Prophylaxis of HAE attacks with oral deucrictibant: CHAPTER-1 results

Emel Aygören-Pürsün[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[21,22], Rafael Crabbé[23], Susan Mulders[24], Minying Royston[25], Li Zhu[25], Jochen Knolle[26], Anne Lesage[27], Peng Lu[25], Marc A. Riedl[28]

[1]University Hospital Frankfurt, Department for Children and Adolescents, Goethe University Frankfurt, Frankfurt, Germany; [2]AllerVie Health, Clinical Research Center of Alabama, Birmingham, AL, USA; [3]AOR Villa Sofia-Cervello, UOC di Patologia Clinica e Immunol., Palermo, Italy; [4]University Hospital of Padua, Department of Systems Medicine, Padua, Italy; [5]University de Montréal, CHU de Montréal, Montréal, QC, Canada; [6]St James's Hosp. and Trinity College, Wellcome Trust CRF, Dublin, Ireland; [7]University Hospital Southampton NHS Foundation Trust, Southampton, UK; [8]North Bristol NHS Trust, Bristol, UK; [9]Barts Health NHS Trust, Department of Immunol., London, UK; [10]Ospedale di Civitanova Marche, Civitanova Marche, Italy; [11]Cambridge University Hospital NHS Foundation Trust, Department of Clinical Immunology, Cambridge, UK; [12]Medical University of Vienna, Department of Dermatology, Vienna, Austria; [13]Charité – Univ. Berlin, Inst. of Allergol., Corporate Member of Freie Univ. Berlin and Humboldt-Univ. zu Berlin, Berlin, Germany; [14]Fraunhofer Inst. for Translational Medicine and Pharmacol. ITMP, Immunol. and Allergol., Berlin, Germany; [15]Allergy, Asthma and Immunol. Associates, Ltd., Scottsdale, AZ, USA; [16]Jagiellonian Univ. Medical College, Dept. of Clinical and Environmental Allergol., Krakow, Poland; [17]Univ. Hosp. Sussex NHS Foundation Trust, Dept. of Respiratory Medicine, Brighton, UK; [18]Medical University of Sofia, Dept. of Allergology, Sofia, Bulgaria; [19]Washington Univ. School of Medicine, Division of Allergy and Immunol., Dept. of Medicine, St Louis, MO, USA; [20]Ottawa Allergy Research Corporation, Dept. of Medicine, Univ. of Ottawa, Ottawa, ON, Canada; [21]Univ. degli Studi di Milano, Dept. di Scienze Biomediche per la Salute, Milan, Italy; [22]I.R.C.C.S., Policlinico San Donato, Centro Angioedema, UO Medicina, Milan, Italy; [23]RC Consultancy, Bassins, Switzerland; [24]Mulders Clinical Consulting, Groesbeek, The Netherlands; [25]Pharvaris Inc., Lexington, MA, USA; [26]JCK Consult, Frankfurt, Germany; [27]GrayMatters Consulting, Schilde, Belgium; [28]Univ. of California San Diego, Division of Allergy and Immunol., La Jolla, CA, USA

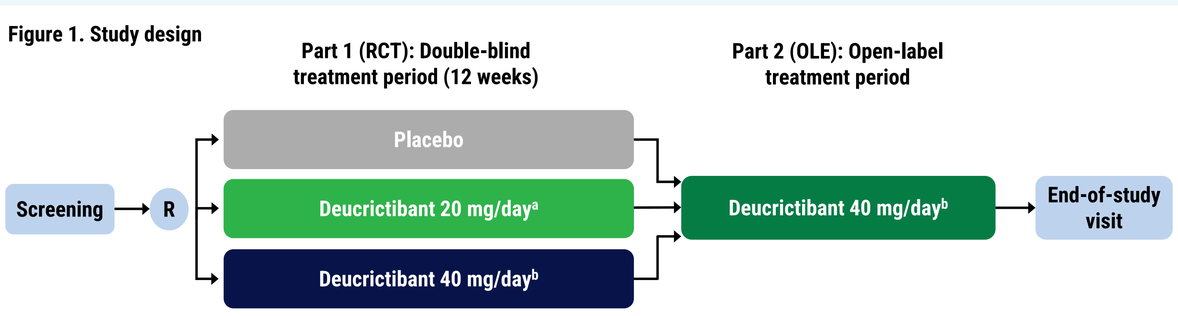
Rationale

- Excess bradykinin is the main mediator of the clinical manifestations of bradykinin-mediated angioedema attacks, including hereditary angioedema (HAE).[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 a selective, orally administered bradykinin B2 receptor antagonist under development for prophylactic and on-demand treatment of HAE attacks.[3,6-13]

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 three consecutive months prior to screening or ≥2 attacks during screening (up to 8 weeks).
- In the double-blind, placebo-controlled part 1 (randomized controlled trial; RCT), participants were randomized to receive one of two 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; OLE, open-label extension; R, randomization; RCT, randomized controlled trial. [a]Deucrictibant IR capsule, 10 mg twice daily. [b]Deucrictibant IR capsule, 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 (the intended formulation of deucrictibant for prophylactic HAE treatment).[12]
- The primary endpoint of the RCT was the time-normalized number of investigator-confirmed HAE attacks.
- The time-normalized number of moderate and severe HAE attacks and HAE attacks treated with on-demand medication were among the secondary endpoints.
- In the ongoing part 2 open-label extension (OLE) 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 with placebo, respectively (**Figure 2** and **Table 1**).

Figure 2. Significant reduction in overall attack rate (primary endpoint)

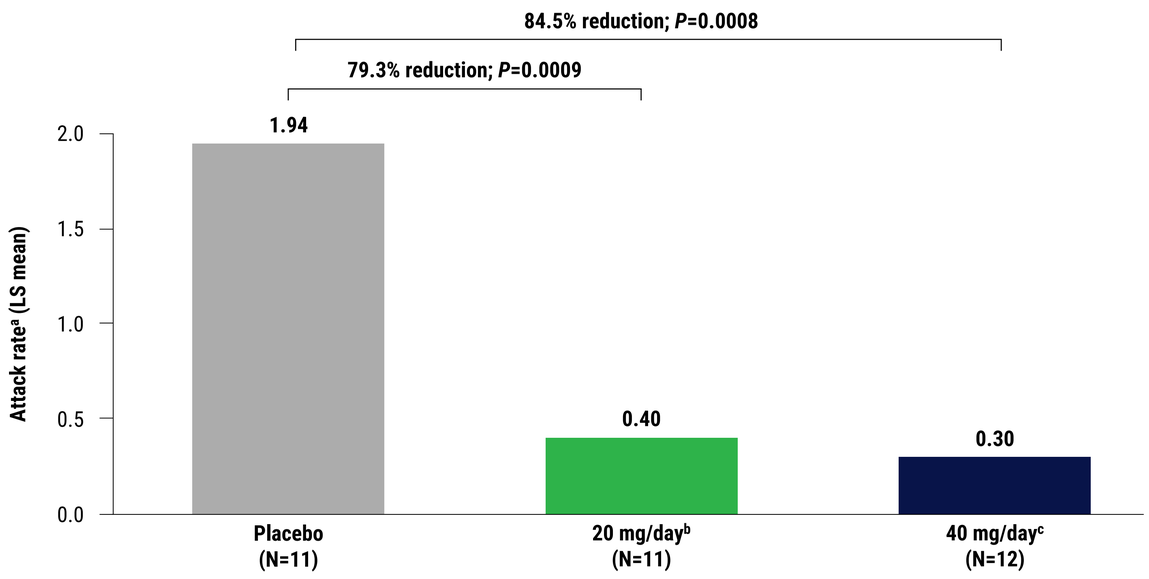


Table 1. Significant reduction in overall attack rate (primary endpoint)

	Placebo (N=11)	Deucrictibant 20 mg/day[b] (N=11)	Deucrictibant 40 mg/day[c] (N=12)
Attack rate[a]			
BL, median	1.67	1.67	1.74
On study, median	2.15	0	0.15
Change from BL, median	0.33	−1.34	−1.59
% change from BL, median	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

BL, baseline; 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]Based on time normalized number of attacks per 4 weeks. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 20 mg twice daily.

Results

- In analyses of the secondary endpoints, deucrictibant 40 mg/day reduced the rate of "moderate and severe" attacks by 92.3% (**Figure 3**) and reduced the rate of attacks treated with on-demand medication by 92.6% (**Figure 4**).

Figure 3. Reduction in "moderate and severe" attack rates

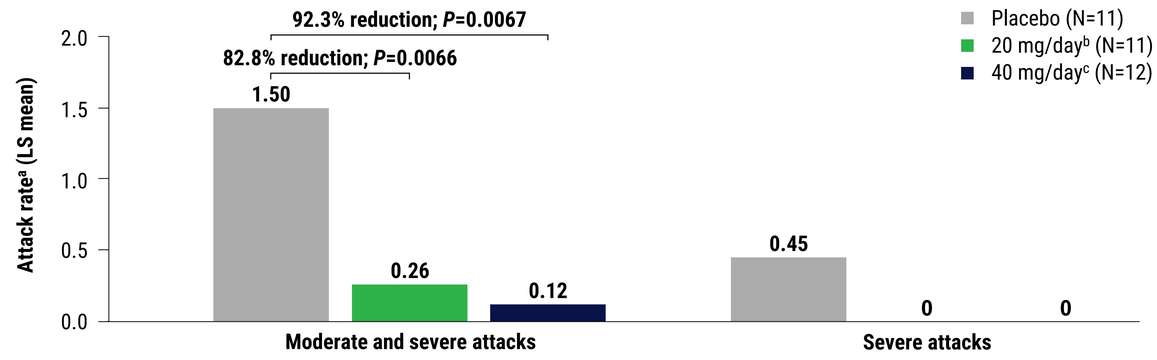
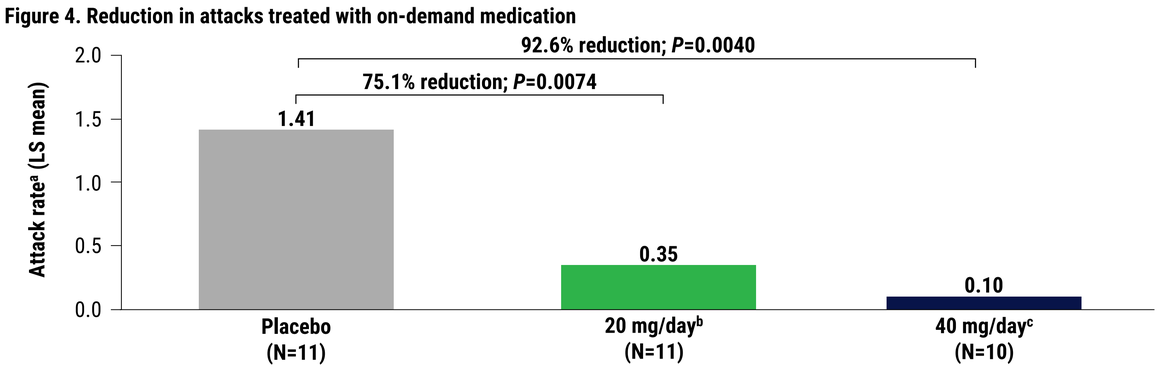


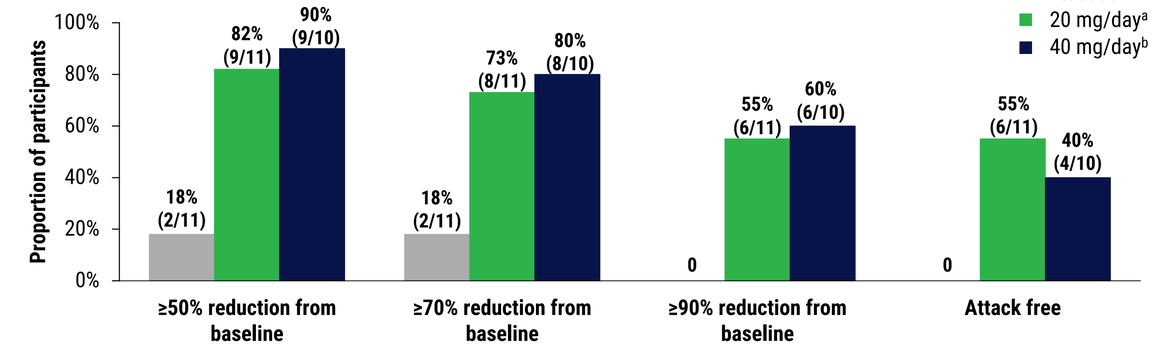
Figure 4. Reduction in attacks treated with on-demand medication



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 this figure are nominal. [a]Based on time normalized number of attacks per 4 weeks. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 20 mg twice daily.

- At 12 weeks, ≥50%, ≥70%, and ≥90% reduction in attack rate from baseline was achieved in 90%, 80%, and 60% of 10 participants receiving deucrictibant 40 mg/day vs 18%, 18%, and 0% of 11 participants receiving placebo (**Figure 5**).

Figure 5. Reduction in attack rate from baseline



IR, immediate release. N = Participants with ≥ 4 weeks of treatment. [a]Deucrictibant IR capsule, 10 mg twice daily. [b]Deucrictibant IR capsule, 20 mg twice daily.

- 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

Adverse events	Placebo (N=11) Participants, n (%)	Placebo (N=11) Events, n	Deucrictibant 20 mg/day[a] (N=11) Participants, n (%)	Deucrictibant 20 mg/day[a] (N=11) Events, n	Deucrictibant 40 mg/day[b] (N=12) Participants, n (%)	Deucrictibant 40 mg/day[b] (N=12) 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
Increased GGT	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, study withdrawal, or death	**0**	**0**	**0**	**0**	**0**	**0**

GGT, gamma-glutamyltransferase; IR, immediate-release; TEAE, treatment-emergent adverse event. N = number of participants who received at least one dose of blinded study treatment. [a]Deucrictibant IR capsule, 10 mg twice daily. [b]Deucrictibant IR capsule, 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 moderate and severe HAE attacks, as well as of 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.** Center for Biologics Evaluation and Research. The voice of the patient – hereditary angioedema. US Food and Drug Administration; May 2018. Accessed August 21, 2024. https://www.fda.gov/media/113509/download; **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 August 21, 2024. **9.** https://www.clinicaltrials.gov/study/ NCT05396105. Accessed August 21, 2024. **10.** https://www.clinicaltrials.gov/study/NCT05047185. Accessed August 21, 2024. **11.** https://clinicaltrials.gov/study/NCT06343779. Accessed August 16, 2024. **12.** Groen K, et al. Presented at: ACAAI; November 10–14, 2022; Louisville, KY, USA. **13.** Maurer M, et al. Presented at: AAAAI; February 24–27, 2023; San Antonio, TX, USA.

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

COI: Grants/research support, honoraria or consultation fees, sponsored speaker bureau – **E.A-P.**: Astria, BioCryst, BioMarin, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Takeda; **J.A.**: BioCryst, BioMarin, CSL Behring, Cycle Pharma, KalVista, Pharming, Pharvaris, Takeda; **F.A.**: CSL Behring, Takeda; **M.C.**: BioCryst, CSL Behring, KalVista, Menarini, MSD, Novartis, Pharming, Pharvaris, Sobi, Takeda, 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, Pharming/Swedish Orphan, Viropharma; **M.D.G.**: CSL Behring; **P.G.**: BioCryst, CSL Behring, KalVista, Pharming, Takeda; **T.K.**: BioCryst, CSL Behring, KalVista, Novartis, Sanofi-Regeneron, Pharvaris, Takeda; **M.M.**: BioCryst, CSL Behring, Intellia, KalVista, Novartis, Octapharma, Pharming, Pharvaris, Takeda; **M.E.M.**: Allakos, Amgen, AstraZeneca, BioCryst, Blueprint, CSL Behring, Cycle Pharma, Genentech, GSK, KalVista, Merck, Novartis, Pharming, Pharvaris, Sanofi-Regeneron, Takeda; **M.S.**: BioCryst, CSL Behring, KalVista, Pharming, Takeda; **M.D.T.**: None; **A.V.**: AstraZeneca, Berlin-Chemie/Menarini Group, CSL Behring, KalVista, Novartis, Pharming, Pharvaris, Sobi, Takeda; **H.J.W.**: BioCryst, BioMarin, CSL Behring, Genentech, GSK, Takeda; **W.H.Y.**: Aimmune, ALK Abello, Amgen, AnaptysBio, Areteia, Aslan, AstraZeneca, Astria, BioCryst, Bristol Myers Squibb, Celgene, CSL Behring, DBV Technologies, Dermira, Eli Lilly, Escient, Galderma, Genentech, Glenmark, GSK, Haleon, Incyte, Ionis, Merck, Moderna, Novartis, Novavax, Pharming, Pharvaris, Providence, Regeneron, RPAT Therapeutics, Roche, Sanofi, Stallergenes, Takeda, Upstream Bio, VBI; **A.Z.**: BioCryst, CSL Behring, KalVista, Pharming, Takeda; **R.C.**: Employee of RC 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., P.L.**: Employees of Pharvaris, hold stock/stock options in Pharvaris; **J.K.**: Employee of JCK Consulting 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; **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.
Acknowledgments: Medical writing services were provided by Andrea Cifelli, on behalf of Two Labs Pharma Services.

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