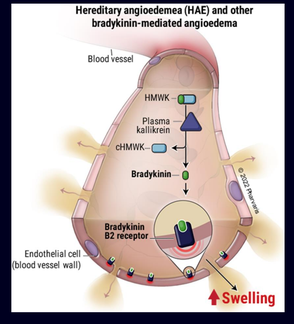
Pharmacokinetics of PHVS719, Extended-Release Tablet Formulation of PHA121, a First-in-Class Oral Human Bradykinin B2-Receptor Antagonist

Groen K.[1], Crabbé R.[2], Knolle J.[3], Gibson C.[4], Lesage A.[3], Lu P.[5]

[1]DGr Pharma, Oudenbosch, The Netherlands, [2]RC Consultancy, Bassins, Switzerland, [3]Pharvaris GmbH, Zug, Switzerland, [4]AnalytiCon Discovery GmbH, Postdam, Germany, [5]Pharvaris Inc., Lexington, MA, United States of America

Introduction



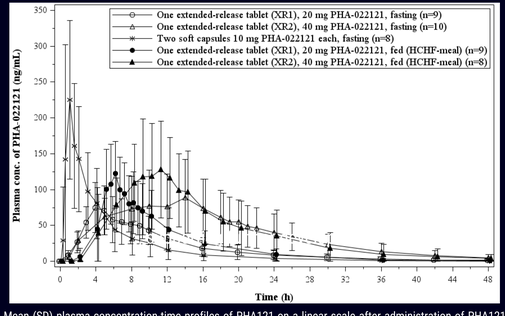
- Excess bradykinin is the cause of clinical signs and symptoms of hereditary angioedema (HAE) attacks[1].
- Efficacy and tolerability of bradykinin-B2-receptor antagonism for treatment of HAE attacks were proven in clinical trials and confirmed in >10 years of experience in real-world practice[2-4].
- PHA-022121 (PHA121) is a novel, orally-available bradykinin B2 receptor antagonist that is 20-25-fold more potent than icatibant at competing with bradykinin at the endogenous human B2 receptor, as evaluated in *in vitro* and *ex vivo* preclinical studies[5,6].
- In an *in vivo* bradykinin challenge study in humans, oral PHA121 inhibited effects of bradykinin with higher potency and longer estimated duration than subcutaneous icatibant[7,8].
- PHA121 is being developed in two formulations specifically designed to meet the required attributes for oral on-demand treatment of HAE attacks (PHVS416) and for oral prophylactic treatment to prevent HAE attacks (PHVS719)[9].

Methods

- An open-label, single-dose, randomized, five-period, five-sequence, crossover, explorative Phase 1 pharmacokinetics (PK) study evaluated the bioavailability of two different extended-release (XR) formulations of PHA121 (PHVS719; XR1 at 20 mg and XR2 at 40 mg) under fasting (= overnight fast ≥10 hours + ≥4 hours after dosing) or fed (= 30 minutes after start of high-fat, high-calorie breakfast) conditions, in comparison to a single dose of PHVS416 soft capsule under fasting conditions.
- Ten healthy adult male volunteers (age 18-65 years, body mass index ≥18 and ≤30 kg/m^2, body weight ≥50 kg at screening) received the following treatments in a randomized order with 7 days of washout between successive dose administrations:
  - Treatment A: single oral dose of 1 XR1 tablet 20 mg PHA121, under fasting conditions
  - Treatment B: single oral dose of 1 XR2 tablet 40 mg PHA121, under fasting conditions
  - Treatment C: single oral dose of 2 soft capsules 10 mg PHA121, under fasting conditions
  - Treatment D: single oral dose of 1 XR1 tablet 20 mg PHA121, under fed conditions
  - Treatment E: single oral dose of 1 XR2 tablet 40 mg PHA121, under fed conditions
- Concentrations of PHA121, the active ingredient in PHVS719, in human EDTA plasma samples were determined using a validated LC-MS/MS method.
- Descriptive statistics were calculated for the plasma concentrations of PHA121. The primary PK parameters were C_{max}, t_{max} AUC_{12h}, AUC_{24h}, and AUC_{last}.
- To measure the bioavailability of PHA121, mean plasma concentrations were measured over 48 hours, specifically focused on time to clinically relevant exposure of 13.8 ng/mL (the EC_{85} determined in a Phase 1 bradykinin challenge in healthy volunteers) and time of maintenance of that exposure level.

Results

- Eight subjects completed the study. One subject discontinued from the study at period 3 check-in due to positive breath alcohol test and another subject discontinued during period 2 due to a TEAE (neck pain).



Mean (SD) plasma concentration-time profiles of PHA121 on a linear scale after administration of PHA121 as XR tablet 1 (20 mg), XR tablet 2 (40 mg) under fasting or fed conditions or as soft capsules (20 mg)

- Administration of PHVS416 resulted in rapid clinical exposure of PHA121 above EC_{85} (13.8 ng/ml) within 30 minutes. Administration of PHVS719 (XR1 at 20 mg, XR2 at 40 mg) under fasted conditions yielded exposure above EC_{85} by ~2 hours and maintained it for ≥30 hours. The overall exposure was not affected by food.

Single dose pharmacokinetics of PHA-022121 in plasma (mean [SD], t_{max} and t_{last}: median [range])	Single oral dose of 20 mg PHA-022121 as XR1 formulation, fasting (Treatment A)	Single oral dose of 40 mg PHA-022121 as XR2 formulation, fasting (Treatment B)	Single oral dose of 20 mg PHA-022121 as soft capsules formulation, fasting (Treatment C)	Single oral dose of 20 mg PHA-022121 as XR1 formulation, fed (Treatment D)	Single oral dose of 40 mg PHA-022121 as XR2 formulation, fed (Treatment E)
n	9	10	8	9	8
C_{max} (ng/mL)	89.8 (31.8)	111 (46.1)	272 (130)	128 (50.1)	160 (76.8)
t_{max} (h)	4.00 (3.00 - 5.00)	9.00 (5.00 - 18.00)	1.00 (0.50 - 1.00)	6.00 (4.00 - 7.50)	11.00 (8.00 - 14.12)
C_{24h} (ng/mL)	9.06 (6.88)	40.3 (25.5)	3.71 (4.16)	9.36 (8.27)	35.4 (36.1)
AUC_{12h} (ng.h/mL)	547 (192)	662 (291)	796 (424)	669 (305)	826 (326)
AUC_{24h} (ng.h/mL)	753 (314)	1427 (643)	896 (510)	941 (491)	1586 (795)
AUC_{last} (ng.h/mL)	847 (387)	1829 (854)	931 (551)	1023 (566)	1912 (1144)

Summarized pharmacokinetic results of PHA-022121 after administration of PHA121 as different formulations (XR tablet 20 mg, XR tablet 40 mg or sof capsules) under fasting or fed conditions

- The 24-hour area-under-the-curve (AUC_{24h}) exposure of PHA121 after 1 dose of PHVS719 XR2 40 mg was comparable to that observed in Phase 1 studies with PHVS416 soft capsules 20 mg dosed bid with food. CHAPTER-1 is a Phase 2 clinical trial* evaluating the safety and efficacy of PHA121 as active ingredient for the prevention of HAE attacks.
- Study drugs were well tolerated. Ten treatment-emergent adverse events (TEAEs) in 5 subjects were reported, with no specific safety pattern or trend and mostly occurring after only 1 of the administrations of study drugs. No severe AEs or serious AEs were reported.
- A total of 9 TEAEs were assessed as Grade 1 in severity, 8 assessed as related to study drug and 1 (neck pain) assessed as unrelated to study drug; 1 TEAE (post-procedural hypotension) was assessed as Grade 2 and unrelated to study drug. All TEAEs were resolved prior to the end of the study (n=7) or after study completion (n=3).

		Reported Incidence by Treatment Group n (%)					
		A N = 9	B N = 10	C N = 8	D N = 9	E N = 8	Total N = 10
Presence of TEAE	Subjects with TEAEs	1 (11.1%)	3 (30.0%)	0 (0%)	1 (11.1%)	0 (0%)	5 (50.0%)
	Subjects with No TEAEs	8 (88.9%)	7 (70.0%)	8 (100.0%)	8 (88.9%)	8 (100.0%)	5 (50.0%)
CTCAE Grade/Severity	Grade 1	1 (11.1%)	3 (30.0%)	0 (0%)	1 (11.1%)	0 (0%)	5 (50.0%)
	Grade 2	0 (0%)	1 (10.0%)	0 (0%)	0 (0%)	0 (0%)	1 (10.0%)
	Grade 3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Grade 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Relationship to IMP	Related	1 (11.1%)	3 (30.0%)	0 (0%)	1 (11.1%)	0 (0%)	5 (50.0%)
	Unrelated	0 (0%)	1 (10.0%)	0 (0%)	0 (0%)	0 (0%)	1 (10.0%)

Summary of TEAEs for each treatment. TEAEs (preferred term) included: dizziness (grade 1) in 1 subject; post-procedural hypotension (grade 2), contusion (grade 1, unrelated to study drug), neck pain (grade 1, unrelated to study drug), post-procedural discomfort (grade 1), bilirubin conjugated increased (grade 1), blood bilirubin increased (grade 1) in 1 subject; blood glucose increased (grade 1) in 3 subjects.

Conclusions

- In a Phase 1 study, PHVS719 demonstrated the required pharmacological attributes for prophylactic treatment of HAE attacks:
  - Upon administration of a single dose of PHVS719 extended-release XR2 tablet, therapeutic exposure was reached within few hours and was sustained for >24 hours, independently from food intake.
  - PHVS719 was well tolerated with TEAEs of Grade 1 (90%) or Grade 2 (10%) severity, all TEAEs reported as resolved, and no severe or serious adverse events.

*The FDA has placed a clinical hold on the clinical trials of PHA121[10,11] in the U.S. Regulators in ex-U.S. countries have been notified of U.S. clinical hold. Visit https://ir.pharvaris.com/ for the latest information and updates.

References

1. Busse PJ et al. *N Engl J Med* 2020; 382: 1136-1148. 2. Cicardi M et al. *N Engl J* Med 2010; 363: 532-541. 3. Lumry WR et al. *Ann Allergy Asthma Immunol* 2011; 107: 529-537. 4. Maurer M et al. *Clin Exp Allergy* 2022; 52: 1048-1058. 5. Lesage A et al. *Front Pharmacol* 2020; 11: 916. 6. Lesage A et al. *Int Immunopharmacol* 2022; 105: 108523. 7. Lesage A et al. AAAAI 2020. 8. Derendorf H et al. ACAAI 2020. 9. Maurer M et al. HAEi Global Leadership Workshop 2022. 10. https://clinicaltrials.gov/ct2/show/NCT04618211, accessed on 26 October 2022. 11. https://clinicaltrials.gov/ct2/show/NCT05047185, accessed on 26 October 2022.

PHARVARIS