PHA-022121, a Selective Bradykinin-B2-Receptor Antagonist, Is Safe and Shows Rapid Oral Bioavailability in Humans

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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. PHA-022121 is a first-in-class orally bioavailable small molecule, highly selective B2 receptor antagonist with superior potency and pharmacological activity in animal models (1).

Methods

PHA-022121 was administered as oral solution in a double-blind placebo-controlled **single ascending dose** first-in-human study in healthy volunteers:

Dose	Part 1 (PK)	Part 2 (PD #)
1 mg *	N=6	
2 mg *	N=6	
4.5 mg *	N=6	
12 mg *	N=6	N=8
22 mg *	N=6	N=8
22 mg §	N=6	
Placebo	N=12	N=4

* fasted condition
§ after high caloric/high fat (HCHF) breakfast
# pharmacodynamic (PD) results covered in poster P151 (2)

Safety was assessed by physical examination, vital signs, adverse events, safety laboratory and electrocardiogram (ECG) until 72 h post-dosing.

Plasma pharmacokinetic (PK) parameters of PHA-022121 were assessed until 72 h post-dosing.

Results

Pharmacokinetics

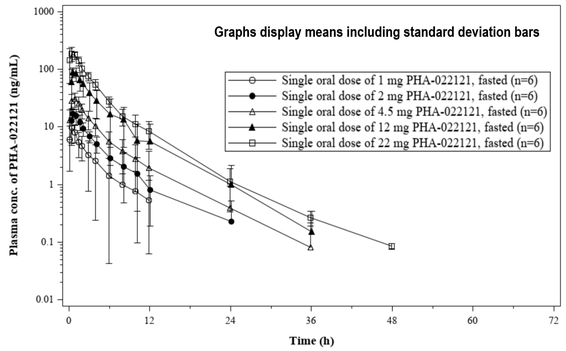
PHA-022121 was very rapidly absorbed and reached peak plasma levels within 30 to 60 minutes after dosing in all subjects under fasted conditions. The systemic exposure was dose proportional with a mean $t_{1/2}$ ranging from 3.5 to 5.6 h between doses.

Plasma levels for PHA-022121 reached therapeutic efficacious threshold concentration (estimated EC_{50} 2.4 ng/mL and EC_{85} 13.8 ng/mL ; see poster P151 (2)) within 15 min for all doses and were maintained for approximately 12 h with doses of 12 and 22 mg.

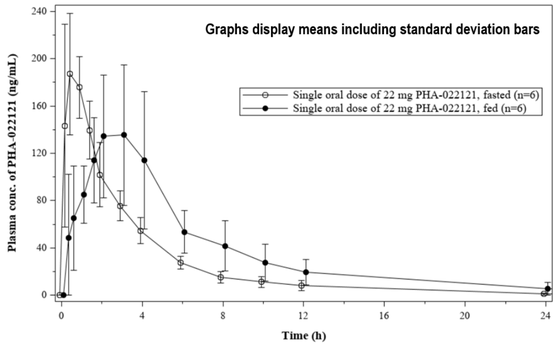
Pharmacokinetics of PHA-022121 #

Dose	1 mg *	2 mg *	4.5 mg *	12 mg *	22 mg *	22 mg §
	N=6	N=6	N=6	N=6	N=6	N=6
C_{max}, ng/mL	11.1 (4.03)	19.8 (3.70)	32.9 (7.66)	97.3 (28.1)	213 (49.5)	145 (56.2)
t_{max}, h	0.50 (0.25-1.00)	0.75 (0.25-1.02)	1.00 (0.50-1.00)	0.50 (0.25-1.00)	0.75 (0.25-1.02)	3.00 (2.00-3.00)
$C_{0.25h}$, ng/mL	5.99 (4.28)	12.9 (8.10)	13.0 (7.00)	60.3 (40.6)	143 (85.9)	48.3 (53.9)
C_{12h}, ng/mL	0.528 (0.670)	0.810 (0.619)	1.93 (1.87)	5.58 (5.66)	8.34 (4.24)	19.6 (10.7)
AUC_{last}, ng.h/mL	33.0 (25.9)	66.0 (27.0)	129 (56.5)	369 (194)	681 (113)	1015 (490)
$t_{1/2}$, h	3.49 (1.32)	4.26 (1.91)	4.36 (1.29)	4.25 (0.831)	5.61 (0.707)	5.31 (1.54)
V_z/F, L	190 (95.7)	181 (34.3)	222 (43.7)	235 (96.3)	252 (30.9)	180 (51.8)
CL/F, L/h	42.3 (25.4)	33.8 (11.9)	37.6 (11.1)	40.9 (20.7)	31.5 (5.60)	25.3 (9.77)

means (standard deviation), median (range) for t_{max} * fasted condition § after HCHF breakfast



Administration of the 22 mg dose with a HCHF breakfast led to a 32% lower C_{max}, a 49% higher AUC_{last}, and a delay of median t_{max} by approximately 2 h. Plasma levels still reach levels that are expected to be therapeutically effective within 15 min and are maintained for more than 12 h.



Safety

All doses up to 22 mg were well tolerated. The total incidence and pattern of (treatment-emergent) adverse events (AEs) was similar between active and placebo groups. In total 17 AEs were reported by 12 out of 52 subjects on active drug versus 7 AEs in 5 out of 16 placebo treated subjects. No serious or severe adverse events occurred. All related adverse events were of mild intensity and resolved rapidly.

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

Dose	1 mg *	2 mg *	4.5 mg *	12 mg *	22 mg *	22 mg §	Placebo
n (%)	N=6	N=6	N=6	N=14	N=14	N=6	N=16
Any AE	2 (33.3%)	1 (16.7%)	1 (16.7%)	5 (35.7%)	2 (14.3%)	1 (16.7%)	5 (31.3%)
Any related AE	0	0	0	2 (14.3%)	1 (7.1%)	0	1 (6.3%)
Any severe AE	0	0	0	0	0	0	0
Any serious AE	0	0	0	0	0	0	0

n and % refer to number and percentage of patients * fasted condition § after HCHF breakfast

Conclusion

PHA-022121 is an orally available and safe bradykinin B2 receptor antagonist that is rapidly absorbed and has dose proportional pharmacokinetics.

The PK/PD profile (2) suggests that a rapid onset of action (< 30 min) and prolonged efficacy (≥ 12 h) with a single dose of PHA-022121 in treatment of acute HAE attacks can be expected.

References

(1) 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.

(2) Derendorf H, Lesage AS, Crabbé R, Lu P, Groen K, Rodriguez M, Leal N, Knolle J. Bradykinin Challenge Provides Surrogate Endpoints For Hereditary Angioedema Treatment Using Bradykinin-B2-Receptor Antagonists. Poster P151 ACAAI Annual Scientific Meeting 2020.