Long-term safety and efficacy of oral deucrictibant for HAE prophylaxis

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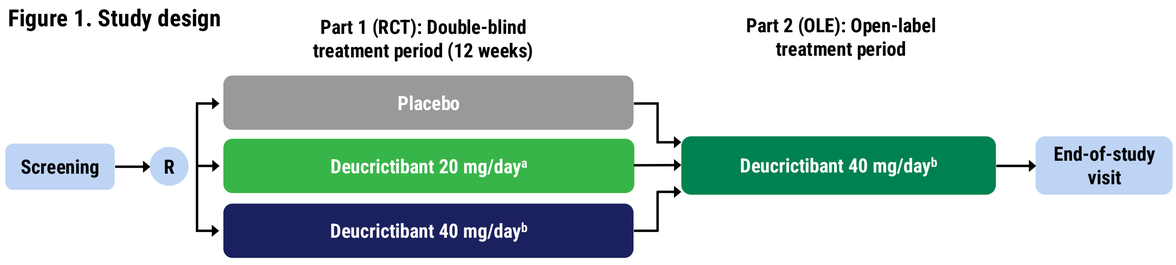
Rationale

- Excess bradykinin is the main mediator of the clinical manifestations of bradykinin-mediated angioedema, including 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 a selective, orally administered bradykinin B2 receptor antagonist under development for prophylactic and on-demand treatment of HAE attacks.[3,6-12]
- CHAPTER-1 (NCT05047185)* is a two-part Phase 2 study evaluating the efficacy and safety of deucrictibant for long-term prophylaxis of HAE attacks.[12]
- In the double-blind placebo-controlled randomized controlled trial period (RCT; part 1), deucrictibant demonstrated[13]:
  - Reduction in attack rate
  - Reduction in occurrence of moderate and severe attacks, and attacks treated with rescue medication
  - Well-tolerated safety profile at both studied doses.

Methods

- In the ongoing open-label extension period (OLE; part 2), participants receive open-label treatment with deucrictibant 40 mg/day to evaluate long-term safety and efficacy of deucrictibant administered for prophylaxis against HAE attacks (**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.

- Eligible participants were aged ≥18 and ≤75 years, diagnosed with HAE-1/2, not receiving other prophylactic treatments at screening, and experienced ≥3 attacks within 3 months prior to screening or ≥2 attacks during screening (up to 8 weeks).
- Deucrictibant immediate-release (IR) capsule was dosed twice per day as a proof-of-concept for the once-daily deucrictibant extended-release (XR) tablet, which is the intended formulation of deucrictibant for prophylactic HAE treatment.[14]
- 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 ongoing OLE.

Results

- This part 2 data cutoff (10 June 2024) included 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.
- Deucrictibant was well-tolerated, with one treatment-related treatment-emergent adverse event (TEAE) of tooth discoloration (**Table 1**).
- 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 1**).

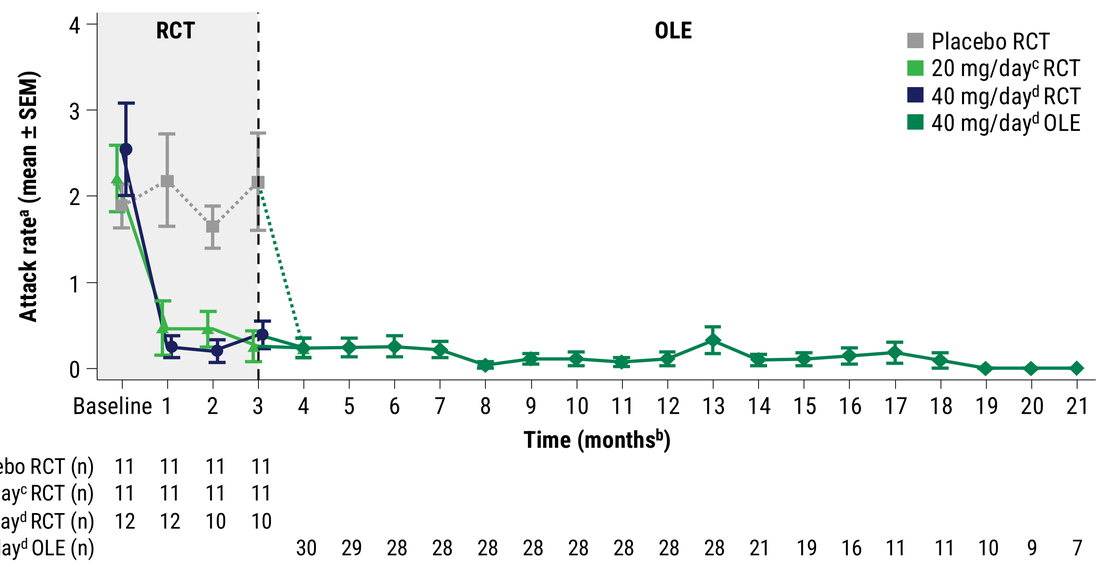
Table 1. Adverse events in the OLE

	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)	
Adverse events	Participants, n (%)	Events, n	Participants, n (%)	Events, n	Participants, n (%)	Events, n	Participants, n (%)	Events, n
TEAEs	**5 (55.6)**	**25**	**7 (63.6)**	**31**	**6 (60.0)**	**16**	**18 (60.0)**	**72**
Treatment-related TEAEs	**1 (11.1)**	**1**	**0**	**0**	**0**	**0**	**1 (3.3)**	**1**
Tooth discoloration	1 (11.1)	1	0	0	0	0	1 (3.3)	1
Serious TEAEs	**0**	**0**	**1 (9.1)**	**1**	**1 (10.0)**	**1**	**2 (6.7)**	**2**
Tendon injury	0	0	0	0	1 (10.0)	1	1 (3.3)	1
Hip arthroplasty (arthritis)	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; TEAE, treatment emergent adverse event. N = number of participants who received at least one dose of blinded study treatment in the OLE by the cutoff date of 10 June 2024. [a]Deucrictibant IR capsule, 20 mg twice daily. [b]Deucrictibant IR capsule, 10 mg twice daily.

- Following early-onset reduction in attack rate with deucrictibant in the first month of the RCT, attack rate remained low during long-term (up to >1.5 years) deucrictibant 40 mg/day treatment in the OLE (**Figure 2**).

Figure 2. Reduced attack rate in the RCT remained low in the OLE

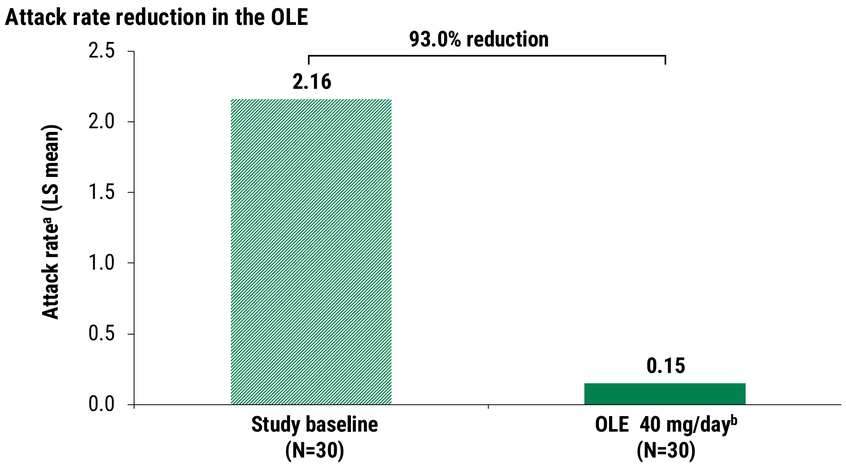


IR, immediate release; OLE, open-label extension; RCT, randomized controlled trial; SEM, standard error of the mean. (n) = number of patients analyzed at each timepoint.
[a]Based on time normalized number of attacks per 4 weeks; [b]1 month = 4 weeks; [c]Deucrictibant IR capsule, 10 mg twice daily; [d]Deucrictibant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

Results

- Deucrictibant 40 mg/day reduced the attack rate in the OLE by 93.0% compared to CHAPTER-1 RCT study baseline (**Figure 3**).

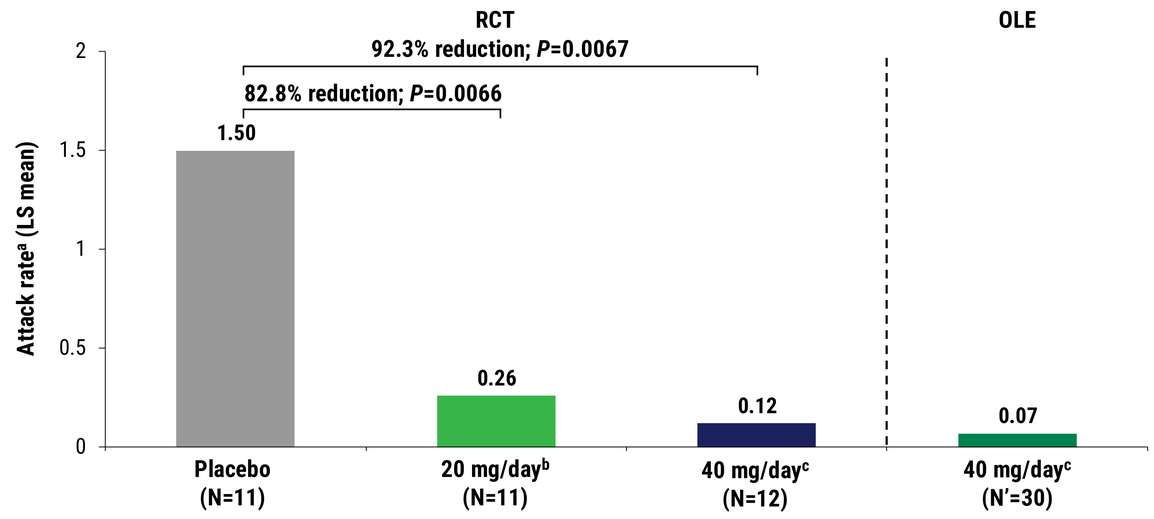
Figure 3. Attack rate reduction in the OLE



IR, immediate release; OLE, open-label extension. 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, 20 mg twice daily.

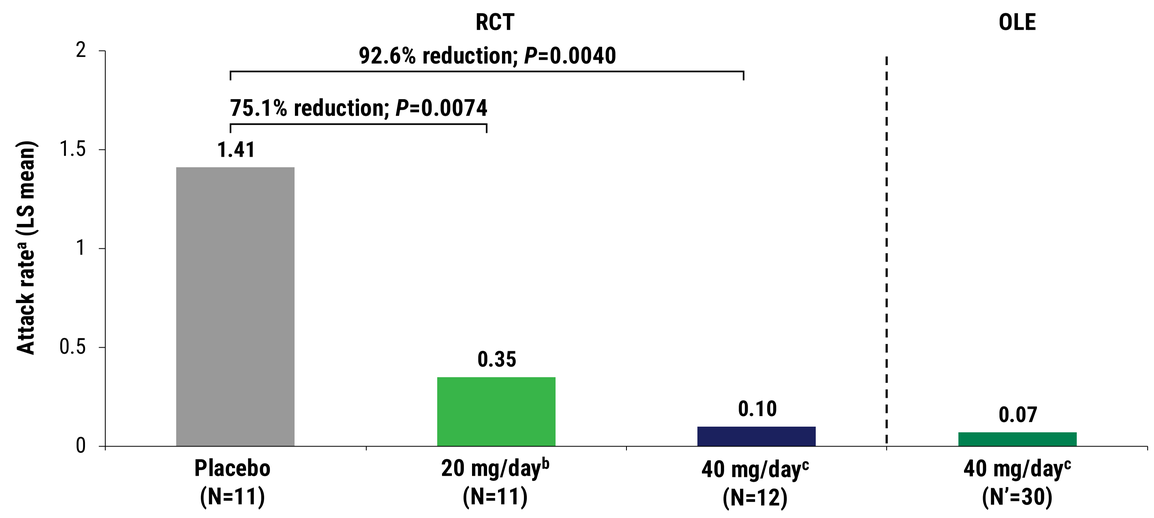
- The reduced rate of "moderate and severe" attacks (**Figure 4**) and attacks treated with on-demand medication (**Figure 5**) remained low in the OLE.

Figure 4. 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 5. Reduced rate of on-demand–treated 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.

Conclusions

- **In the current analysis of the ongoing Phase 2 CHAPTER-1 open-label extension study, deucrictibant 40 mg/day was well-tolerated, with no new safety signals observed.**
- **Results of this analysis provide evidence that during treatment with deucrictibant 40mg/day:**
  - **Following early-onset reduction, attack rate remained low through >1.5 years.**
  - **An early-onset reduction of attack rate in participants switching from placebo to deucrictibant 40 mg/day in the OLE comparable to that in participants initiating deucrictibant in the RCT was observed.**
  - **Rate of moderate and severe attacks, and attacks treated with on-demand medication remained low.**
- **Results of the ongoing CHAPTER-1 open-label extension study provide further evidence on the long-term safety and efficacy of deucrictibant for prevention of HAE attacks and support further development of deucrictibant 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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