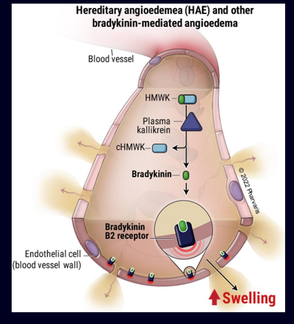
Introduction



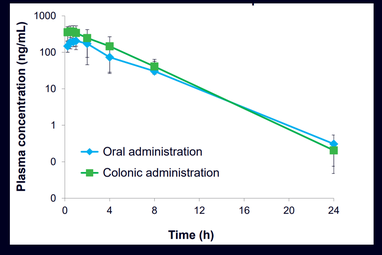
- Excess bradykinin is the cause of clinical signs and symptoms of hereditary angioedema (HAE) attacks[1].
- Efficacy and tolerability of bradykinin-B2-receptor antagonism for treatment of HAE attacks were proven in clinical studies and confirmed in >10 years of experience in real-world practice[2-4].
- PHA-022121 (PHA121) is a novel, orally-available bradykinin B2 receptor antagonist that is 20-25-fold more potent than icatibant at competing with bradykinin at the endogenous human B2 receptor, as evaluated in *in vitro* and *ex vivo* preclinical studies[5,6].
- In an *in vivo* bradykinin challenge study in humans oral PHA121 inhibited effects of bradykinin with higher potency and longer estimated duration than subcutaneous icatibant[7,8].
- PHA121 is being developed in two formulations specifically designed to meet the requirements for oral on-demand treatment of HAE attacks (PHVS416), as well as for oral prophylactic treatment to prevent HAE attacks (PHVS719)[9].

Methods

- Colonic absorption of PHA121 was investigated in rats receiving a single dose of 2 mg/kg PHA-121 either by oral gavage or intracolonic administration via a catheter surgically implanted into the ascending colon.
- Mass balance and absolute bioavailability in humans were assessed in an open-label, single-dose mass balance study with a microtracer dose of ^{14}C-PHA-022121 in healthy subjects.
- An *in vitro* dissolution experiment was conducted with PHVS719 in conditions mimicking fasted and fed gastrointestinal environments to measure dissolution of the active ingredient, PHA121, over time
- Pharmacokinetics of an extended-release (XR) formulation of PHA121 (PHVS719) under fasting or fed conditions was evaluated in an open-label, single-dose, randomized, five-period, five-sequence, crossover, explorative Phase 1 study[10].

Results

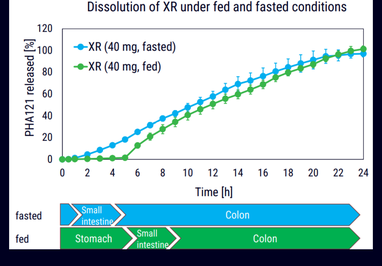
- Direct intracolonic dosing of PHA121 resulted in a good systemic exposure to PHA121, comparable to that observed after oral administration, thus confirming the colonic absorption.



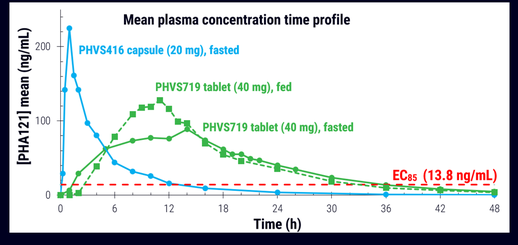
- In humans, absolute availability of PHA121 after oral administration was 57%, with approximately 3.2% of PHA121 excreted via feces.

Single dose mass balance study with PHA121 in human	Excretion of PHA121, recovery over 72 h in %		Oral bioavailability, Fpo
	Urine	Feces	
	0.09	3.2	57%

- An *in vitro* dissolution experiment conducted with PHVS719 in conditions mimicking fasted and fed gastrointestinal environments showed a linear dissolution of PHA121 over time.



- Administration of PHVS416 resulted in rapid clinically relevant exposure of PHA121 above EC_{85} (13.8 ng/ml) within 30 minutes. Administration of PHVS719 40 mg under fasted conditions yielded exposure EC_{85} by ~2 hours and maintained it for ≥30 hours. The overall exposure was not affected by food.
- The 24-hour area-under-the-curve (AUC_{24h}) exposure of PHA121 after 1 dose of PHVS719 40 mg is comparable to that observed in Phase 1 studies with PHVS416 soft capsules dosed 20 mg bid with food.



Conclusions

- PHVS719, the extended-release formulation of PHA121, meets the required characteristics for prophylactic treatment to prevent HAE attacks.
- The almost complete colonic absorption of PHA121 results into durable therapeutic exposure for ≥24 hours, supporting once-daily dosing for prophylaxis.
- The safety and efficacy of PHA121 as active ingredient for the prevention of HAE attacks are being evaluated in the Phase 2 CHAPTER-1 proof-of-concept clinical trial* (PHVS416 formulation, bid)[11].

*The FDA has placed a clinical hold on the clinical trials of PHA121[11,12] 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.

References

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