L23

PHA-022121, a Novel and Potent Bradykinin B2 Receptor Antagonist for Oral Treatment of Hereditary Angioedema

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Introduction

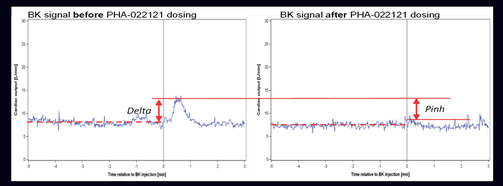
Bradykinin B2 receptor antagonism has been demonstrated to be effective in treating acute HAE attacks but is currently not available as oral treatment. Inhibition of bradykinin-induced cardiovascular effects in healthy subjects correlates well with efficacy in HAE attacks (1).

PHA-022121 is a novel orally available, highly selective B2 receptor antagonist with superior potency and activity in pharmacological models (2).

Methods

PHA-022121 was orally administered in two double-blind, placebo-controlled single ascending dose studies (range 1-50 mg) with pharmacokinetic (PK) and safety follow-up for 72 h. Oral doses of 12 and 22 mg PHA-022121 were evaluated for inhibition of bradykinin-induced cardiovascular effects over time. PHA-022121-mediated pharmacodynamic (PD) effects were evaluated with a nonlinear mixed-effect PK/PD model and compared with historical icatibant data (1).

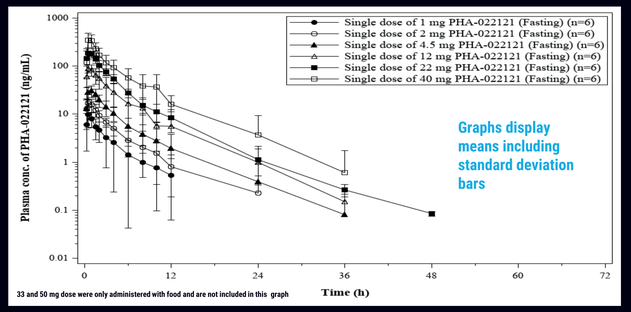
Figure: Instantaneous percent inhibition (Pinh) versus a run-in established bradykinin challenge maximum effect change in cardiac output. The absolute bradykinin challenge effect is also shown (Delta)



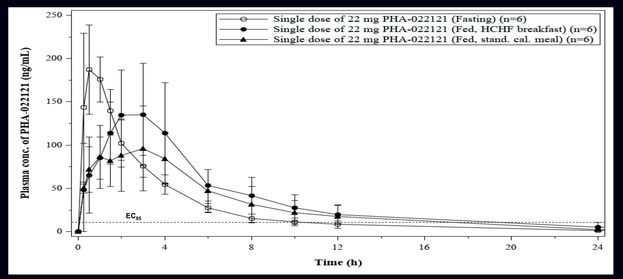
Results

Pharmacokinetics

PHA-022121 was rapidly absorbed and reached peak plasma levels within 30 to 60 min after dosing in all subjects under fasted conditions. The PK profile was dose proportional with a mean $t_{1/2}$ ranging from 3.5 to 5.6 h.

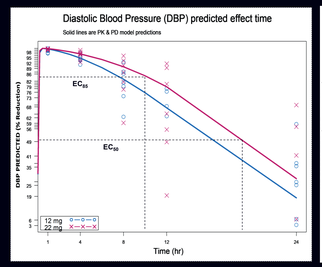


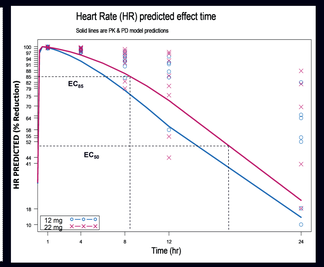
After a 22 mg dose, mean C_{max} of PHA-022121 was 32% lower after a high calorie high fat (HCHF) breakfast and 46% lower after a standard caloric meal (SCM), compared to fasting conditions. Mean AUC_{inf} was 42% higher after a HCHF breakfast mainly caused by one outlier and comparable after SCM (+8%). Median t_{max} of PHA-022121 was delayed by 2.25 h after a HCHF breakfast and by 0.50 h after SCM. Absorption was still fast and plasma levels reached levels that were 4xEC_{85} within 15 min. No consistent gender difference was observed for the PK profile.



PK/PD Modeling

PK/PD analysis showed significant inhibition of bradykinin-induced cardiovascular changes with an average composite EC_{50} of 2.4 and EC_{85} of 13.8 ng/mL. Fifteen minutes after a 12-mg dose in fasting conditions, plasma levels reached 60.3 ng/mL, largely above these therapeutic thresholds. The in vivo PHA-022121 EC_{50} value of 2.4 ng/mL corresponds to a potency of 170 pM (free plasma concentration), consistent with *in vitro* potencies of PHA-022121 (K_b150 pM and 350 pM at recombinant and endogenous human bradykinin B2 receptor).





Quantitative PK/PD modeling indicates that single oral doses of PHA-022121 will maintain pharmacologically active drug levels for a substantially longer time than 30 mg sc icatibant.

Table: Expected 50% confidence level of duration of effect in hours after single oral doses of 10, 20 and 30 mg of PHA-022121 and 30 mg icatibant sc

		PHA-022121			Icatibant
Response	**Effect level**	**10 mg**	**20 mg**	**30 mg**	**30 mg**
Diastolic blood pressure	85%	7.0	9.5	11.5	5.5
	50%	14.5	19.0	21.0	7.5
Mean blood pressure	85%	6.5	9.5	11.0	5.5
	50%	16.0	21.0	23.0	7.5
Heart rate	85%	6.0	9.0	10.5	5.5
	50%	13.0	16.5	19.0	8.0
Cardiac output	85%	8.0	11.0	9.0	-
	50%	16.5	21.0	16.5	-
Cutaneous blood flow	85%	-	-	-	6.0
	50%	-	-	-	8.0

Safety

Adverse events (AEs) were reported by 25% of the subjects in the combined group of all subjects treated with PHA-022121, identical to the 25% incidence with placebo. There was no dose related increase in the incidence of AEs. AEs reported by more than 1 subject after PHA-022121, were headache (6.6% vs 12.5% placebo), nasopharyngitis (3.9% vs 8.3% placebo), nausea (3.9% vs 0% placebo), oropharyngeal pain (3.9% vs 0% placebo), and upper abdominal pain (2.63% vs 0% placebo). All AEs were mild or moderate and subsided rapidly and completely.

No clinically relevant changes in safety laboratory parameters, vital signs and ECG parameters were observed.

n (%)	PHA-022121 (N=76)	Placebo (N=24)
Any AE	19 (25.0%)	6 (25.0%)
AEs in more than 1 subject		
Headache	5 (6.6%)	3 (12.5%)
Nasopharyngitis	3 (3.9%)	2 (8.3%)
Nausea	3 (3.9%)	0
Oropharyngeal pain	3 (3.9%)	0
Upper abdominal pain	2 (2.6%)	0

n and % refer to the number and percentage of subjects

Conclusion

PHA-022121 is an orally available and well tolerated bradykinin B2 receptor antagonist with linear pharmacokinetics. PK/PD analysis indicates that effective bradykinin inhibiting concentrations can be reached within 15 min and maintained for at least 12 h, which makes it well suited for development as a single oral dose treatment of acute HAE attacks.

References

(1) FDA Office of Clinical Pharmacology Review FirazyrR, Application Number 022150Orig1s000 (2011). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022150Orig1s000ChemR.pdf.

(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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