PHA-022121, a First in Class Oral Bradykinin B2 Receptor Antagonist in Clinical Development: Proof of Concept Study in a Translational Monkey Bradykinin Challenge Model

Rationale

Pharvaris is developing PHA-022121 as a first-in-class novel small-molecule antagonist of the B2 receptor, for oral on-demand treatment and prevention of hereditary angioedema attacks. The objective of the translational study was to investigate whether PHA-022121 was able to attenuate blood pressure changes induced by intravenous bradykinin (BK) injection. Icatibant had shown efficacy in a bradykinin challenge study in healthy volunteers, and this model is here back-translated to the monkey.

Methods

We developed, for the first time, a bradykinin challenge model in conscious cynomolgus monkey. We validated the model using the reference icatibant, a marketed B2-receptor antagonist with a similar mode of action to the investigational compound. The study was conducted using telemetry for blood pressure recording, and a remote-control infusion pump for intravenous delivery of bradykinin. In an initial part of the study, the individual bradykinin dose was identified for each animal.

Results and Conclusions

- The model was validated by the efficacy using icatibant.
- We found that both icatibant and PHA-022121 potently inhibit bradykinin-induced blood pressure changes in freely moving monkeys.
- PHA-022121 inhibited the BK-induced changes in blood pressure at all doses tested (0.1, 0.3, 1, 3 and 10 mg/kg given orally) already at 1 hour after administration.
- The duration of the effect was dose-dependent.
- The bradykinin challenge model was back-translated from healthy volunteers to monkeys.
- Pharvaris will next explore the activity of PHA-022121 in a bradykinin challenge model in healthy volunteers. These human data will help the dose selection for phase 2 clinical studies.

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Study Design

Test compound or vehicle (icatibant sc or PHA-022121 po)

Icatibant Inhibition of BK-induced Change in MABP in Monkey

- Modelled after icatibant bradykinin (BK) challenge in healthy volunteers (POC Phase I study)
- Mean arterial blood pressure (MABP) was measured
- Criteria for BK-induced MABP change: a transient drop of 20-40 mmHg
- An individualized bradykinin dose was administered (pretest challenge 1) and adjusted if required (pretest challenge 2)
- The bradykinin challenge was repeated every hour after test compound dosing

Time Course of BK (iv) Challenge

PHA-022121 Inhibition of BK-induced Change in MABP in Monkey

- The monkey dose of icatibant used was equivalent to the human therapeutic dose of 30 mg; a similar 6-hour duration of action was seen in both
- Icatibant showed maximum inhibition at 2 hours after SC dosing
- PHA-022121 showed maximum inhibition at the first timepoint tested (1 hour after PO dosing), demonstrating fast onset of action.

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