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

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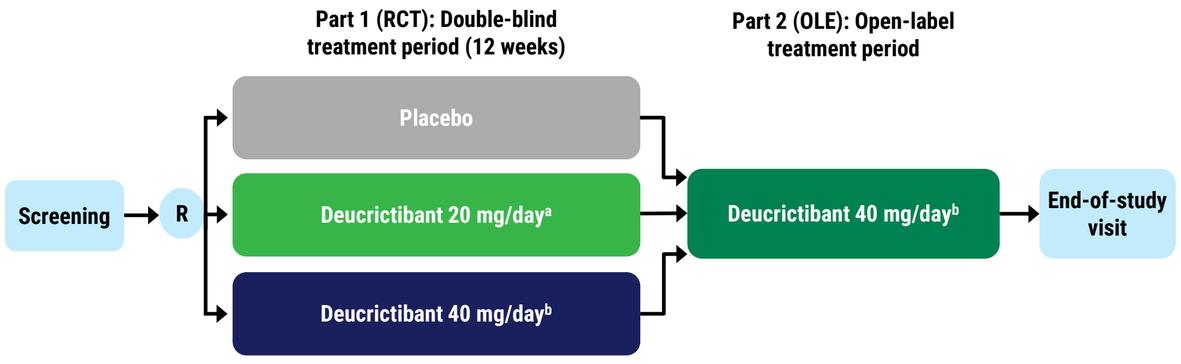
Rationale

- 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.[3,6-12]

Methods

- CHAPTER-1 (NCT05047185)[12]*, 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).[13,14]
- 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, HAE attacks treated with on-demand medication, and percentage of days with symptoms were among the secondary endpoints.
- In the ongoing Part 2 open-label extension (OLE) of the CHAPTER-1 study,[12] 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)

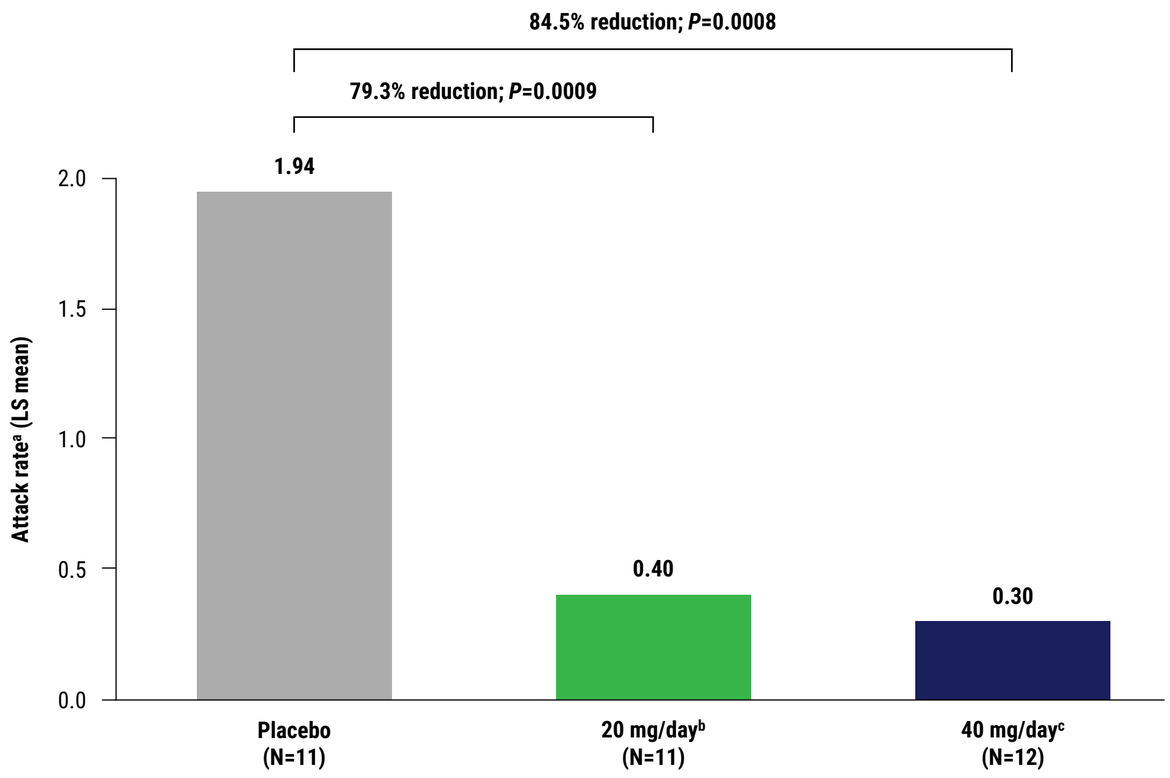


Table 1. Significant reduction in overall attack rate (primary endpoint)

	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

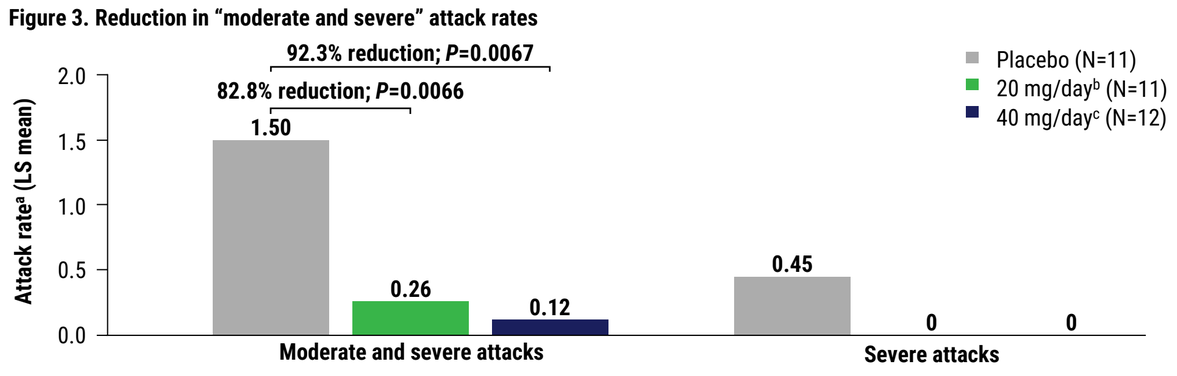
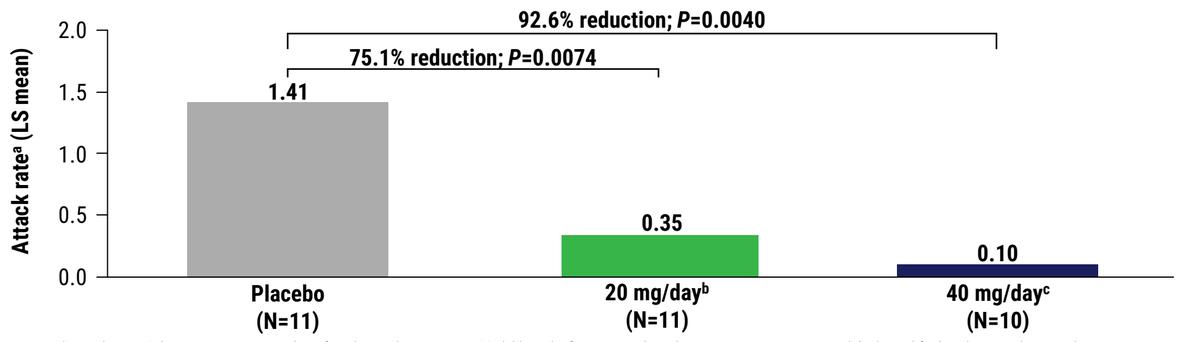


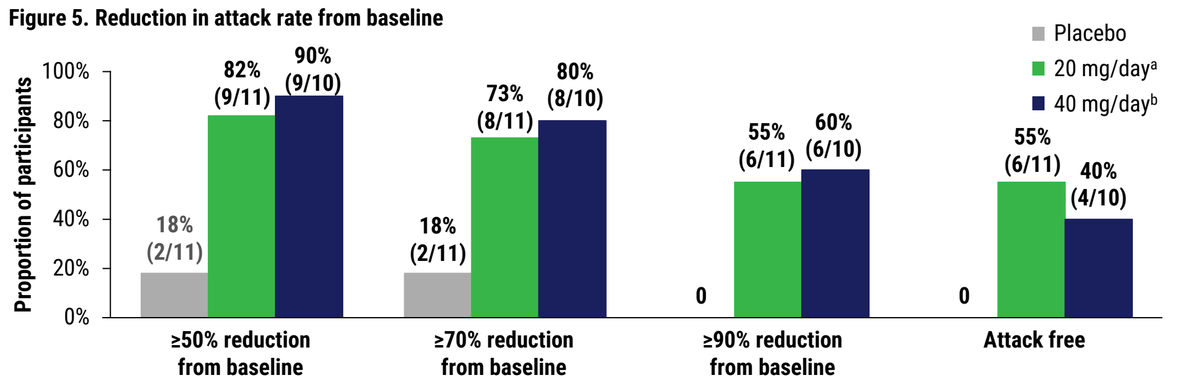
Figure 4. Reduction in attacks treated with on-demand medication



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**).

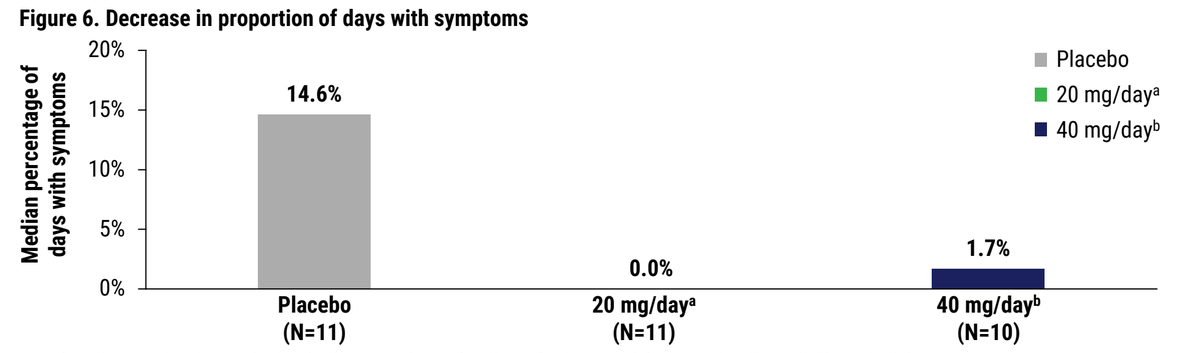
Figure 5. Reduction in attack rate from baseline



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 20 mg/day and 40 mg/day decreased the median percentage of days with symptoms to 0.0% and 1.7%, respectively, compared with 14.6% with placebo (**Figure 6**).

Figure 6. Decrease in proportion of days with symptoms



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, achieved clinically meaningful reductions in occurrence of moderate and severe HAE attacks and HAE attacks treated with on-demand medication, and decreased the time with HAE symptoms.**
- **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.**

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

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