

Long-Term Safety and Efficacy of Oral Deucricitbant for Prophylaxis in Hereditary Angioedema: Final Results of the Phase 2 CHAPTER-1 Open-Label Extension Study

John Anderson¹, Michael E. Manning², H. James Wedner³, Umar Katbeh⁴, Marc A. Riedl⁵
Presented by **Lindsay Adair**⁶

¹AllerVie Health, Clinical Research Center of Alabama, Birmingham, AL, USA; ²Allergy, Asthma and Immunology Associates, Ltd., Scottsdale, AZ, USA; ³Washington University School of Medicine, St. Louis, MO, USA; ⁴Pharvaris GmbH, Zug, Switzerland; ⁵University of California San Diego, La Jolla, CA, USA; ⁶Pharvaris Inc., Lexington, MA, USA

Key takeaways

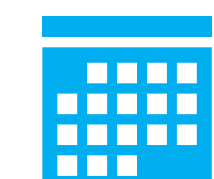
Final data from the completed open-label extension (OLE) of the Phase 2 CHAPTER-1 study investigating oral deucricitbant provide first evidence on the long-term safety and efficacy of bradykinin B2 receptor antagonism for prophylaxis against bradykinin-mediated angioedema attacks.

Safety



Deucricitbant was generally well tolerated with no safety signals observed in laboratory parameters, vital signs, or ECG findings

Efficacy



Up to ~34 months

Attack rate was reduced by week 1 and remained low for up to ~34 months

0.12

Overall on-study mean attack rate during the OLE



Attack-free

Approximately half of participants were attack-free during the OLE

ECG, electrocardiogram; OLE, open-label extension.

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

Background

- Hereditary angioedema (HAE):** a bradykinin-mediated condition with painful swelling attacks affecting multiple locations in the body.¹
- Unmet need:** additional prophylactic treatments offering injectable-like efficacy™, a well-tolerated profile, and ease of administration.²⁻⁵
- Oral deucricitbant:** a selective bradykinin B2 receptor antagonist under development for prophylaxis and on-demand treatment of bradykinin-mediated attacks.⁶⁻¹⁴

Objective

To evaluate the safety and efficacy of deucricitbant for long-term prophylaxis of HAE attacks in adults in the open-label extension (OLE) of the CHAPTER-1 study.¹¹

Methods

- CHAPTER-1 (NCT05047185)*:** a two-part, Phase 2 study.¹¹
 - Part 1 randomized controlled trial (RCT) and Part 2 OLE were completed.
- Eligibility:** adults diagnosed with HAE-1/2, not receiving other prophylactic treatments at screening, and with a pre-specified minimum number of attacks in the 3 months prior to screening.

Figure 1. CHAPTER-1 study design

IR, immediate-release; OLE, open-label extension; RCT, randomized controlled trial. n = number of participants randomized in each treatment group in the RCT. N = number of participants. *Deucricitbant IR capsule, 10 mg twice daily. †Deucricitbant IR capsule, 20 mg twice daily. ‡Twenty-one participants rolled over to the ongoing CHAPTER-4 open-label study (NCT0679881)¹³ in which deucricitbant extended-release tablet is self-administered.

Methods

- Participants:** all 30 participants who completed the RCT continued into the OLE.
 - In the RCT, these 30 participants were randomized to deucricitbant 20 mg/day (n=11) or 40 mg/day (n=10), or placebo (n=9).

Results

Participants in the OLE

- Thirty participants in the OLE received deucricitbant 40 mg/day for a mean (SD) treatment duration of 22.2 (8.1) months.
 - Maximum deucricitbant exposure during the entire study was 33.8 months.
 - For the 14 participants who were attack-free during the OLE, the mean (SD) duration on treatment was 22.4 (7.6) months.
- Twenty-one participants were on study at the time of CHAPTER-1 study end and all continued into the ongoing CHAPTER-4 open-label study (NCT0679881)¹³ in which deucricitbant extended-release (XR) tablet, 40 mg, is self-administered. None of the nine discontinuations in the CHAPTER-1 OLE were reported as treatment-related or associated with an adverse event.

Safety analysis

- Deucricitbant was generally well tolerated, with one treatment-related treatment-emergent adverse event (TEAE) reported: isolated, mild, asymptomatic increased gamma-glutamyltransferase (<2 upper limit of normal).
- No clinically significant abnormalities in laboratory parameters, vital signs, or electrocardiogram findings.
 - Blood pressure remained stable during the OLE.
- No treatment-related severe or serious TEAEs were reported.
- No TEAEs leading to study drug discontinuation, study withdrawal, or death were reported.

Table 1. Adverse events in the OLE

	Placebo to 40 mg/day ^a (N=9)		20 mg/day ^b to 40 mg/day ^a (N=11)		40 mg/day ^a to 40 mg/day ^a (N=10)		Total (N=30)	
	Participants, n (%)	Events, no.	Participants, n (%)	Events, no.	Participants, n (%)	Events, no.	Participants, n (%)	Events, no.
TEAEs	8 (88.9)	40	8 (72.7)	45	8 (80.0)	25	24 (80.0)	110
Treatment-related TEAEs	0	0	0	0	1 (10.0)	1	1 (3.3)	1
Gamma-glutamyltransferase increased ^c	0	0	0	0	1 (10.0)	1	1 (3.3)	1
Serious TEAEs ^d	0	0	1 (9.1)	2	1 (10.0)	1	2 (6.7)	3
Tendon injury	0	0	0	0	1 (10.0)	1	1 (3.3)	1
Arthritis	0	0	1 (9.1)	1	0	0	1 (3.3)	1
Osteoarthritis	0	0	1 (9.1)	1	0	0	1 (3.3)	1
Treatment-related serious TEAEs	0	0	0	0	0	0	0	0
TEAEs leading to study drug discontinuation, study withdrawal, or death	0	0	0	0	0	0	0	0

IR, immediate-release; OLE, open-label extension; RCT, randomized controlled trial; TEAE, treatment-emergent adverse event. TEAE defined as adverse events that started or pre-existing adverse events that worsened during the period between the first study dose in OLE and 4 weeks after the last dose in OLE or the end-of-study visit, whichever was later. N = number of participants who received ≥1 dose of study treatment in the OLE. *Deucricitbant IR capsule, 20 mg twice daily. †Deucricitbant IR capsule, 10 mg twice daily. ‡Started during the RCT, resolved while continuing deucricitbant treatment during the OLE, and reoccurred by end of the OLE; alanine aminotransferase, aspartate aminotransferase, bilirubin, and alkaline phosphatase levels were normal. ††Three serious TEAEs required reconstruction surgery, hip replacement, or knee replacement. These were not considered treatment-related.

Results

Figure 2. Blood pressure remained stable during long-term treatment with deucricitbant

Efficacy analysis

Figure 3. Attack rate was reduced by week 1 and week 13 and remained low for up to ~34 months

Figure 4. Average of 92.4% attack reduction from study baseline^a

IR, immediate-release; OLE, open-label extension; RCT, randomized controlled trial. N = number of participants in the OLE. *92.4% is the average participant-level reduction from CHAPTER-1 RCT baseline and excludes one participant with 4 days of OLE treatment and no attacks. †Based on time-normalized number of attacks per 4 weeks. ‡Crude mean attack rate at baseline. †Crude mean attack rate in the OLE. †Deucricitbant IR capsule, 20 mg twice daily.

Results

Figure 5. Moderate-to-severe attack rate was reduced in the RCT and remained low in the OLE

IR, immediate-release; LS, least squares; OLE, open-label extension; RCT, randomized controlled trial. n = number of participants randomized in each treatment group in the RCT. N = number of participants in the OLE. LS mean estimates of attack rate are based on Poisson regression models adjusted for baseline attack rate and time on treatment. No multiplicity adjustment was applied. *The P-values in this figure are nominal. †Based on time-normalized number of attacks per 4 weeks. †Deucricitbant IR capsule, 10 mg twice daily. †Deucricitbant IR capsule, 20 mg twice daily.

Figure 6. On-demand treated attack rate was reduced in the RCT and remained low in the OLE

IR, immediate-release; LS, least squares; OLE, open-label extension; RCT, randomized controlled trial. n = number of participants randomized in each treatment group in the RCT. N = number of participants in the OLE. LS mean estimates of attack rate are based on Poisson regression models adjusted for baseline attack rate and time on treatment. No multiplicity adjustment was applied. *The P-values in this figure are nominal. †Based on time-normalized number of attacks per 4 weeks. †Deucricitbant IR capsule, 10 mg twice daily. †Deucricitbant IR capsule, 20 mg twice daily.

Figure 7. Attack rate reduced relative to RCT study baseline with approximately half of participants attack-free during the OLE

IR, immediate-release; OLE, open-label extension; RCT, randomized controlled trial. *Participants with ≥4 weeks of treatment in the OLE receiving 40 mg/day (deucricitbant IR capsule, 20 mg twice daily).

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*CHAPTER-1 was a Pharvaris-sponsored clinical trial. [ClinicalTrials.gov identifier: NCT05047185](https://clinicaltrials.gov/ct2/show/study/NCT05047185). The term injectable-like efficacy is a registered trademark of Pharvaris GmbH.

CDI: J.A.: Astria, BioCryst, CSL Behring, Ionis, KalVista, Pharming, Pharvaris, Takeda; M.E.M.: AstraZeneca, Astria, BioCryst, Blueprint, Celldex, Cogent, CSL Behring, GSK, Intellia, Ionis, KalVista, Merck, Novartis, Pharming, Pharvaris, Regeneron, Takeda, Teva; H.J.W.: BioCryst, BioMarin, CSL Behring, Genentech, GSK, Takeda; U.K., L.A.: employees of Pharvaris, hold stocks in Pharvaris; M.A.R.: Astria, BioCryst, BioMarin, Celldex, CSL Behring, Cycle Pharma, Grifols, Intellia, Ionis, KalVista, Novartis, Pharming, Pharvaris, Sanofi-Regeneron, Takeda.

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