

# Multiple dose administration of PHA-022121, an orally available, bradykinin B2 receptor antagonist is well tolerated and shows a favorable pharmacokinetic profile for prophylactic treatment of HAE

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## Introduction

Bradykinin B2 receptor antagonism has been demonstrated to be effective in treating acute HAE attacks but is currently not available as oral treatment. Inhibition of bradykinin-induced cardiovascular effects in healthy subjects correlates well with efficacy in HAE attacks (1).

PHA-022121 is a novel orally available, highly selective B2 receptor antagonist with superior potency and activity in pharmacological models (2). The single-dose escalation clinical studies have shown that PHA-022121 is an orally available and well tolerated compound with linear pharmacokinetics (PK) (3). In the bradykinin challenge pharmacodynamic (PD) assessment, PHA-022121 demonstrated significant inhibition of bradykinin-induced cardiovascular changes with a mean composite EC<sub>50</sub> of 2.4 ng/mL and EC<sub>85</sub> of 13.8 ng/mL. Further PK/PD analysis indicated that effective bradykinin B2 receptor inhibition can be reached within 15 min after taking PHA-022121 and maintained for at least 12 h, which makes it well suited for development as an oral prophylactic treatment of HAE attacks.

This multiple-dose ascending clinical study is designed to assess safety, tolerability, and PK of different twice daily (BID) dosing regimens of PHA-022121, with administration after standard caloric meals.

## Methods

This study consists of four double-blind, randomized, placebo-controlled, multiple ascending doses in 38 male and female healthy volunteers. PHA-022121 was orally administered after standardized meals at dose levels of 12, 22, 33 and 50 mg BID (12 h interval) for 9 days and a morning dose on Day 10 with safety and PK assessments during treatment and follow-up for 72 h after that last dose. PHA-022121 was administered as an oral solution (same formulation as the single-dose studies).

In the 12, 22, and 33 mg dose cohorts, 8 subjects received active drug and 2 received placebo. In the 50 mg dose cohort, only 8 subjects were recruited (6 active and 2 placebo) due to COVID-19-related constraints in the clinical trial unit.

## Results

### Safety

PHA-022121 was well tolerated up to the highest dose of 50 mg BID. All reported treatment-emergent adverse events (TEAEs) were mild in intensity and resolved completely. The total incidence and type of AEs was comparable between active and placebo groups. Lab safety, vital signs and ECG parameters remained well within normal limits in all subjects.

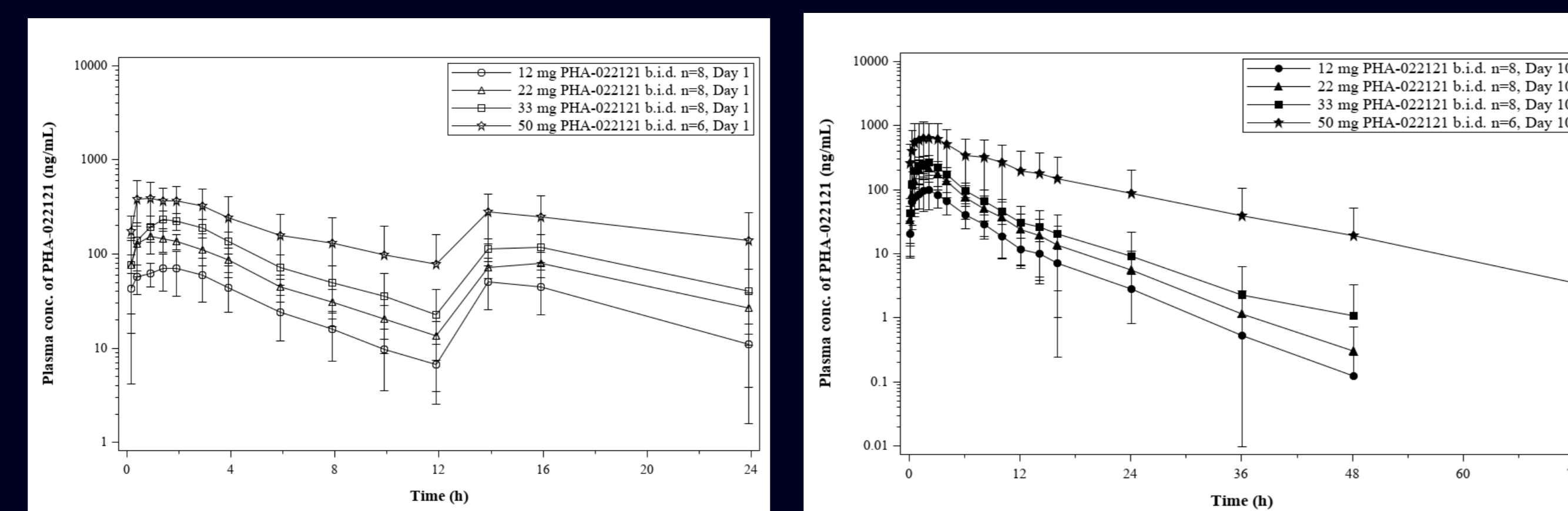
Table 1: Treatment-related TEAEs reported in ≥10 % of study population

System Organ Class (SOC)	Patients n (%)				
	PHA-022121 (12 mg, N=8)	PHA-022121 (22 mg, N=8)	PHA-022121 (33 mg, N=8)	PHA-022121 (50 mg, N=6)	Placebo (N=8)
Overall	3 (37.5%)	4 (50.0%)	4 (50.0%)	4 (66.7%)	5 (62.5%)
Gastrointestinal disorders	2 (25.0%)	0 (0.0%)	2 (25.0%)	4 (66.7%)	4 (50.0%)
Nervous system disorders	2 (25.0%)	3 (37.5%)	2 (25.0%)	2 (33.3%)	2 (25.0%)
Respiratory, thoracic and mediastinal disorders	2 (25.0%)	1 (12.5%)	2 (25.0%)	3 (50.0%)	3 (37.5%)
General disorders and administration site conditions	0 (0.0%)	0 (0.0%)	1 (12.5%)	2 (33.3%)	0 (0.0%)

### Pharmacokinetics

Semi-logarithmic plasma concentration-time curves on Days 1 and 10 are presented in Figure 1, and the derived PK parameters are provided in Table 2. PHA-022121 was well absorbed with median times to reach peak plasma levels within 1.00 to 1.75 h after dosing under fed conditions.

Figure 1: Semi-logarithmic mean (including standard deviation bars) plasma concentration-time profiles of PHA-022121 on Day 1 and Day 10 in healthy adult subjects after administration of oral doses of PHA-022121 (12, 22, 33, and 50 mg) BID under fed conditions



Both on Day 1 and Day 10, plasma exposure of PHA-022121 increased approximately dose-proportionally over the dose range from 12 to 50 mg with a higher interindividual variability observed for the 50 mg dose than for the other dose-levels.

Overall, C<sub>max</sub> and AUC<sub>0-12h</sub> on Day 1 and Day 10 were dose proportional over the investigated dose range of 12 to 50 mg BID PHA-022121 with a mean t<sub>1/2</sub> ranging from 4.8 to 7.3 h after the Day 10 dose.

PHA-022121 was rapidly absorbed and maintained plasma levels above the EC<sub>85</sub> of 13.8 ng/mL through Day 1 even at the lowest dose of 12 mg. Steady-state conditions were generally reached within three days of treatment. At steady state, which was reached within 72 hours, plasma levels remained consistently above the therapeutic threshold (EC<sub>85</sub>) for all doses.

Table 2: Summarized plasma PHA-022121 PK parameters after administration of oral doses of PHA-022121 (12, 22, 33, and 50 mg) BID under fed conditions

PK Parameters [mean ± SD, t <sub>max</sub> : median (range)]	PHA-022121 (12 mg)		PHA-022121 (22 mg)		PHA-022121 (33 mg)		PHA-022121 (50 mg)	
	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
n	8	8	8	8	8	8	6	6
C <sub>max,12h</sub> , ng/mL	79.4 ± 31.5	114 ± 48.4	181 ± 60.6	243 ± 94.5	255 ± 49.4	286 ± 66.3	435 ± 178	693 ± 480
t <sub>max,12h</sub> , h	1.75 (0.25-3.00)	1.49 (0.25-2.00)	1.00 (0.50-3.00)	1.75 (1.00-3.00)	1.51 (0.52-3.00)	1.75 (0.50-3.00)	1.00 (0.50-3.00)	1.75 (1.00-4.00)
AUC <sub>0-12h</sub> , ng.h/mL	382 ± 160	579 ± 226	764 ± 189	1179 ± 549	1124 ± 235	1472 ± 448	2376 ± 1450	4858 ± 3885
C <sub>trough</sub> , ng/mL		20.6 ± 12.0		33.9 ± 20.8		43.1 ± 28.6		257 ± 248
t <sub>1/2</sub> , h		5.06 ± 0.752		4.84 ± 1.14		6.02 ± 2.82		7.26 ± 2.48

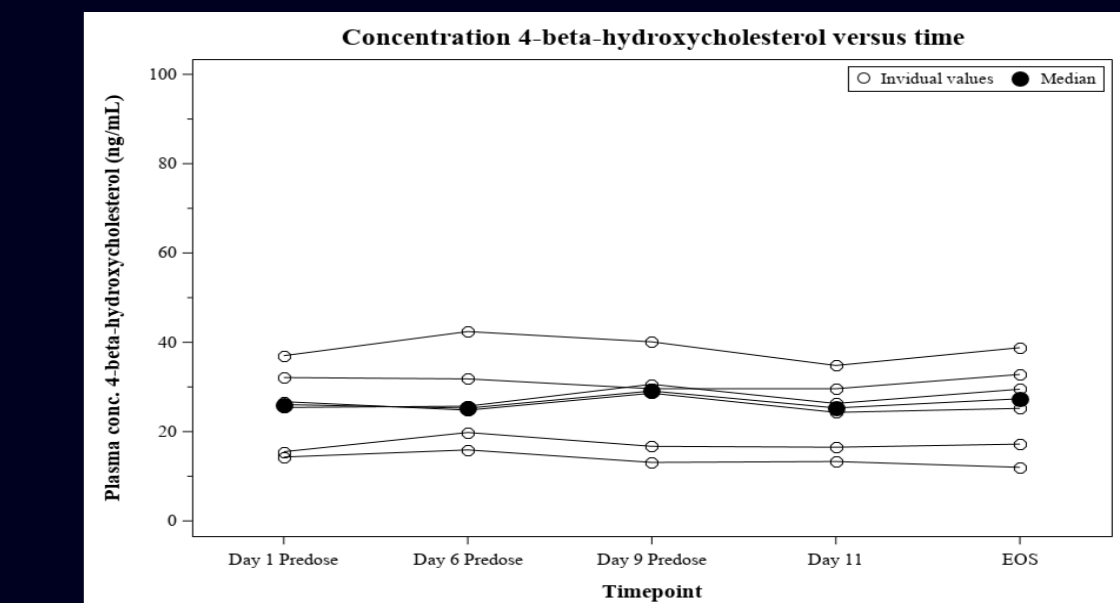
Plasma trough levels at steady state (Day 10) remained well above the EC<sub>85</sub> value of 13.8 ng/mL for all doses tested (Table 2).

Plasma concentrations of 4β-hydroxycholesterol was used as a marker to investigate whether PHA-022121 has an induction or inhibition potential on CYP3A4 activity.

For the cohort receiving 50 mg PHA-022121 BID, the linear individual plasma concentration-time plot for 4β hydroxycholesterol is provided in Figure 2.

After a dosing period of 10 days with any of the PHA-022121 doses, there were no indications for neither an increase nor a decrease in the CYP3A4 activity, based on plasma 4β hydroxycholesterol concentrations.

Figure 2. Scatter of the 4β hydroxycholesterol plasma concentrations at several timepoints after administration of oral doses of 50 mg PHA-022121 BID under fed (0.5 h after a standard meal) conditions in healthy adult subjects.



## Conclusions

- Repeated oral dosing of PHA-022121 in doses up to 50 mg BID was well tolerated with approximately dose-proportional exposure.

- The PK/PD profiles suggest that therapeutic plasma levels of PHA-022121 can be achieved from Day 1 onwards for all dose regimens in the study and steady-state plasma exposure is reached within 72 hours.

- Repeated dosing for 10 days resulted in about 1.0- to 1.6-fold accumulation in C<sub>max</sub>, C<sub>trough</sub>, and AUC for PHA-022121.

- Ten days of BID dosing with PHA-022121 does not lead to an increase or decrease in the CYP3A4 activity.

- All dosing regimens maintain plasma trough levels at steady state that are well above the anticipated EC<sub>85</sub> for clinical efficacy.

- All data support further clinical development of PHA-022121 as a prophylactic treatment for HAE.

## References

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- (2) Lesage AS, Loenders B, Knolle J. 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. JACI 2020; 145: AB346.
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