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

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Key takeaways

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

Safety

Deucrictibant 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 monthly 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 deucrictibant:** a selective bradykinin B2 receptor antagonist under development for prophylaxis and on-demand treatment of bradykinin-mediated attacks.[6-14]

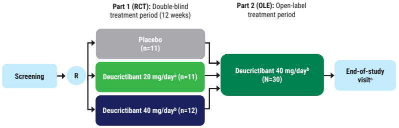
Objective

To evaluate the safety and efficacy of deucrictibant for long-term prophylaxis of HAE attacks in adults in the open-label extension (OLE) of the CHAPTER-1 study.[13]

Methods

- **CHAPTER-1 (NCT05047185)*:** a two-part, Phase 2 study.[13]
  - 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; R, randomization; RCT, randomized controlled trial. n = number of participants randomized in each treatment group in the RCT. N = number of participants. [a]Deucrictibant IR capsule, 10 mg twice daily. [b]Deucrictibant IR capsule, 20 mg twice daily. [c]Twenty-one participants rolled over to the ongoing CHAPTER-4 open-label study (NCT06679881)[12] in which deucrictibant extended-release tablet is self-administered.

- **Participants:** all 30 participants who completed the RCT continued into the OLE.
  - In the RCT, these 30 participants were randomized to deucrictibant 20 mg/day (n=11) or 40 mg/day (n=10), or placebo (n=9).
- **Key OLE objectives:** evaluate the long-term safety (primary objective) and efficacy of deucrictibant for prophylaxis against HAE attacks.

Results

Participants in the OLE

- Thirty participants in the OLE received deucrictibant 40 mg/day for a mean (SD) treatment duration of 22.2 (8.1) months.
  - Maximum deucrictibant exposure during the entire study was 33.8 months.
  - For the 14 participants that 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 (NCT06679881)[12] in which deucrictibant 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

- Deucrictibant 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 (additional details in poster D1.322).
- No treatment-related severe or serious TEAEs were reported.
- No TEAEs leading to study drug discontinuation, study withdrawal, or death.

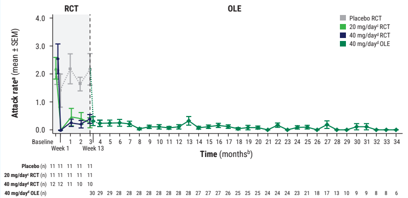
Table 1. Adverse events in the OLE

	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, n	Participants, n (%)	Events, n	Participants, n (%)	Events, n	Participants, n (%)	Events, n
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. [a]Deucrictibant IR capsule, 20 mg twice daily. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Started during the RCT, resolved while continuing deucrictibant treatment during the OLE, and reoccurred by end of the OLE; alanine aminotransferase, aspartate aminotransferase, bilirubin, and alkaline phosphatase levels were normal. [d]Three serious TEAEs required reconstruction surgery, hip replacement, or knee replacement. These were not considered treatment-related.

Efficacy analysis

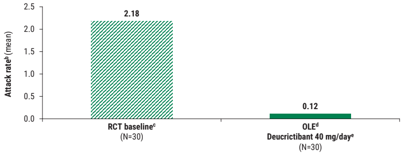
Figure 2. Attack rate was reduced by week 1 and week 13 and remained low for up to ~34 months



IR, immediate-release; OLE, open-label extension; RCT, randomized controlled trial; SEM, standard error of the mean. n = number of participants analyzed at each timepoint. [a]Based on time normalized number of attacks per 4 weeks. [b]1 month = 4 weeks. [c]Deucrictibant IR capsule, 10 mg twice daily. [d]Deucrictibant IR capsule, 20 mg twice daily.

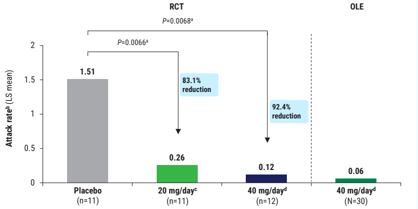
Results

Figure 3. Average of 92.4% attack reduction from study baseline[a]



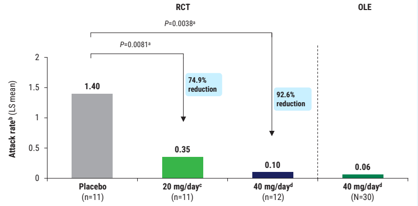
IR, immediate-release; OLE, open-label extension; RCT, randomized controlled trial. N = number of participants in the OLE. [a]92.4% is the average participant-level reduction from CHAPTER-1 RCT baseline and excludes one participant with 4 days of OLE treatment and no attacks. [b]Based on time-normalized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

Figure 4. 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. [a]The *P*-values in this figure are nominal. [b]Based on time-normalized number of attacks per 4 weeks. [c]Deucrictibant IR capsule, 10 mg twice daily. [d]Deucrictibant IR capsule, 20 mg twice daily.

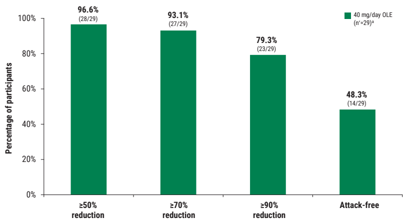
Figure 5. On-demand treated attack rate was reduced in the RCT and remained low in the OLE



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

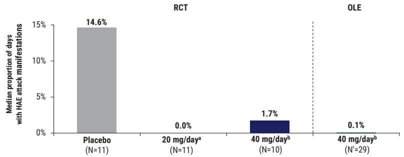
Results

Figure 6. 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. [a]Participants with ≥4 weeks of treatment in the OLE receiving 40 mg/day (deucrictibant IR capsule, 20 mg twice daily).

Figure 7. Median proportion of days with HAE attack manifestations was reduced in the RCT and remained low in the OLE



HAE, hereditary angioedema; IR, immediate-release; OLE, open-label extension; RCT, randomized controlled trial. N = Number of participants with ≥4 weeks of treatment in the RCT. N' = Number of participants with ≥4 weeks of treatment in the OLE. [a]Deucrictibant IR capsule, 10 mg twice daily. [b]Deucrictibant IR capsule, 20 mg twice daily.

- Attack rate decreased during the RCT and remained low through the OLE regardless of baseline attack rate:
  - For participants with ≥1 to <2 attacks per month at baseline, mean attack rate per 4 weeks in the RCT was 1.79, 0.24, and 0.28 for participants in the placebo, deucrictibant 20 mg/day, and deucrictibant 40 mg/day groups, respectively, and 0.09 for participants in the OLE.
  - For participants with ≥2 attacks per month at baseline, mean attack rate per 4 weeks in the RCT was 2.20, 0.65, and 0.20 for participants in the placebo, deucrictibant 20 mg/day, and deucrictibant 40 mg/day groups, respectively, and 0.16 for participants in the OLE.

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