P-38

Efficacy of the oral bradykinin B2 receptor antagonist deucrictibant immediate-release capsule (PHVS416) by attack location in the RAPIDe-1 phase 2 clinical trial for treatment of hereditary angioedema attacks

A. Valerieva[1], E. Aygören-Pürsün[2], L. Bouillet[3], A. Du-Thanh[4], R. Hakl[5], A. Kessel[6], S. Kiani-Alikhan[7], M. Magerl[8], A. Reshef[9], M. Staevska[1], M. Stobiecki[10], R. Crabbé[11], H. Chen[12], L. Zhu[12], G. Giannattasio[13], M. Maurer[8]

[1]Department of Allergology, Clinic of Allergology, University Hospital "Alexandrovska", Medical University of Sofia, Sofia, Bulgaria; [2]Department for Children and Adolescents, University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt, Germany; [3]National Reference Center for Angioedema (CREAK), Department of Internal Medicine, Grenoble Alpes University, Laboratoire T-RAIG, UMR 5525 TIMC-IMAG (UGA-CNRS), Grenoble, France; [4]Department of Dermatology, University Montpellier, Montpellier, France; [5]Department of Clinical Immunology and Allergology, St. Anne's University Hospital in Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic, Brno, Czech Republic; [6]Bnai Zion Medical Center, Technion-Israel Institute of Technology, Haifa, Israel; [7]Department of Immunology, Royal Free London NHS Foundation Trust, London, United Kingdom; [8]Institute of Allergology, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, and Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany; [9]Allergy, Immunology and Angioedema Center, Barzilai University Hospital, Ashkelon, Israel; [10]Department of Clinical and Environmental Allergology, Jagiellonian University Medical College, Krakow, Poland; [11]RC Consultancy, Bassins, Switzerland; [12]Pharvaris Inc., Lexington, MA, USA; [13]Pharvaris GmbH, Zug, Switzerland

Introduction

- Approved therapies for hereditary angioedema (HAE) attacks are administered parenterally with substantial treatment burden due to administration time and risk of pain or other injection site reactions[1-4], with treatment of many attacks being delayed or forgone.[5-6]
- An unmet need exists for on-demand oral therapies that are effective and well-tolerated and may reduce the treatment burden enabling prompt administration as recommended by international clinical guidelines.[7-9]
- Deucrictibant immediate-release (IR) capsule (PHVS416) is an investigational formulation containing deucrictibant (PHA121), a highly potent, specific, and orally bioavailable competitive antagonist of the bradykinin B2 receptor.[10-11]
- In the Phase 2 RAPIDe-1 trial (NCT04618211[12]) deucrictibant IR capsule reduced time to onset of symptom relief and to attack resolution measured through the visual analogue scale-3 (VAS-3) and substantially reduced use of rescue medication.[13-15]

Methods

- RAPIDe-1 was a Phase 2, double-blind, placebo-controlled, randomized, crossover, dose-ranging trial of deucrictibant IR capsule for the acute treatment of angioedema attacks in patients with type 1 and 2 HAE.
- A primary analysis was performed including 147 qualifying HAE attacks treated by 62 patients with double-blinded placebo or deucrictibant IR capsule 10, 20, or 30 mg (modified intent-to-treat analysis, mITT = all randomized patients with ≥1 treated HAE attack and VAS results at both pre-treatment and ≥1 post-treatment time point).
- VAS-3 is a 3-symptom composite assessment including individual VAS scales for abdominal pain, skin swelling, and skin pain and in RAPIDe-1 it was assessed every ~30 min until 4 hours and then at 5, 6, 8, 24, 48 hours post-treatment with study drug
- VAS score ranges from 0 (no symptoms) to 100 (worst symptom severity)
- In these post-hoc analyses, treatment VAS-3 outcomes were analysed according to attack location, i.e., abdominal (individual VAS >0 for abdominal pain), peripheral (individual VAS >0 for skin swelling and/or skin pain) or both

Results

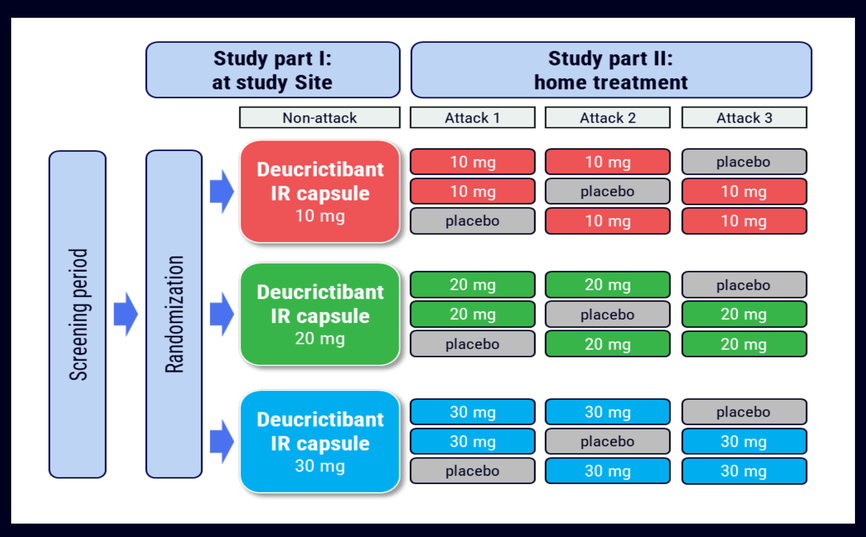

Figure 1. RAPIDe-1 trial design schematic

	Placebo	Deucrictibant IR capsule 10 mg	Deucrictibant IR capsule 20 mg	Deucrictibant IR capsule 30 mg
Number of attacks	51	37	28	31
Abdominal – n (%)	10 (19.6)	10 (27.0)	7 (25.0)	6 (19.4)
Peripheral – n (%)	30 (58.8)	22 (59.5)	17 (60.7)	20 (64.5)
Abdominal and peripheral – n (%)	11 (21.6)	5 (13.5)	4 (14.3)	5 (16.1)

Table 1. Proportion of abdominal, peripheral and combined (abdominal and peripheral) attacks

	Placebo	Deucrictibant IR capsule 10 mg	Deucrictibant IR capsule 20 mg	Deucrictibant IR capsule 30 mg
Abdominal attacks				
Number of attacks	20	15	11	11
Attacks with ≥30% reduction in individual VAS within 48-hour timepoint	7 (35.0)	13 (86.7)	11 (100.0)	10 (90.9)
Median time (hours) to ≥30% reduction in individual VAS (95% CI)	20.0 (2.9, 20.0)	1.9 (0.9, 2.0)	1.4 (0.9, 2.5)	2.9 (1.5, 7.5)
Hazard ratio vs. placebo (95% CI)	-	8.33 (2.92, 23.77)	7.39 (2.36, 23.20)	3.45 (1.28, 9.29)
Nominal p value	-	<0.0001	0.0006	0.0143
Peripheral attacks				
Number of attacks	41	27	21	25
Attacks with ≥30% reduction in individual VAS within 48-hour timepoint	15 (36.6)	24 (88.9)	18 (85.7)	24 (96.0)
Median time (hours) to ≥30% reduction in individual VAS (95% CI)	8.0 (6.1, NE)	2.5 (1.6, 3.4)	3.4 (2.0, 7.5)	2.9 (2.0, 3.9)
Hazard ratio vs. placebo (95% CI)	-	3.28 (1.70, 6.32)	2.38 (1.10, 5.18)	3.66 (1.99, 6.75)
Nominal p value	-	0.0004	0.0285	<0.0001

Combined (abdominal and peripheral) assessed in each group according to the relevant VAS

Table 2. Onset of symptom relief (≥30% reduction in individual VAS) in abdominal and peripheral attacks

	Placebo	Deucrictibant IR capsule 10 mg	Deucrictibant IR capsule 20 mg	Deucrictibant IR capsule 30 mg
Abdominal attacks				
Number of attacks	20	15	11	11
Attacks with ≥50% reduction in individual VAS within 48-hour timepoint	5 (25.0)	12 (80.0)	11 (100.0)	9 (81.8)
Median time (hours) to ≥50% reduction in individual VAS (95% CI)	NE (4.8, NE)	2.1 (0.9, 2.9)	1.9 (0.9, 5.1)	3.9 (2.5, 7.5)
Hazard ratio vs. placebo (95% CI)	-	8.91 (2.68, 29.69)	6.26 (1.58, 24.87)	3.64 (1.29, 10.27)
Nominal p value	-	0.0004	0.0092	0.0148
Peripheral attacks				
Number of attacks	41	27	21	25
Attacks with ≥50% reduction in individual VAS within 48-hour timepoint	13 (31.7)	24 (88.9)	18 (85.7)	23 (92.0)
Median time (hours) to ≥50% reduction in individual VAS (95% CI)	22.8 (20.0, 24.1)	3.4 (2.5, 7.5)	6.0 (3.0, 8.5)	4.0 (3.5, 5.8)
Hazard ratio vs. placebo (95% CI)	-	3.99 (2.07, 7.70)	3.11 (1.52, 6.37)	4.30 (2.30, 8.04)
Nominal p value	-	<0.0001	0.0019	<0.0001

Combined (abdominal and peripheral) assessed in each group according to the relevant VAS

Table 3. ≥50% reduction in individual VAS in abdominal and peripheral attacks

	Placebo	Deucrictibant IR capsule 10 mg	Deucrictibant IR capsule 20 mg	Deucrictibant IR capsule 30 mg
Abdominal attacks				
Number of attacks	20	15	11	11
Attacks with complete/almost complete resolution (VAS ≤10) in individual VAS within 48-hour timepoint	4 (20.0)	12 (80.0)	11 (100.0)	11 (81.8)
Median time (hours) to complete/almost complete resolution (VAS ≤10) in individual VAS (95% CI)	20.8 (5.1, NE)	2.5 (1.4, 7.5)	2.9 (1.4, 20.0)	9.0 (2.5, 42.1)
Hazard ratio vs. placebo (95% CI)	-	9.79 (3.03, 31.70)	4.70 (1.27, 17.34)	3.43 (1.18, 10.01)
Nominal p value	-	0.0001	0.0203	0.0238
Peripheral attacks				
Number of attacks	41	26	20	25
Attacks with complete/almost complete resolution (VAS ≤10) in individual VAS within 48-hour timepoint	10 (24.4)	21 (80.8)	15 (75.0)	22 (88.0)
Median time (hours) to complete/almost complete resolution (VAS ≤10) in individual VAS (95% CI)	47.2 (23.3, NE)	20.0 (5.8, 24.3)	24.0 (8.5, NE)	20.0 (7.2, 22.0)
Hazard ratio vs. placebo (95% CI)	-	4.81 (2.34, 9.88)	2.11 (1.10, 4.06)	3.68 (1.80, 7.55)
Nominal p value	-	<0.0001	0.0246	0.0004

Combined (abdominal and peripheral) assessed in each group according to the relevant VAS

Table 4. Complete/almost complete resolution (VAS ≤10) in individual VAS in abdominal and peripheral attacks

Conclusions

- **In post-hoc analyses of treatment outcomes by attack location, deucrictibant IR capsule demonstrated consistent rapid onset of symptom relief and resolution of HAE attacks with abdominal, peripheral and combined (abdominal and peripheral) attack location**
- **Results of analyses by attack location are consistent with results of RAPIDe-1 primary analyses**

References

[1]Berinert® [package insert], https://labeling.cslbehring.com/pi/us/berinert/en/berinert-prescribing-information.pdf (accessed 25 April 2023). [2]Firazyr® [package insert], https://www.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf (accessed 25 April 2023). [3]Kalbitor® [package insert], https://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf (accessed 25 April 2023). [4]Ruconest® [package insert], https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf (accessed 25 April 2023). [5]Tuong LA et al. Allergy Asthma Proc 2014;35:250-4. [6]US Food and Drug Administration, Center for Biologics Evaluation and Research. The voice of the patient – Hereditary angioedema. May, 2018. https://www.fda.gov/media/113509/download (accessed 25 April 2023). [7]Betschel S et al. Allergy Asthma Clin Immunol 2019;15:72. [8]Busse PJ et al. J Allergy Clin Immunol Pract 2021 2021;9:132-50. [9]Maurer M et al. Allergy 2022;77:1961-90. [10]Lesage A et al. Front Pharmacol 2020;11:916. [11]Lesage A et al. Int Immunopharmacol 2022;105:108523. [12]https://clinicaltrials.gov/ct2/show/NCT04618211 (accessed 25 April 2023). [13]Maurer M et al. AAAAI 2023;411; [14]Farkas H et al. 13th C1-inhibitor Deficiency and Angioedema Workshop 2023;O-19. [15]Riedl MA et al. 13th C1-inhibitor Deficiency and Angioedema Workshop 2023;P-25.

This presentation includes data for an investigational product not yet approved by regulatory authorities

Presented at the 13th C1-inhibitor Deficiency and Angioedema Workshop Budapest (Hungary), 4–7 May 2023