Efficacy and Safety of Bradykinin B2 Receptor Antagonism With Oral Deucrictibant in Prophylaxis of Hereditary Angioedema Attacks: Results of CHAPTER-1 Phase 2 Trial

Marc A. Riedl[1], John Anderson[2], Francesco Arcoleo[3], Mauro Cancian[4], Hugo Chapdelaine[5], Niall Conlon[6], Efrem Eren[7], Mark Gompels[8], Sofia Grigoriadou[9], Maria D. Guarino[10], Padmalal Gurugama[11], Tamar Kinaciyan[12], Markus Magerl[13,14], Michael E. Manning[15], Marcin Stobiecki[16], Michael D. Tarzi[17], Anna Valerieva[18], H. James Wedner[19], William H. Yang[20], Andrea Zanichelli[21], Rafael Crabbé[22], Susan Mulders[23], Minying Royston[24], Li Zhu[24], Jochen Knolle[25], Anne Lesage[26], Peng Lu[24], Emel Aygören-Pürsün[27]

[1]Division of Allergy and Immunology, University of California San Diego, La Jolla, CA, USA; [2]Clinical Research Center of Alabama, AllerVie Health, Birmingham, AL, USA; [3]UOC di Patologia Clinica e Immunologia, AOR Villa Sofia-Cervello, Palermo, Italy; [4]Department of Systems Medicine, University Hospital of Padua, Padua, Italy; [5]CHU de Montréal, Université de Montréal, Montréal, Canada; [6]Wellcome Trust CRF, St. James's Hospital and Trinity College, Dublin, Ireland; [7]University Hospital Southampton NHS Foundation Trust, Southampton, UK; [8]North Bristol NHS Trust, Bristol, UK; [9]Barts Health NHS Trust, London, UK; [10]Ospedale di Civitanova Marche, Civitanova Marche, Italy; [11]Department of Clinical Immunology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; [12]Department of Dermatology, Medical University of Vienna, Vienna, Austria; [13]Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [14]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany; [15]Allergy, Asthma and Immunology Associates, Ltd., Scottsdale, AZ, USA; [16]Department of Clinical and Environmental Allergology, Jagiellonian University Medical College, Krakow, Poland; [17]Department of Immunology, Brighton and Sussex University Hospitals NHS Trust, Brighton, UK; [18]Department of Allergology, Clinic of Allergology, University Hospital Alexandrovska, Medical University of Sofia, Sofia, Bulgaria; [19]Division of Allergy and Immunology, Department of Medicine, Washington University School of Medicine, St Louis, MO, USA; [20]Ottawa Allergy Research Corporation, Department of Medicine, University of Ottawa, Ottawa, Canada; [21]Operative Unit of Medicine, Angioedema Center, IRCCS Policlinico San Donato, San Donato Milanese, Italy, and Department of Biomedical Sciences for Health, University of Milan, Milan, Italy; [22]RC Consultancy, Bassins, Switzerland; [23]Mulders Clinical Consulting, Groesbeek, The Netherlands; [24]Pharvaris Inc., Lexington, MA, USA; [25]JCK Consult, Frankfurt, Germany; [26]GrayMatters Consulting, Schilde, Belgium; [27]Department for Children and Adolescents, University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt, Germany

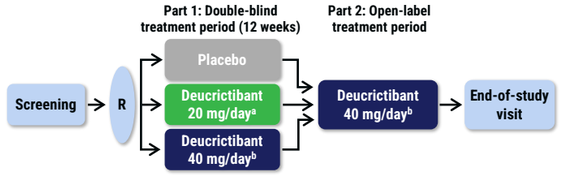
Rationale

- Excess bradykinin is the cause of the clinical manifestations of hereditary angioedema (HAE) attacks.[1]
- Despite the availability of approved therapies, an unmet need remains for additional prophylactic treatments combining injectable-like efficacy, a well-tolerated profile, and ease of administration.[2-5]
- Deucrictibant is an orally administered, highly potent, specific antagonist of the bradykinin B2 receptor under development for on-demand and prophylactic treatment of HAE attacks.[3,6-10]

Methods

- CHAPTER-1 (NCT05047185)[10,†] is a two-part, Phase 2 study evaluating the efficacy, safety, and tolerability of deucrictibant for long-term prophylaxis against angioedema attacks in HAE-1/2.
- Eligible participants were ≥18 and ≤75 years, diagnosed with HAE-1/2, were not receiving other prophylactic treatments at the time of screening, and experienced ≥3 attacks within the past 3 consecutive months prior to screening or ≥2 attacks during screening (up to 8 weeks).
- In placebo-controlled part 1, participants were randomized to receive 1 of 2 doses of double-blinded deucrictibant (20 or 40 mg/day) or placebo for 12 weeks of treatment (**Figure 1**).

Figure 1. Study design



IR, immediate-release; R, randomization.
[a]Deucrictibant IR capsules, 10 mg twice daily. [b]Deucrictibant IR capsules, 20 mg twice daily.

- Deucrictibant immediate-release (IR) capsule was dosed twice per day as a proof-of-concept for the once-daily deucrictibant extended-release tablet, which is the intended formulation of deucrictibant for prophylactic HAE treatment.[11]
- The primary endpoint was the time-normalized number of investigator-confirmed HAE attacks, expressed as monthly HAE attack rate.
- The time-normalized number of moderate and severe HAE attacks and HAE attacks treated with on-demand medication were among the prespecified secondary endpoints.
- In the ongoing part 2 open-label portion of the CHAPTER-1 study,[10] participants may continue treatment with deucrictibant 40 mg/day.

Results

- Thirty-four participants were enrolled and randomized at sites in Canada, Europe, the United Kingdom, and the United States.
- The primary endpoint was met, with deucrictibant 20 mg/day and 40 mg/day significantly reducing the monthly attack rate by 79.3% (*P*=0.0009) and 84.5% (*P*=0.0008) compared to placebo, respectively (**Figure 2** and **Table 1**).

Figure 2. Overall monthly attack rate

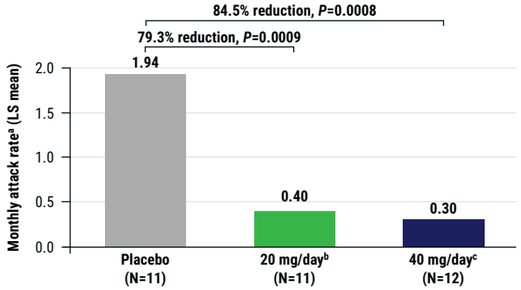


Table 1. Overall monthly attack rate

	Placebo (N=11)	Deucrictibant 20 mg/day[b] (N=11)	Deucrictibant 40 mg/day[c] (N=12)
Monthly attack rate[a]			
Baseline, median	1.67	1.67	1.74
On study, median	2.15	0	0.15
Change from baseline, median	0.33	−1.34	−1.59
% change from baseline	17%	−100%	−96%
Model-based inference			
LS mean	1.94	0.40	0.30
% reduction vs placebo	–	79.3%	84.5%
P value	–	0.0009	0.0008

IR, immediate-release; LS, least squares; N, number of randomized participants. Model-based inferences are based on a Poisson regression model adjusted for baseline attack rate and time on treatment. No multiplicity adjustment was applied.
[a]Number of attacks/4 weeks. [b]Deucrictibant IR capsules, 10 mg twice daily. [c]Deucrictibant IR capsules, 20 mg twice daily.

- In analyses of the secondary endpoints, deucrictibant 40 mg/day reduced the occurrence of moderate and severe attacks by 92.3% (**Figure 3**) and of attacks treated with on-demand medication by 92.6% (**Figure 4**).
- A consistent reduction in monthly attack rate was observed with deucrictibant treatment regardless of baseline attack rate (**Figure 5**).

Figure 3. Moderate and severe attacks

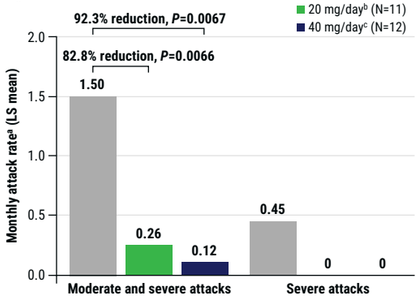


Figure 4. On-demand treated attacks

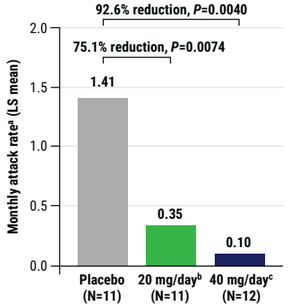
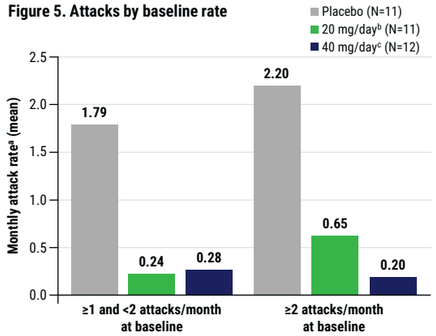


Figure 5. Attacks by baseline rate



IR, immediate-release; LS, least squares; N, number of randomized participants. Model-based inferences are based on a Poisson regression model adjusted for baseline attack rate and time on treatment. No multiplicity adjustment was applied. The *P* values in these figures are nominal. [a]Number of attacks/4 weeks. [b]Deucrictibant IR capsules, 10 mg twice daily. [c]Deucrictibant IR capsules, 20 mg twice daily.

Results

- Deucrictibant was well tolerated at both doses, and all reported treatment-related treatment-emergent adverse events (TEAEs) were mild in severity (**Table 2**).
- No serious TEAEs, no severe TEAEs, and no TEAEs leading to treatment discontinuation, study withdrawal, or death were reported (**Table 2**).

Table 2. Adverse events

Events	Placebo (N=11)		Deucrictibant 20 mg/day[a] (N=11)		Deucrictibant 40 mg/day[b] (N=12)	
	Participants, n (%)	Events, n	Participants, n (%)	Events, n	Participants, n (%)	Events, n
TEAEs	**7 (63.6)**	**16**	**6 (54.5)**	**11**	**7 (58.3)**	**12**
Treatment-related TEAEs	**1 (9.1)**	**1**	**2 (18.2)**	**2**	**1 (8.3)**	**1**
Nausea	0	0	1 (9.1)	1	0	0
Gamma-glutamyltransferase increased	0	0	0	0	1 (8.3)	1
Dizziness postural	0	0	1 (9.1)	1	0	0
Headache	1 (9.1)	1	0	0	0	0
Serious TEAEs	**0**	**0**	**0**	**0**	**0**	**0**
Treatment-related serious TEAEs	**0**	**0**	**0**	**0**	**0**	**0**
TEAEs leading to study drug discontinuation, withdrawal, or death	**0**	**0**	**0**	**0**	**0**	**0**

IR, immediate-release; N, number of randomized participants; TEAE, treatment-emergent adverse event (defined as an adverse event that occurred after the first administration of double-blinded study treatment). [a]Deucrictibant IR capsules, 10 mg twice daily. [b]Deucrictibant IR capsules, 20 mg twice daily.

Conclusions

- **In the Phase 2 CHAPTER-1 trial, deucrictibant significantly reduced the occurrence of HAE attacks and achieved clinically meaningful reduction in occurrence of both moderate and severe HAE attacks, as well as HAE attacks treated with on-demand medication.**
- **CHAPTER-1 results provide evidence on the efficacy and safety of deucrictibant for the prevention of HAE attacks and support its further development as a potential prophylactic therapy for HAE.**

References

1. Busse PJ, et al. *N Engl J Med*. 2020;382:1136-48. **2.** Bouillet L, et al. *Allergy Asthma Proc*. 2022;43:406-12. **3.** Betschel SD, et al. *J Allergy Clin Immunol Pract*. 2023;11:2315-25. **4.** 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 January 9, 2024. **5.** Covella B, et al. *Future Pharmacol*. 2024;4:41-53. **6.** Lesage A, et al. *Front Pharmacol*. 2020;11:916. **7.** Lesage A, et al. *Int Immunopharmacol*. 2022;105:108523. **8.** https://clinicaltrials.gov/study/NCT04618211. Accessed January 9, 2024. **9.** https://www.clinicaltrials.gov/study/NCT05396105. Accessed January 9, 2024. **10.** https://www.clinicaltrials.gov/study/NCT05047185. Accessed January 9, 2024. **11.** Groen K, et al. Presented at ACAAI 2022. November 10–14, 2022; Louisville, KY, USA.

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

COI: Research grant support, consultancy fees, speaker fees, advisory board, investigator, and/or clinical trial fees - **M.A.R.:** Astria, BioCryst, Biomarin, CSL Behring, Cycle Pharma, Fresenius-Kabi, Grifols, Ionis, Ipsen, KalVista, Ono Pharma, Pfizer, Pharming, Pharvaris, RegenxBio, Sanofi-Regeneron, Takeda; **J.A.:** BioCryst, BioMarin, CSL Behring, Cycle Pharmaceuticals, KalVista, Pharming, Pharvaris, Takeda; **F.A.:** CSL Behring, Takeda; **M.C.:** BioCryst, CSL Behring, KalVista, Menarini, MSD, Novartis, Pharming, Pharvaris, Shire/Takeda, Sobi, UCB; **H.C.:** AstraZeneca (Alexion), CSL Behring, KalVista, Merck, Novartis, Pharming, Pharvaris, Roche, Sanofi, Sobi, Takeda; **N.C.:** Novartis, Takeda; **E.E.:** none; **M.G.:** BioCryst, CSL Behring, Novartis; **S.G.:** Baxter, CSL Behring, Dyax, Grifols, Jerini/Shire, Pharming/Swedish Orphan, Viropharma; **M.D.G.:** CSL Behring; **P.G.:** BioCryst, CSL Behring, KalVista, Pharming, Shire, Takeda; **T.K.:** BioCryst, CSL Behring, KalVista, Novartis, Pharvaris, Sanofi-Regeneron, Shire/Takeda; **M.M.:** BioCryst, CSL Behring, Intellia, KalVista, Novartis, Octapharma, Pharming, Pharvaris, Shire/Takeda; **M.E.M.:** Allakos, Amgen, AstraZeneca, BioCryst, Blueprint, CSL Behring, Cycle, Genentech, GSK, KalVista, Merck, Novartis, Pharming, Pharvaris, Sanofi/Regeneron, Takeda; **M.S.:** BioCryst, CSL Behring, KalVista, Pharming, Shire/Takeda; **M.D.T.:** none; **A.V.:** AstraZeneca, Berlin-Chemie/Menarini Group, CSL Behring, Novartis, Pharming, Pharvaris, Shire/Takeda, Sobi, Teva; **H.J.W.:** BioCryst, BioMarin, CSL Behring, Genentech, GSK, Takeda; **W.H.Y.:** Aimmune, ALK, Amgen, AnaptysBio, Aslan Therapeutics, AstraZeneca, BioCryst, Celgene, CSL Behring, DBV Technologies, Dermira, Eli Lilly, Galderma, Genentech/Roche, Glenmark, GSK, Halecon, Incyte Biosciences, Ionis, Merck, Novartis, Novavax, Pharming, Pharvaris, Providence, Regeneron, Sanofi Genzyme, Shire/Takeda, VBI; **A.Z.:** BioCryst, CSL Behring, KalVista, Pharming, Takeda; **R.C.:** employee of CO Consultancy and consultant to Pharvaris, holds stocks in Pharvaris; **S.M.:** employee of Mulders Clinical Consulting and consultant to Pharvaris, holds stocks in Pharvaris; **M.R., L.Z.:** employees of Pharvaris, hold stock/stock options in Pharvaris; **J.K.:** employee of JCK Consult and consultant to Pharvaris, holds stocks/stock options in Pharvaris; **A.L.:** employee of GrayMatters Consulting and consultant to Pharvaris, holds stocks/stock options in Pharvaris; advisor to Kosa Pharma; **P.L.:** employee of Pharvaris, holds stock/stock options in Pharvaris; **E.A-P.:** Astria, BioCryst, Biomarin, Centogene, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Shire/Takeda. **Acknowledgments:** Medical writing support was provided by Cara Bertozzi, PhD, and Holly Richendrfer, PhD, of Two Labs Pharma Services.

†CHAPTER-1 is a Pharvaris-sponsored clinical trial. ClinicalTrials.gov identifier: NCT05047185.