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

John Anderson[1], Francesco Arcoleo[2], Emel Aygören-Pürsün[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]AllerVie Health, Clinical Research Center of Alabama, Birmingham, AL, USA; [2]AOR Villa Sofia-Cervello, UOC di Patologia Clinica e Immunologia, Palermo, Italy; [3]University Hospital Frankfurt, Department for Children and Adolescents, Goethe University Frankfurt, Frankfurt, Germany; [4]University Hospital of Padua, Department of Systems Medicine, Padua, Italy; [5]Université de Montréal, CHU de Montréal, Montréal, QC, Canada; [6]St. James's Hospital 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, London, UK; [10]Ospedale di Civitanova Marche, Civitanova Marche, Italy; [11]Cambridge University Hospitals NHS Foundation Trust, Department of Clinical Immunology, Cambridge, UK; [12]Medical University of Vienna, Department of Dermatology, Vienna, Austria; [13]Charité – Universitätsmedizin Berlin, Institute of Allergology, 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]Jagiellonian University Medical College, Department of Clinical and Environmental Allergology, Krakow, Poland; [17]Brighton and Sussex University Hospitals NHS Trust, Department of Immunology, Brighton, UK; [18]University Hospital Alexandrovska, Department of Allergology, Clinic of Allergology, Medical University of Sofia, Sofia, Bulgaria; [19]Washington University School of Medicine, Division of Allergy and Immunology, Department of Medicine, St Louis, MO, USA; [20]Ottawa Allergy Research Corporation, Department of Medicine, University of Ottawa, Ottawa, ON, Canada; [21]Universita degli Studi di Milano, Dipartimento 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]University of California, San Diego, Division of Allergy and Immunology, La Jolla, CA, USA

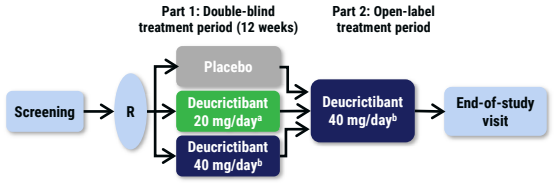
Introduction

- Excess bradykinin is the main mediator 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 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, 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 with placebo, respectively (**Figure 2** and **Table 1**).

Figure 2. Overall monthly attack rate

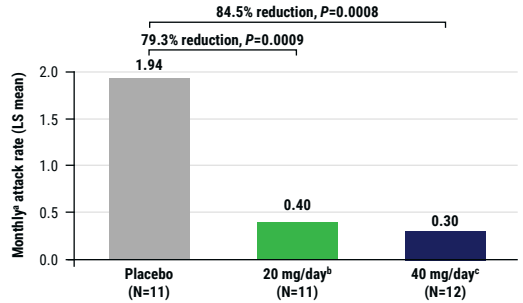


Table 1. Overall monthly attack rate

	Placebo (N=11)	Deucrictibant 20 mg/day[b] (N=11)	Deucrictibant 40 mg/day[c] (N=12)
Monthly[a] attack rate			
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]1 month = 4 weeks. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 20 mg twice daily.

- In analyses of the secondary endpoints, deucrictibant 40 mg/day reduced the occurrence of moderate or 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

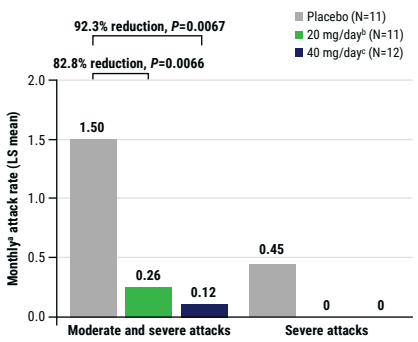


Figure 4. On-demand treated attacks

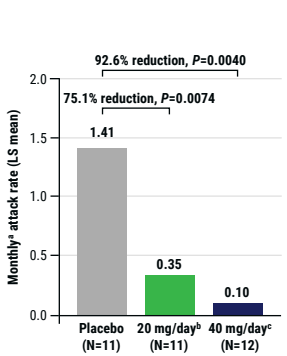
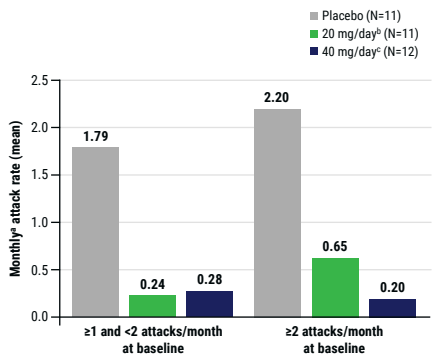


Figure 5. Attacks by baseline rate



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]1 month = 4 weeks. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 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; TEAE, treatment-emergent adverse event. N = number of participants who received at least 1 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 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 March 13, 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 March 13, 2024. **9.** https://www.clinicaltrials.gov/study/NCT05396105. Accessed March 13, 2024. **10.** https://www.clinicaltrials.gov/study/NCT05047185. Accessed March 13, 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: Grants/research support, honoraria or consultation fees, sponsored speaker bureau – **J.A.**: BioCryst, BioMarin, CSL Behring, Cycle Pharmaceuticals, KalVista, Pharming, Pharvaris, Takeda; **F.A.**: CSL Behring, Takeda; **E.A-P.**: Astria, BioCryst, Biomarin, Centogene, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Shire/Takeda, Sobi, UCB; **M.C.**: BioCryst, CSL Behring, KalVista, Menarini, MSD, Novartis, Pharming, Pharvaris, Shire/Takeda, Sobi; **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, Jeinni/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, Halcon, 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 CG 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; Behring, Intellia, KalVista, **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 Cara Bertozzi, PhD, and Holly Richendrfer, PhD, of Two Labs Pharma Services.

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

Conflicts of interest disclosure

Grants/research support, honoraria or consultation fees, sponsored speaker bureau

J.A.: BioCryst, BioMarin, CSL Behring, Cycle Pharmaceuticals, KalVista, Pharming, Pharvaris, Takeda; **F.A.**: CSL Behring, Takeda; **E.A-P.**: Astria, BioCryst, Biomarin, Centogene, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Shire/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, Haleon, 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 CG 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; Behring, Intellia, KalVista; **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 Cara Bertozzi, PhD, and Holly Richendrfer, PhD, of Two Labs Pharma Services.

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

©2024

Introduction

- Excess bradykinin is the main mediator 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]

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 March 13, 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 March 13, 2024. **9**. https://www.clinicaltrials.gov/study/NCT05396105. Accessed March 13, 2024. **10**. https://www.clinicaltrials.gov/study/NCT05047185. Accessed March 13, 2024.

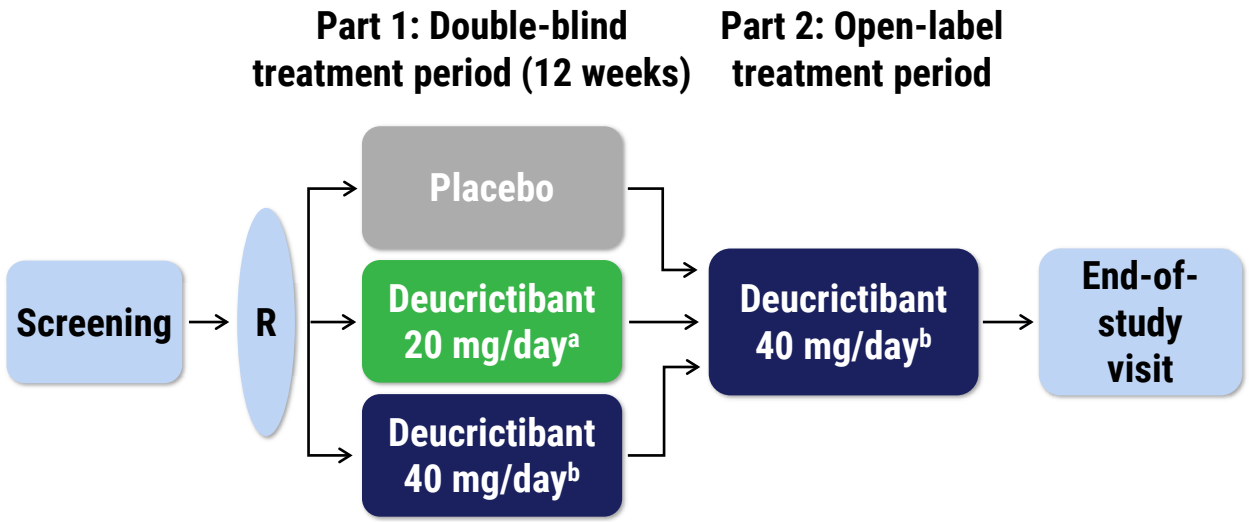
©2024

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

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.
- 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**).
- Primary endpoint:
  - Time-normalized number of investigator-confirmed HAE attacks, expressed as monthly HAE attack rate.
- Secondary endpoints included:
  - Time-normalized number of moderate and severe HAE attacks.
  - Time-normalized number of HAE attacks treated with on-demand medication.

Figure 1. Study design



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

10. https://www.clinicaltrials.gov/study/NCT05047185. Accessed March 13, 2024. †CHAPTER-1 is a Pharvaris-sponsored clinical trial. ClinicalTrials.gov identifier: NCT05047185.

©2024

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

Results – Overall monthly attack rate

- 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. Overall monthly attack rate

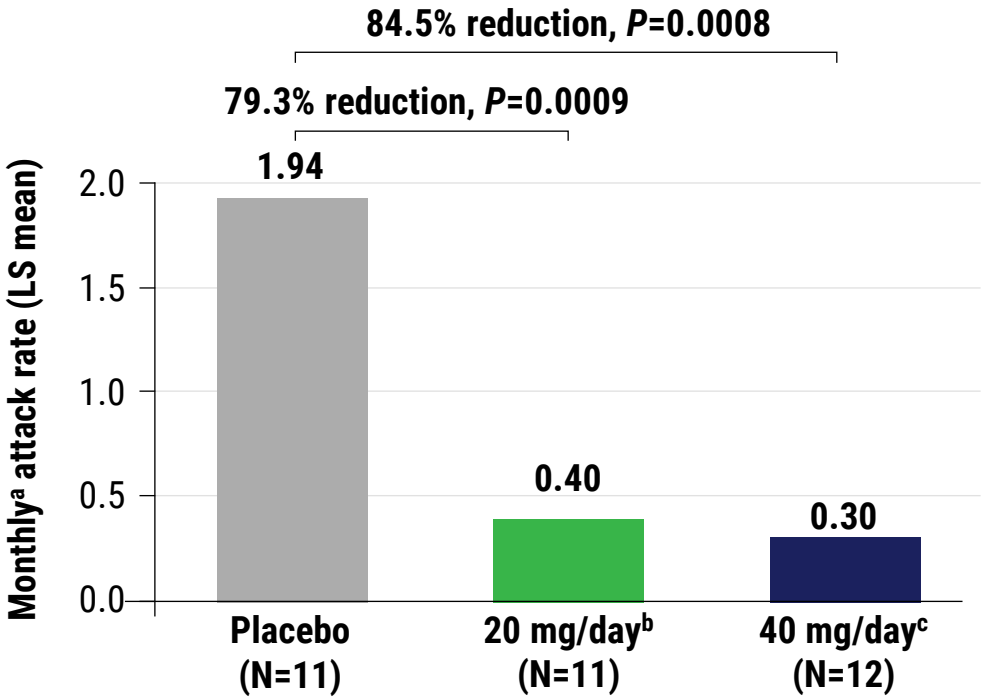


Table 1. Overall monthly attack rate

	Placebo (N=11)	Deucrictibant 20 mg/day[b] (N=11)	Deucrictibant 40 mg/day[c] (N=12)
Monthly[a] attack rate			
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]1 month = 4 weeks. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 20 mg twice daily.

©2024

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

Results – Moderate and severe attacks and on-demand treated attacks

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

Figure 3. Moderate and severe attacks

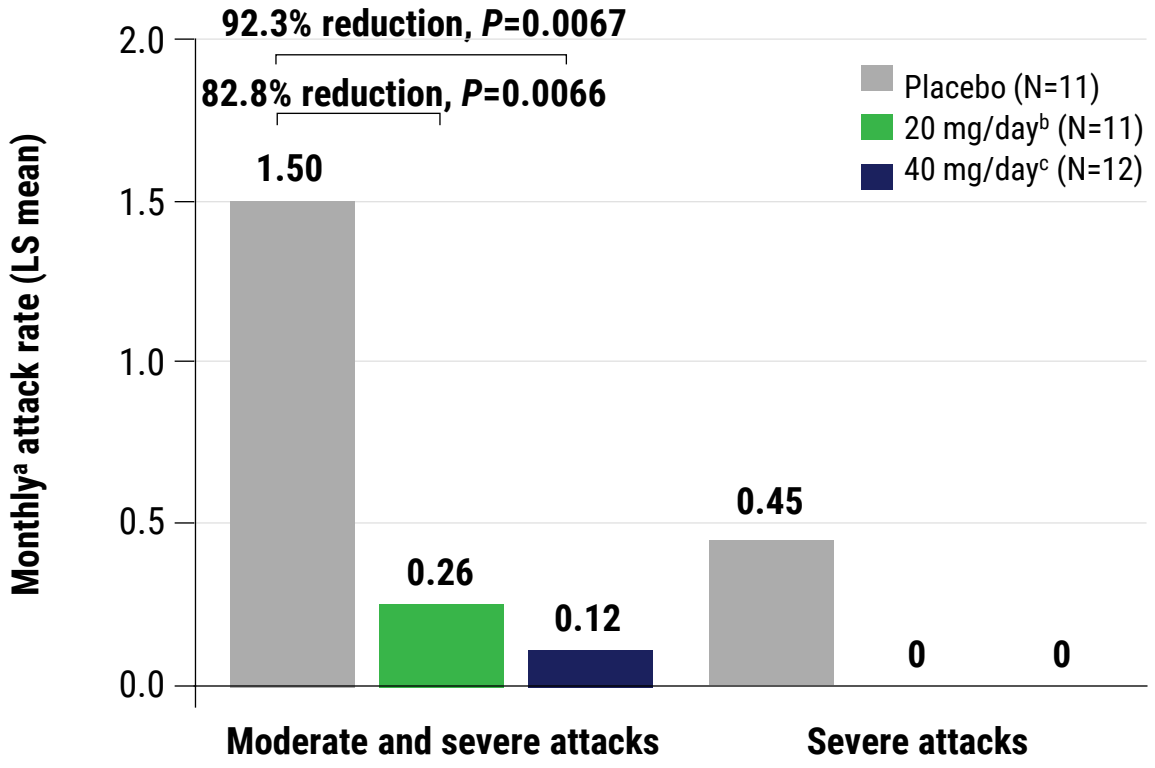
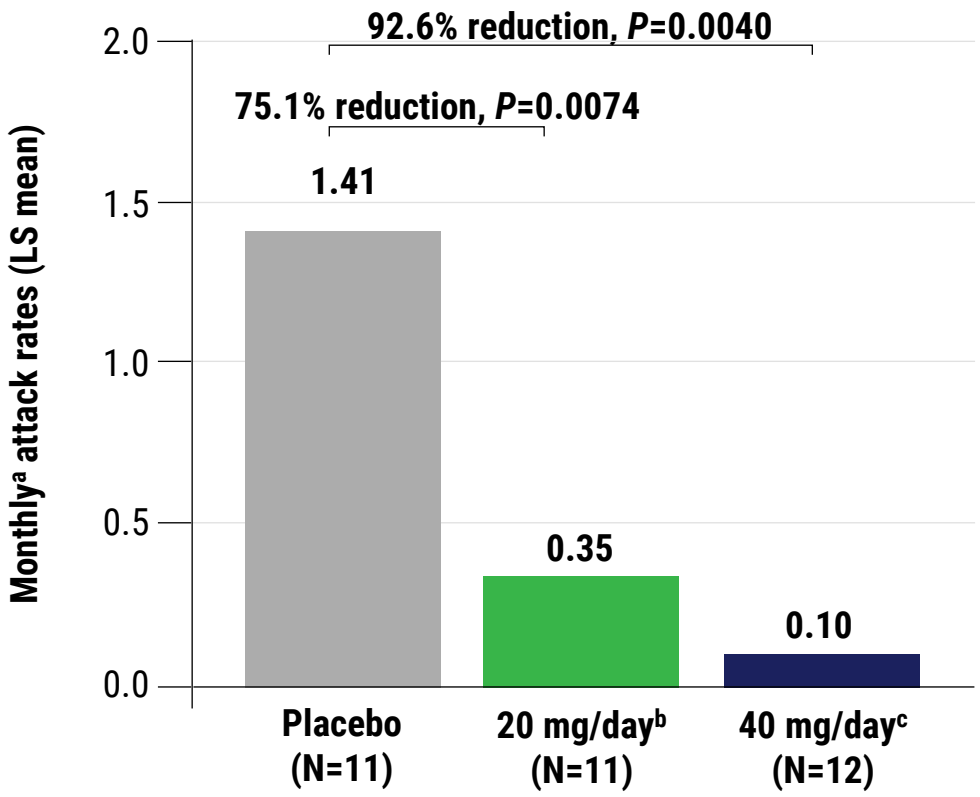


Figure 4. On-demand treated attacks



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]1 month = 4 weeks. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 20 mg twice daily.

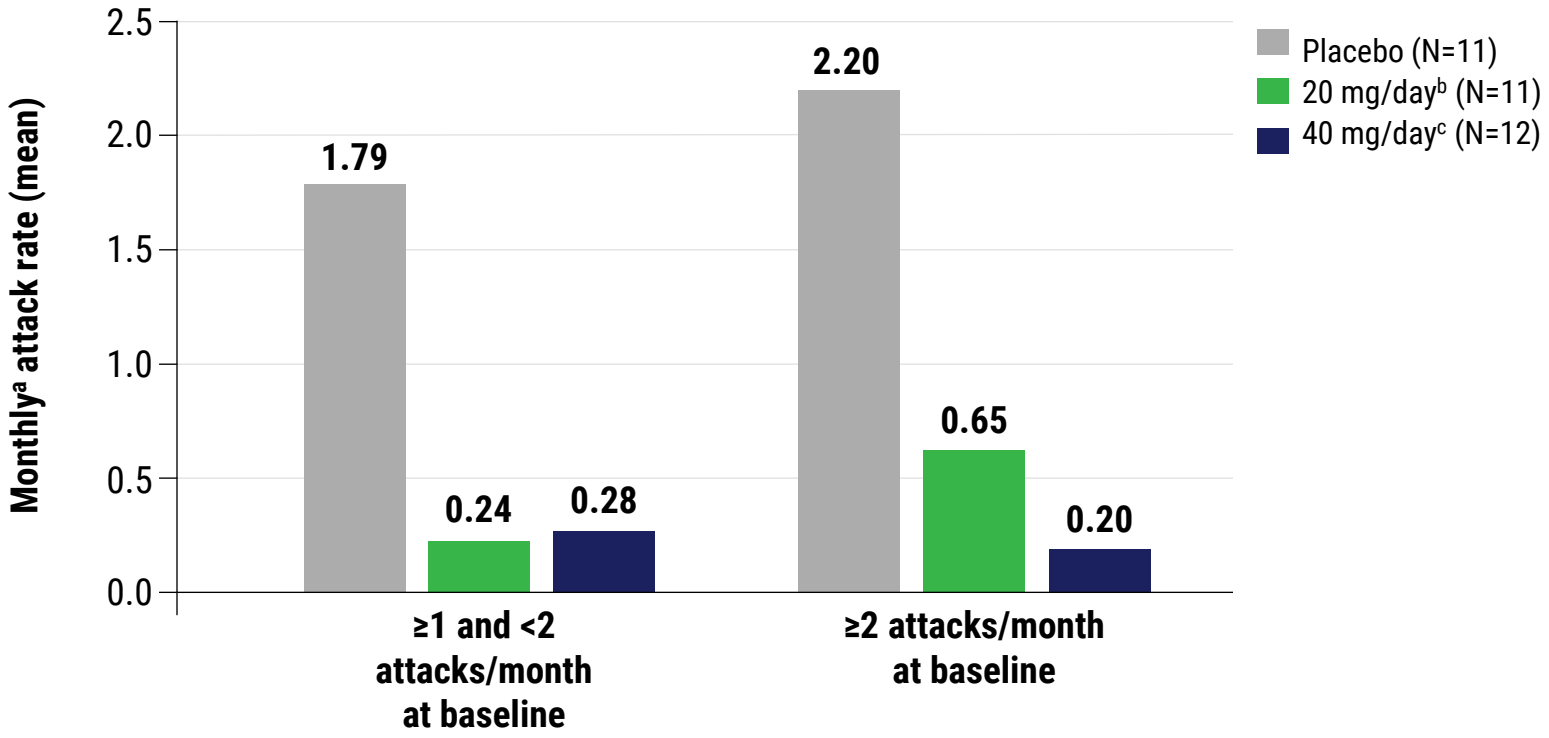
©2024

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

Results – Monthly attack rate by baseline number of attacks

- A consistent reduction in monthly attack rate was observed with deucrictibant treatment regardless of baseline attack rate (**Figure 5**).

Figure 5. Attacks by baseline rate



IR, immediate-release. N = number of randomized participants. [a]1 month = 4 weeks. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 20 mg twice daily.

©2024

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

Results – Adverse events

- 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; TEAE, treatment-emergent adverse event (defined as an adverse event that occurred after the first administration of double-blinded study treatment).
N = number of participants who received at least 1 dose of blinded study treatment. [a]Deucrictibant IR capsule, 10 mg twice daily. [b]Deucrictibant IR capsule, 20 mg twice daily.

©2024

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

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.

©2024

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

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

John Anderson[1], Francesco Arcoleo[2], Emel Aygören-Pürsün[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]AllerVie Health, Clinical Research Center of Alabama, Birmingham, AL, USA; [2]AOR Villa Sofia-Cervello, UOC di Patologia Clinica e Immunologia, Palermo, Italy; [3]University Hospital Frankfurt, Department for Children and Adolescents, Goethe University Frankfurt, Frankfurt, Germany; [4]University Hospital of Padua, Department of Systems Medicine, Padua, Italy; [5]Université de Montréal, CHU de Montréal, Montréal, QC, Canada; [6]St. James's Hospital 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, London, UK; [10]Ospedale di Civitanova Marche, Civitanova Marche, Italy; [11]Cambridge University Hospitals NHS Foundation Trust, Department of Clinical Immunology, Cambridge, UK; [12]Medical University of Vienna, Department of Dermatology, Vienna, Austria; [13]Charité – Universitätsmedizin Berlin, Institute of Allergology, 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]Jagiellonian University Medical College, Department of Clinical and Environmental Allergology, Krakow, Poland; [17]Brighton and Sussex University Hospitals NHS Trust, Department of Immunology, Brighton, UK; [18]University Hospital Alexandrovska, Department of Allergology, Clinic of Allergology, Medical University of Sofia, Sofia, Bulgaria; [19]Washington University School of Medicine, Division of Allergy and Immunology, Department of Medicine, St Louis, MO, USA; [20]Ottawa Allergy Research Corporation, Department of Medicine, University of Ottawa, Ottawa, ON, Canada; [21]Universita degli Studi di Milano, Dipartimento 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]University of California, San Diego, Division of Allergy and Immunology, La Jolla, CA, USA

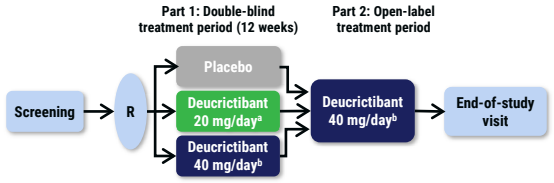
Introduction

- Excess bradykinin is the main mediator 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 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, 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 with placebo, respectively (**Figure 2** and **Table 1**).

Figure 2. Overall monthly attack rate

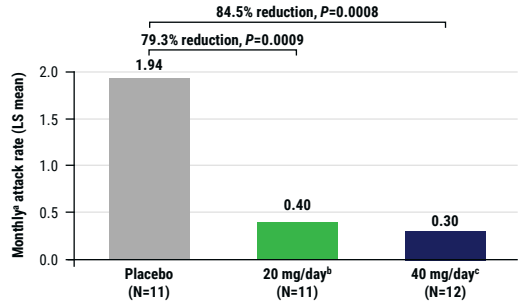


Table 1. Overall monthly attack rate

	Placebo (N=11)	Deucrictibant 20 mg/day[b] (N=11)	Deucrictibant 40 mg/day[c] (N=12)
Monthly[a] attack rate			
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]1 month = 4 weeks. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 20 mg twice daily.

- In analyses of the secondary endpoints, deucrictibant 40 mg/day reduced the occurrence of moderate or 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

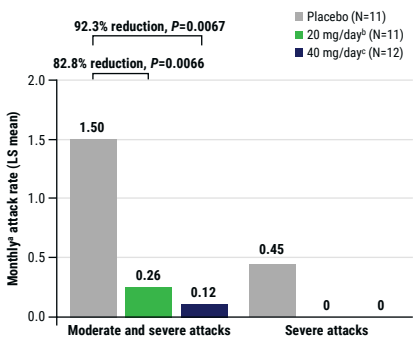


Figure 4. On-demand treated attacks

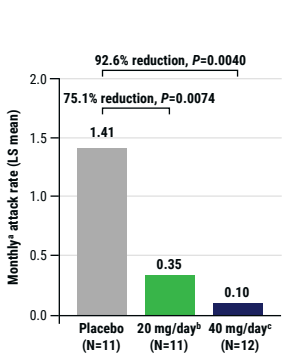
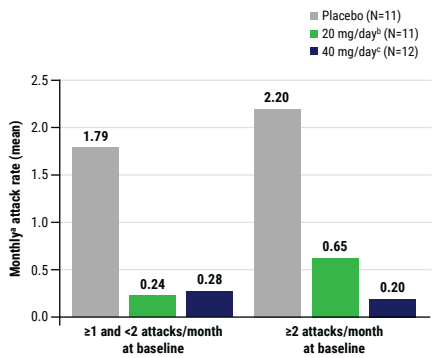


Figure 5. Attacks by baseline rate



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]1 month = 4 weeks. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 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; TEAE, treatment-emergent adverse event. N = number of participants who received at least 1 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 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 March 13, 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 March 13, 2024. **9.** https://www.clinicaltrials.gov/study/NCT05396105. Accessed March 13, 2024. **10.** https://www.clinicaltrials.gov/study/NCT05047185. Accessed March 13, 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: Grants/research support, honoraria or consultation fees, sponsored speaker bureau – **J.A.**: BioCryst, BioMarin, CSL Behring, Cycle Pharmaceuticals, KalVista, Pharming, Pharvaris, Takeda; **F.A.**: CSL Behring, Takeda; **E.A-P.**: Astria, BioCryst, Biomarin, Centogene, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Shire/Takeda, Sobi, UCB; **M.C.**: BioCryst, CSL Behring, KalVista, Menarini, MSD, Novartis, Pharming, Pharvaris, Shire/Takeda, Sobi; **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, Jeinni/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, Halcon, 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 CG 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; Behring, Intellia, KalVista, **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 Cara Bertozzi, PhD, and Holly Richendrfer, PhD, of Two Labs Pharma Services.

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