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Development of Two Novel Oral Formulations of a First-in-Class Bradykinin B2 Receptor Antagonist for On-Demand and Prophylactic Treatment of Hereditary Angioedema

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Rationale: We aim to develop innovative oral treatment options to meet needs of people with HAE. Studies show that PHA121 is a potent, oral inhibitor of the bradykinin B2 receptor showing longer duration and faster inhibition of bradykinin (BK) effects than icatibant. Two formulations of PHA121 are in development for HAE: a softgel capsule to rapidly relieve symptoms of attacks (PHVS416) and an extended-release (XR) tablet to prevent attacks (PHVS719).

Methods: Oral bioavailability 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.

Results: PHVS416 meets intended attributes for oral on-demand treatment of HAE attacks, with therapeutic exposure achieved within 15 min after dosing and duration of action of a single dose predicted to have pharmacodynamic effects comparable to those of two doses of icatibant. Oral administration of PHA121 resulted into full colonic absorption in rat, supporting feasibility of XR. PHVS719 maintained exposure for >24h in human.

Conclusions: PHA121 is a potent orally available bradykinin B2 receptor antagonist. At the dose administered, PHVS416 shows a fast onset of action and a duration of exposure comparable to two icatibant doses. PHVS719 shows full coverage of the anticipated therapeutic exposure for 24h, supporting once-daily dosing for prophylaxis. Efficacy and safety for on-demand and prophylactic treatment of HAE, respectively, are explored in ongoing clinical trials.