Bradykinin Challenge Provides Surrogate Endpoints For Hereditary Angioedema Treatment Using Bradykinin-B2-Receptor Antagonists

Hartmut Derendorf[1], Anne S Lesage[2], Raf Crabbé[3], Peng Lu[4], Kees Groen[5], Monica Rodriguez[6], Nerea Leal[6], Jochen Knolle[2]

[1] University of Florida, [2] Pharvaris GmbH, [3] RC Consultancy, [4] Pharvaris Inc, [5] DGr Pharma BV, [6] Dynakin S.L.

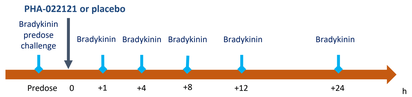
Introduction

The effect of PHA-022121 cardiovascular changes induced by bradykinin (BK) such as blood pressure (systolic, SBP; diastolic, DBP; mean, MAP), heart rate (HR) and cardiac output (CO) was evaluated in a proof-of-concept study in healthy volunteers. PHA-022121 is a new orally active bradykinin-B2-receptor antagonist for the treatment of hereditary angioedema (HAE) (1). Dampened BK-induced effects are closely associated with successful therapeutic outcome for icatibant (2,3), the sole BK antagonist currently available. Although a single subcutaneous (s.c.) injection of icatibant is therapeutically effective, redosing is required in some patients after approximately 6 h coincident with dissipation of BK antagonism (4).

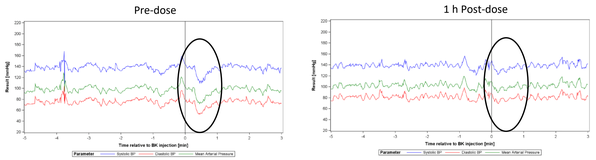
Methods

Bradykinin (BK) Challenge

PHA-022121 (12 and 22 mg) was administered orally (p.o.) to 16 healthy volunteers. Blood samples were drawn over 24 h for pharmacokinetic (PK) analysis. Bradykinin injections were administered to induce cardiovascular responses.



The pharmacodynamic (PD) outcome variables were measured from 5 min before until 5 min after each BK bolus. A % inhibition-of-the-baseline average-to-peak effect was calculated and used as the PD outcome.

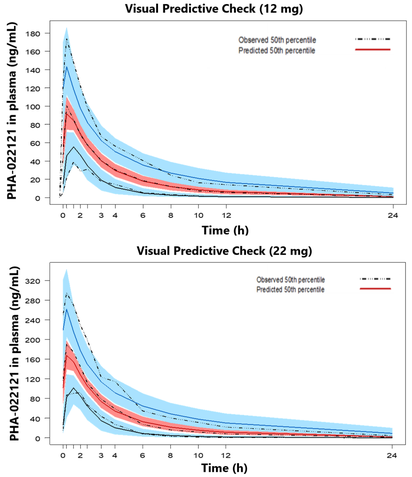


PK/PD Modeling

PHA-022121-induced changes of these BK responses were evaluated with a nonlinear mixed-effect PK/PD model. The results were compared to published results obtained from icatibant (3). PK was analyzed using a two-compartment body model with first-order oral absorption and a lag time. For the PK/PD model a simple E_{max}-model with a direct link was utilized. The PK/PD model was used to simulate PK profiles (N=1000) and calculate probability of durations of effect as well as to visualize effect-time profiles.

Results

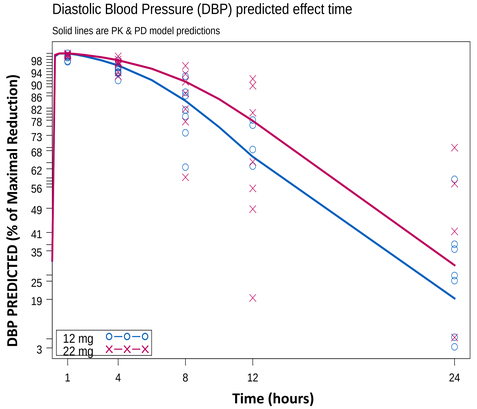
Pharmacokinetics



The dashed lines are the 2.5th, 50th and 97.5th percentiles of the observations. Predicted percentiles (i.e., 2.5th, 50th, and 97.5th, solid lines) with their corresponding 95% confidence intervals (blue and red shaded areas) obtained using N=1000 replicates of the dataset

Population 2-compartment PK model with oral absorption model parameter estimates (CV%) for PHA-022121	
CL/F (L/h)	34.5 (5.9%)
V2/F (L)	101 (4.5%)
Q/F (L/h)	10.7 (15.8%)
V3/F (L)	35.9 (10.7%)
Ka (1/h)	7.97 (25.1%)
Tlag (h)	0.181 (9.9%)
CL/F apparent clearance; V2/F apparent volume for the central compartment; Q/F apparent inter-compartmental clearance; V3/F apparent volume for the peripheral compartment; Ka first order absorption rate constant; Tlag lag time	

PK/PD Modeling



PK/PD parameters for Inhibition of BK challenge by PHA-022121					
	EC_{50} (ng/mL)	CV (%)	EC_{85} (mg/mL)	E_{max} (%)	CV (%)
DBP	2.3	41	13.3	66.8	7
MAP	2.6	20	14.5	73	1
CO	1.7	38	9.5	78.3	2
HR	3.3	45	18.7	76.1	5
CV coefficient of variation; EC_{50} estimated concentration of drug for a half maximal response; EC_{85} estimated concentration of drug for an 85% maximal response; E_{max} maximum response					

- Composite potencies in plasma (EC_{50}) were 2.4 ng/mL for PHA-022121 compared to 9.5 ng/mL for icatibant (3), closely matching respective molar *in vitro* potencies when corrected for MW and protein binding (6,7).
- The composite EC_{85} of PHA-022121 was 13.8 ng/mL.

Comparison of PHA-022121 with Icatibant (3)

Response	Icatibant 30 mg s.c.	PHA-022121 12 mg p.o.	PHA-022121 22 mg p.o.
	Time (h) plasma level above EC_{50} at a 75% confidence level		
DBP	6	11.5	14
MAP	6	12	15.5
HR	6.5	10	13
	Time (h) plasma level above EC_{85} at a 50% confidence level		
DBP	5.5	7.5	10
MAP	5.5	7	10
HR	5.5	6.5	9.5

For the approved dose of 30 mg, icatibant has a 75% probability of being 50% effective for at least 6.5 h and a 50% probability of being 85% effective for 5.5 h. This correlates well with its clinical efficacy (3,4). The table shows that using the same criteria the durations of effect for the investigated doses of PHA-022121 exceed that of 30 mg icatibant s.c. and are approximately twice as long for the higher dose (equivalent to two icatibant injections 6 h apart).

Conclusions

The BK-challenge test allows estimation of therapeutically relevant target concentrations of PHA-022121.

The investigated single oral doses of PHA-022121 (12 and 22 mg) provide equivalent BK-antagonism for a longer time than a 30 mg s.c. icatibant injection.

The longer duration of PHA-022121 effect is expected to be therapeutically relevant, given previous demonstration predicting therapeutic outcome from the BK challenge shown for icatibant.

References

(1) A.S.J. Lesage. B. Loenders, J. Knolle. 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 145: AB346 (2020). https://www.jacionline.org/article/S0091-6749(19)31796-8/fulltext.
(2) K. Leach, B. Rosenkranz, B. J. Bloom, T. G. McCauley. Icatibant Duration of Action During Bradykinin Challenge. JACI 129: AB222 (2012). https://www.jacionline.org/article/S0091-6749(11)02076-8/fulltext.
(3) FDA Office of Clinical Pharmacology Review Firazyr®, Application Number 022150Orig1s000 (2011). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022150Orig1s000ChemR.pdf.
(4) Firazyr®, Prescribing Information, https://www.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf.
(5) P. Lu, A.S.J. Lesage, R. Crabbé, K. Groen. C. Gibson, N. Walther, M. Posch, J. Knolle. PHA-022121, a Selective Bradykinin-B2-Receptor Antagonist, is Safe and Shows Rapid Oral Bioavailability in Humans. . Poster P152 ACAAI Annual Scientific Meeting 2020.
(6) A. Lesage, C. Gibson, F. Marceau, H.D. Ambrosi, J. Saupe, W. Katzer, B. Loenders, X. Charest-Morin, J. Knolle. In Vitro Pharmacological Profile of a New Small Molecule Bradykinin B2 Receptor Antagonist. Frontiers in Pharmacology 11: Article 916 (2020).
(7) A.S.J. Lesage, J. Knolle, F. Marceau, C. Gibson. PHA-022121, the first-in-class orally active bradykinin receptor B2 antagonist for on-demand and prophylactic treatment of HAE. Allergy Asthma Clin Immunol. 15(Supp. 4): 45 (2019).