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

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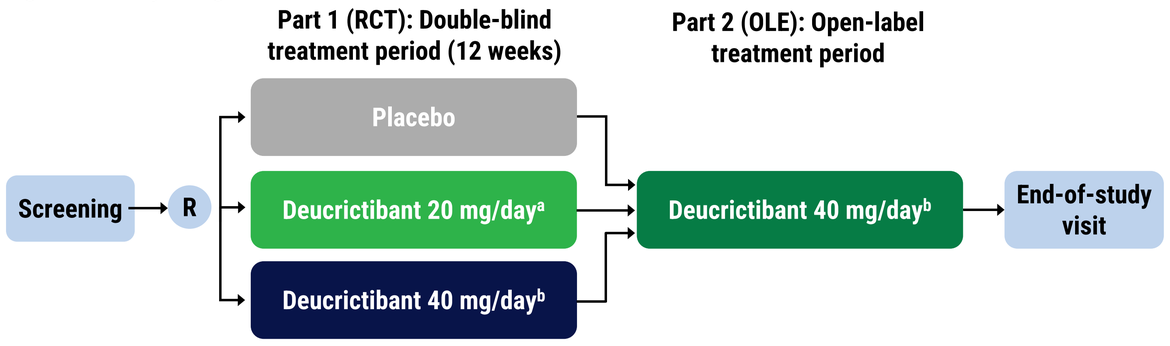
Rationale

- 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



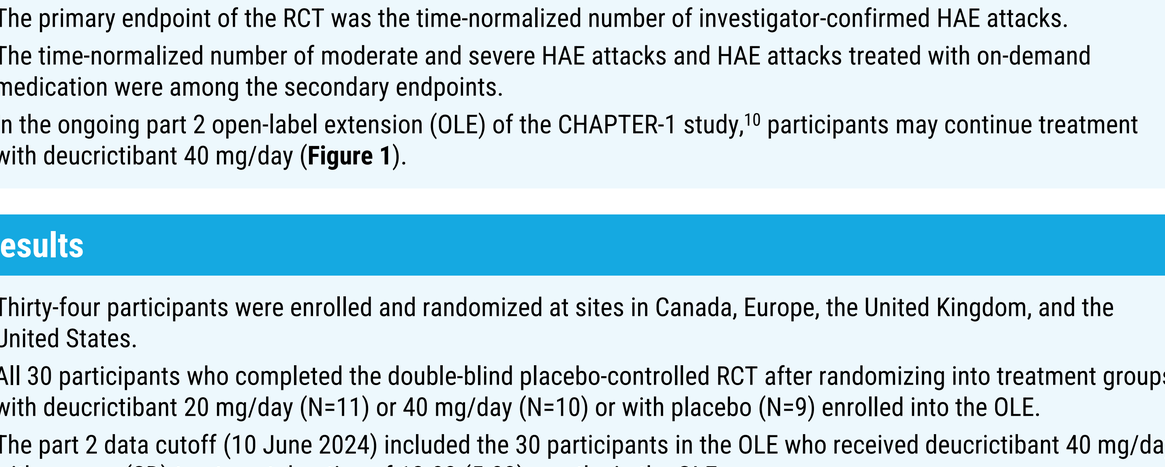
IR, immediate-release; OLE, open-label extension; R, randomization; RCT, randomized controlled trial.
[a]Deucrictibant IR capsule, 10 mg twice daily. [b]Deucrictibant IR capsule, 20 mg twice daily.

- 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).[13]
- 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 (**Figure 1**).

Results

- Thirty-four participants were enrolled and randomized at sites in Canada, Europe, the United Kingdom, and the United States.
- All 30 participants who completed the double-blind placebo-controlled RCT after randomizing into treatment groups with deucrictibant 20 mg/day (N=11) or 40 mg/day (N=10) or with placebo (N=9) enrolled into the OLE.
- The part 2 data cutoff (10 June 2024) included the 30 participants in the OLE who received deucrictibant 40 mg/day with a mean (SD) treatment duration of 12.83 (5.03) months in the OLE.
- Mean age was 39.1 years at CHAPTER-1 part 1 baseline; 60.0% were female.
- The primary endpoint was met in the RCT, 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**).
- Attack rate remained low during long-term (up to >1.5 years) deucrictibant 40 mg/day treatment in the OLE (**Figure 2**).

Figure 2. Attack rate was significantly reduced by deucrictibant and remained low over long-term treatment



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]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.

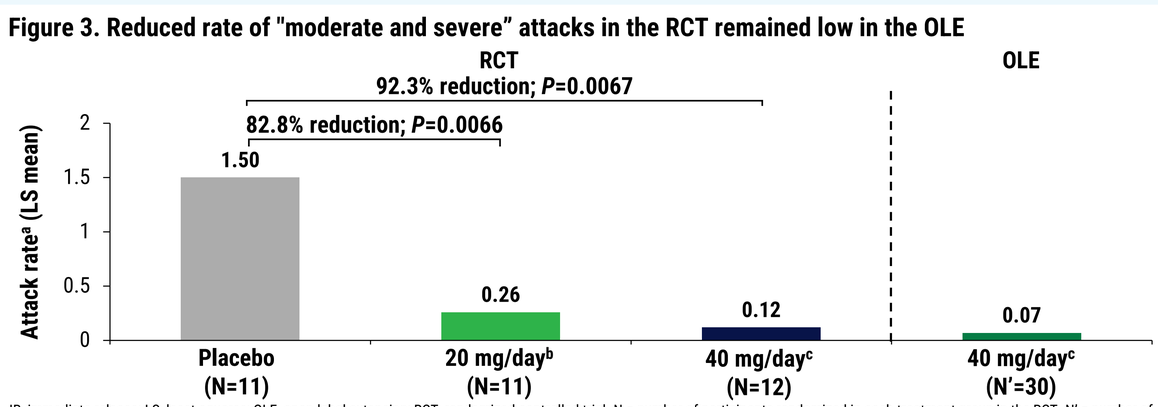
References

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 September 17, 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 September 17, 2024. **9.** https://www.clinicaltrials.gov/study/ NCT05396105. Accessed September 17, 2024. **10.** https://www.clinicaltrials.gov/study/NCT05047185. Accessed September 17, 2024. **11.** https://clinicaltrials.gov/study/NCT06343779. Accessed September 17, 2024. **12.** Maurer M, et al. Presented at: AAAAI; Feb 24–27, 2023; San Antonio, TX, USA. **13.** Groen K, et al. Presented at: ACAAI; Nov 10–14, 2022; Louisville, KY, USA.

Results

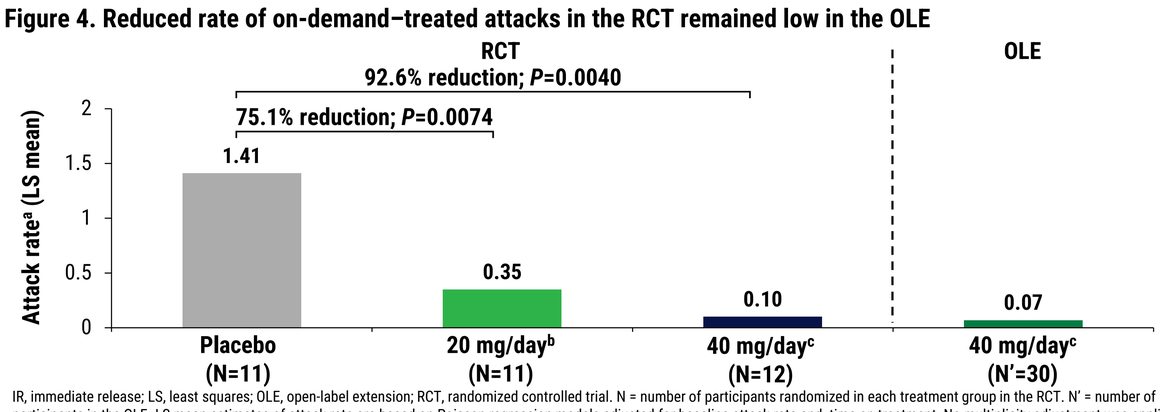
- In analyses of the secondary endpoints in the RCT, deucrictibant 40 mg/day reduced the rate of "moderate and severe" attacks by 92.3% (**Figure 3**) and reduced the rate of attacks treated with on-demand medication by 92.6% (**Figure 4**).
- The reduced rate of "moderate and severe" attacks (**Figure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

Figure 3. Reduced rate of "moderate and severe" attacks in the RCT 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. [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.

Figure 4. Reduced rate of on-demand–treated attacks in the RCT remained low in the OLE



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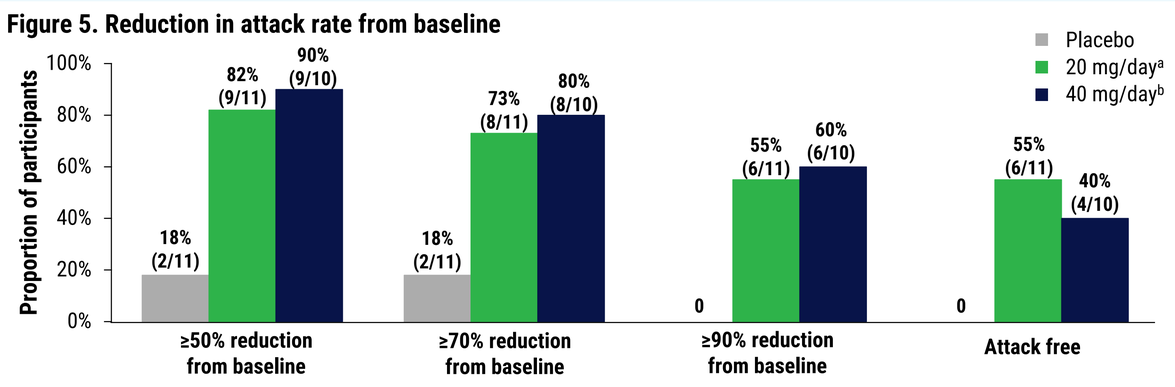
- At 12 weeks, ≥50%, ≥70%, and ≥90% reduction in attack rate from baseline was achieved in 90%, 80%, and 60% of 10 participants receiving deucrictibant 40 mg/day vs 18%, 18%, and 0% of 11 participants receiving placebo (**Figure 5**).

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 in the RCT, and all reported treatment-related treatment-emergent adverse events (TEAEs) were mild in severity (**Table 2**).
- In the RCT, no treatment-related serious or severe TEAEs, no treatment-related TEAEs in laboratory parameters, vital signs, or electrocardiogram findings, and no TEAEs leading to treatment discontinuation, study withdrawal, or death were reported (**Table 2**).
- Deucrictibant was similarly well tolerated in the OLE, with no safety signals, and one treatment-related TEAE of tooth discoloration.

Table 2. Adverse events in the RCT

	Placebo (N=11)		Deucrictibant			
			20 mg/day[a] (N=11)		40 mg/day[b] (N=12)	
Adverse events in the RCT	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
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; RCT, randomized controlled trial; 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.**
- **Results of this analysis provide evidence that during treatment with deucrictibant 40mg/day:**
  - **Following reduction in the RCT, attack rate remained low through >1.5 years.**
  - **Rate of moderate and severe attacks, and attacks treated with on-demand medication reduced in the RCT and remained low in the OLE.**
- **Results from the CHAPTER-1 RCT and its ongoing open-label extension study provide further evidence on the long-term efficacy and safety of deucrictibant for prevention of HAE attacks and support further development of deucrictibant as a potential prophylactic therapy for HAE.**

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

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