

Long-Term Safety and Efficacy of Oral Deucricitbant, a Bradykinin B2 Receptor Antagonist, for Prophylaxis in Hereditary Angioedema: Results of the CHAPTER-1 Open-Label Extension Study

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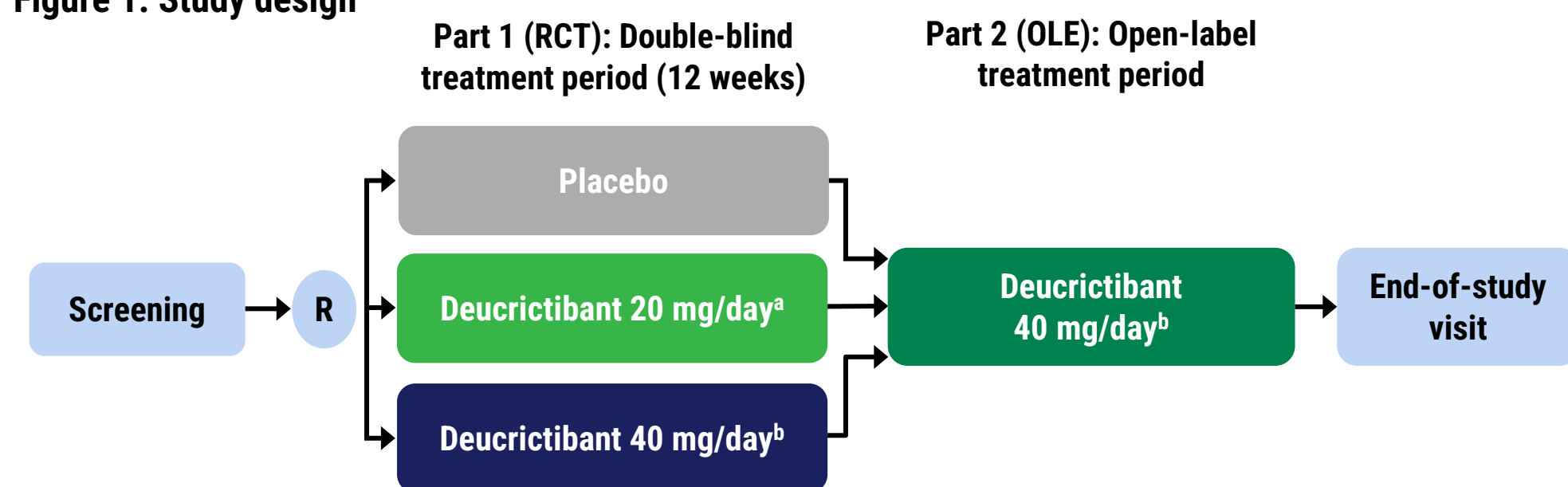
Introduction

- 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
- Deucricitbant 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 deucricitbant for long-term prophylaxis of HAE attacks.¹²
- In the double-blind placebo-controlled randomized controlled trial period (RCT; part 1), deucricitbant demonstrated¹³:
 - Reduction in attack rate
 - Reduction in occurrence of moderate and severe attacks, and attacks treated with on-demand 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 deucricitbant 40 mg/day to evaluate long-term safety and efficacy of deucricitbant 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. *Deucricitbant IR capsule, 10 mg twice daily. ^aDeucricitbant 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).
- Deucricitbant immediate-release (IR) capsule was dosed twice per day as a proof-of-concept for the once-daily deucricitbant extended-release (XR) tablet, which is the intended formulation of deucricitbant for prophylactic HAE treatment.¹⁴
- All 30 participants who completed the double-blind placebo-controlled RCT after randomizing into treatment groups with deucricitbant 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 snapshot (cutoff: 10 June 2024) included 30 participants in the OLE who received deucricitbant 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.
- Deucricitbant 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).
- Following early-onset reduction in attack rate with deucricitbant in the first month of the RCT, attack rate remained low during long-term (up to >1.5 years) deucricitbant 40 mg/day treatment in the OLE (Figure 2).

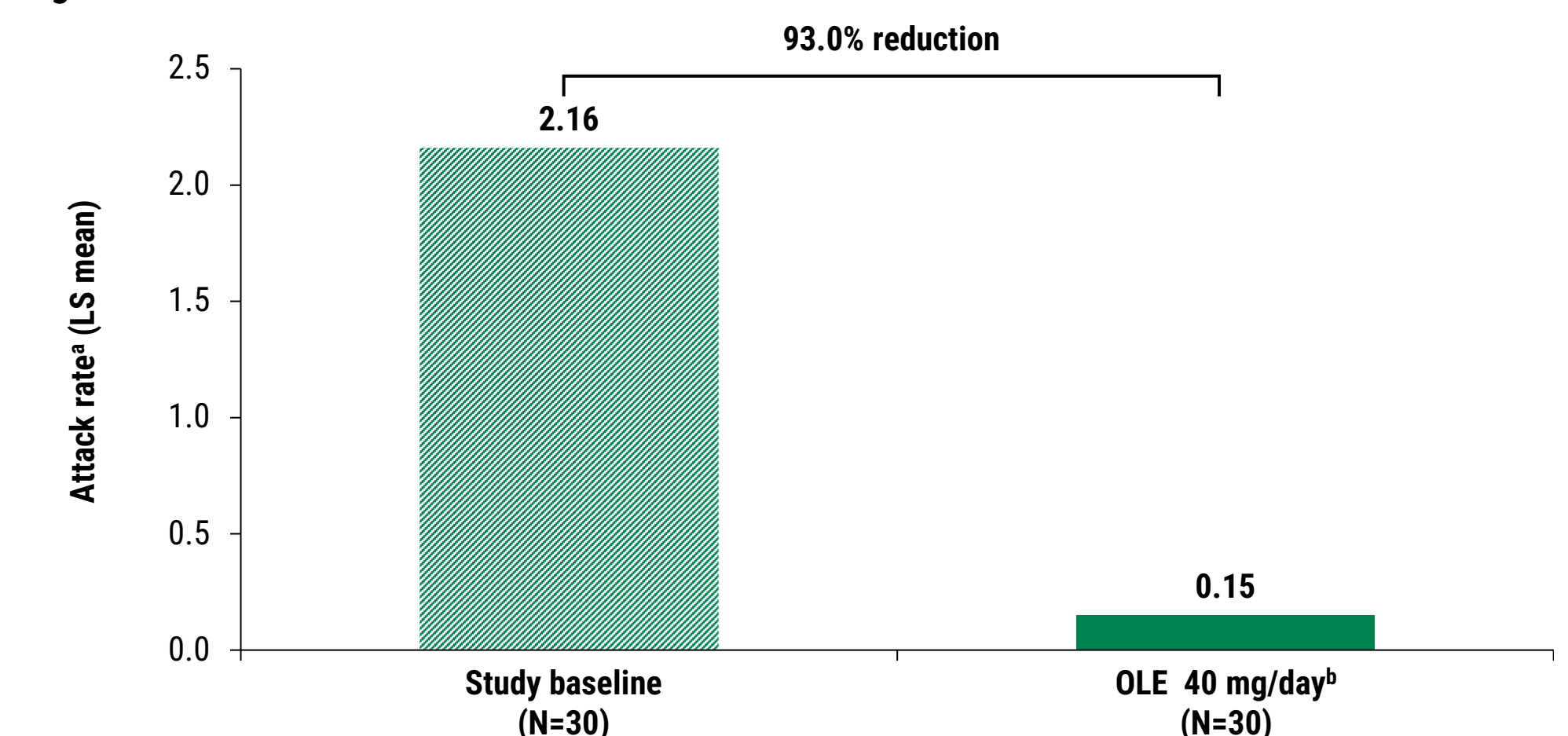
Table 1. Adverse events in the OLE

Adverse events	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	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. ^aDeucricitbant IR capsule, 20 mg twice daily. ^bDeucricitbant IR capsule, 10 mg twice daily.

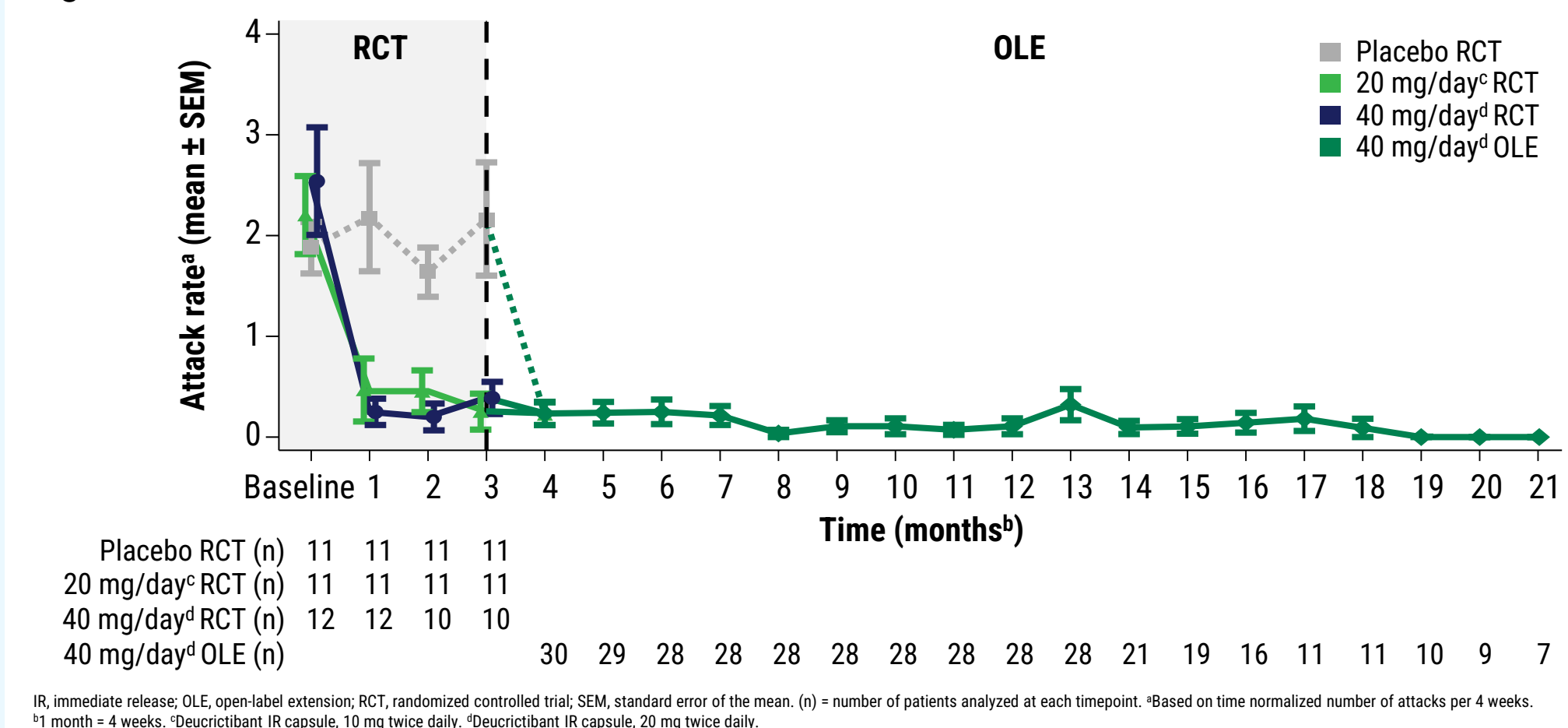
- Deucricitbant 40 mg/day reduced the attack rate in the OLE by 93.0% compared to CHAPTER-1 RCT study baseline (Figure 3).
- The reduced rate of "moderate and severe" attacks (Figure 4) and attacks treated with on-demand medication (Figure 5) remained low in the OLE.

Figure 3. Attack rate reduction in the OLE



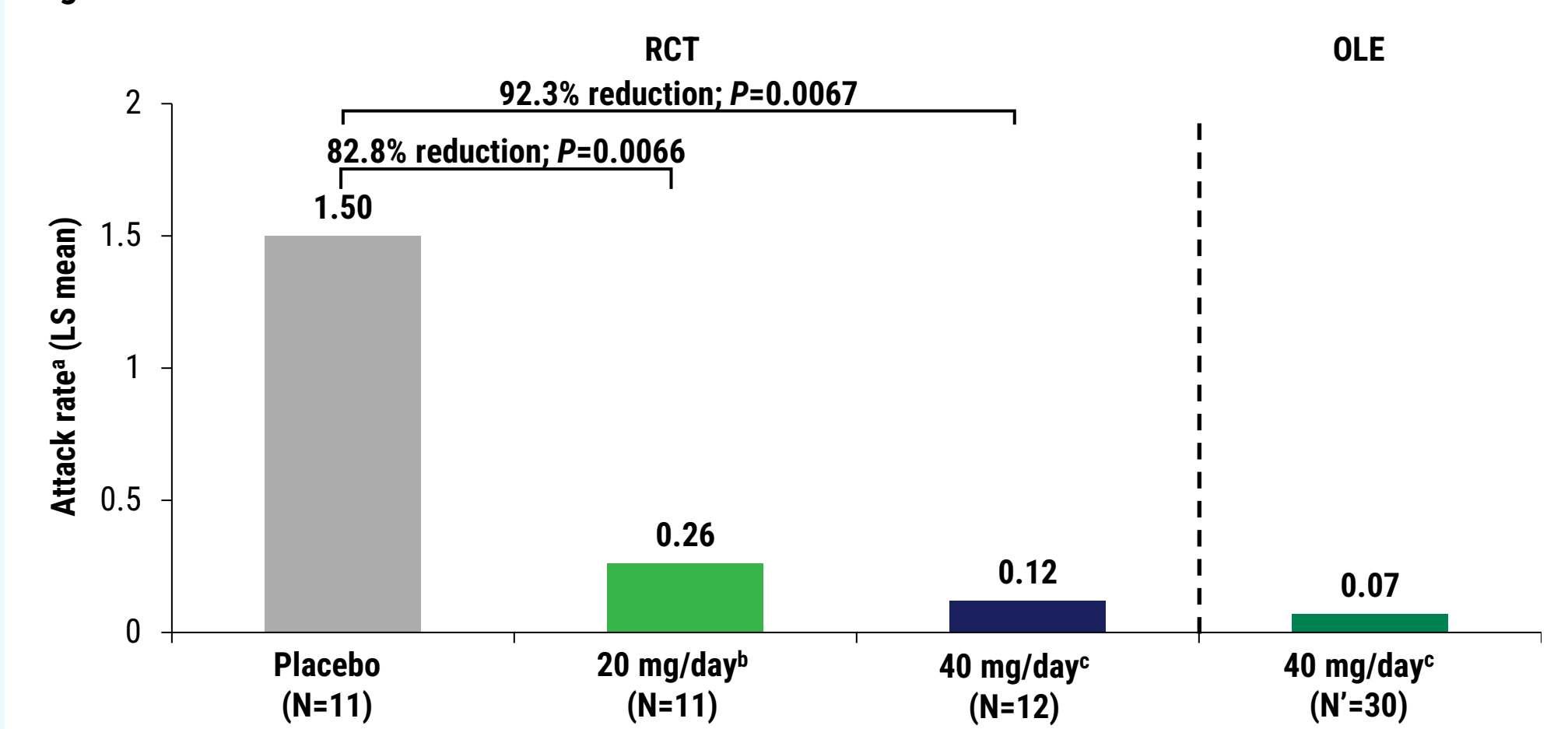
IR, immediate-release; LS, least squares; OLE, open-label extension. N = number of participants in the OLE. LS mean estimates of attack rate are based on Poisson regression models adjusted for baseline attack rate and time on treatment. No multiplicity adjustment was applied. ^aBased on time normalized number of attacks per 4 weeks. ^bDeucricitbant IR capsule, 20 mg twice daily.

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. ^aBased on time normalized number of attacks per 4 weeks. ^bDeucricitbant IR capsule, 10 mg twice daily. ^cDeucricitbant IR capsule, 20 mg twice daily.

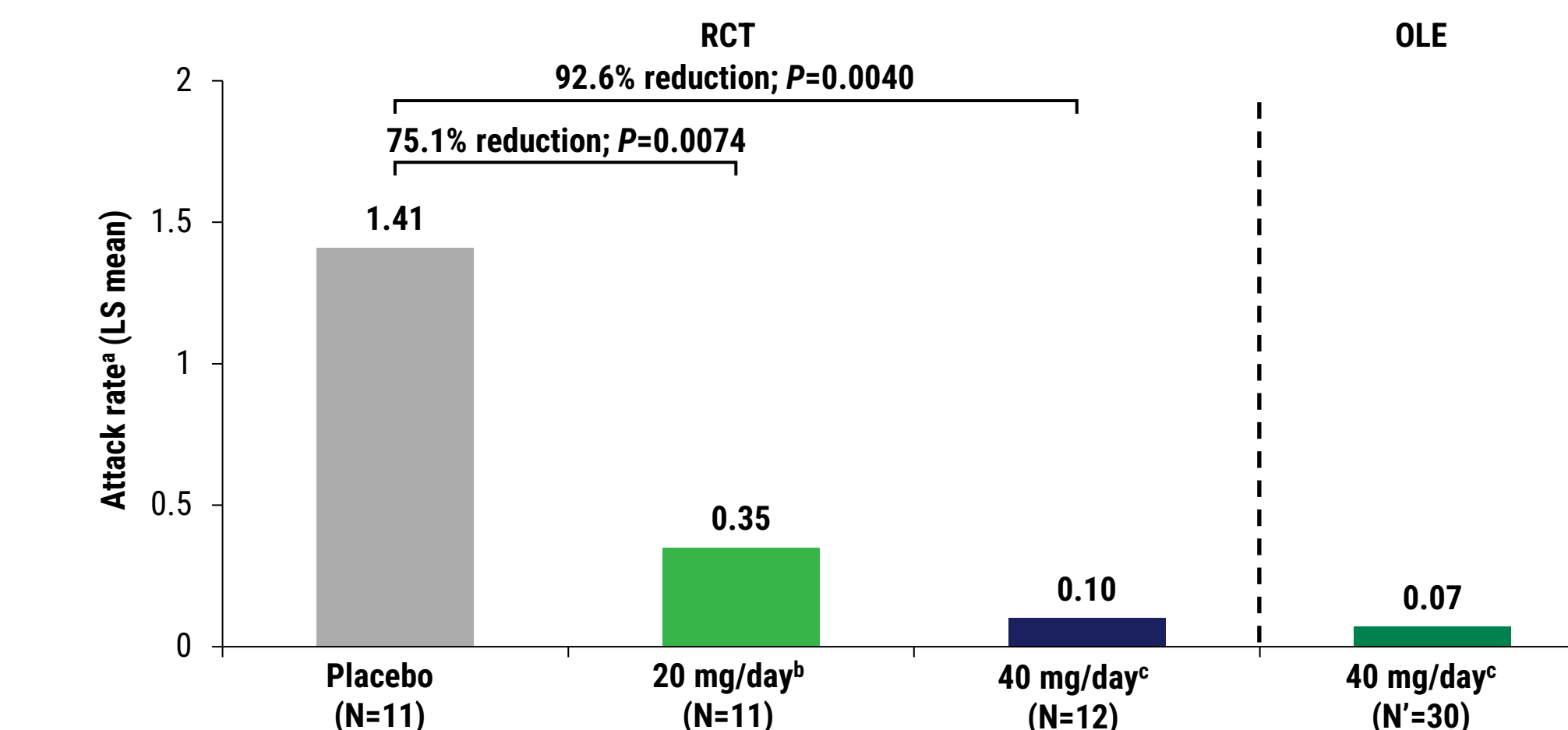
Figure 4. Reduced rate of "moderate and severe" attacks in the RCT remained low in the OLE



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. ^aBased on time normalized number of attacks per 4 weeks. ^bDeucricitbant IR capsule, 10 mg twice daily. ^cDeucricitbant IR capsule, 20 mg twice daily.

Results

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. ^aBased on time normalized number of attacks per 4 weeks. ^bDeucricitbant IR capsule, 10 mg twice daily. ^cDeucricitbant IR capsule, 20 mg twice daily.

Conclusions

- In the current analysis of the ongoing Phase 2 CHAPTER-1 open-label extension study, deucricitbant 40 mg/day was well-tolerated, with no safety signals observed.
- Results of this analysis provide evidence that during treatment with deucricitbant 40 mg/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 deucricitbant 40 mg/day in the OLE comparable to that in participants initiating deucricitbant 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 deucricitbant for prevention of HAE attacks and support further development of deucricitbant as a potential prophylactic therapy for HAE.

References

- Busse PJ, et al. *N Engl J Med*. 2020;382:1136-48.
- Bouillet L, et al. *Allergy Asthma Proc*. 2022;43:406-12.
- Betschel SD, et al. *J Allergy Clin Immunol Pract*. 2023;11:2315-25.
- Center for Biologics Evaluation and Research. The voice of the patient – hereditary angioedema. US Food and Drug Administration; May 2018. Accessed September 19, 2024. <https://www.fda.gov/media/113509/download>;
- Covella B, et al. *Future Pharmacol*. 2024;4:41-53.
- Lesage A, et al. *Front Pharmacol*. 2020;11:916.
- Lesage A, et al. *Int Immunopharmacol*. 2022;105:108523.
- <https://clinicaltrials.gov/study/NCT04618211>. Accessed September 19, 2024.
- <https://www.clinicaltrials.gov/study/NCT05396105>. Accessed September 19, 2024.
- <https://clinicaltrials.gov/study/NCT06343779>. Accessed September 19, 2024.
- Maurer M, et al. Presented at: AAAAI; February 24–27, 2023; San Antonio, TX, USA.
- <https://www.clinicaltrials.gov/study/NCT05047185>. Accessed September 19, 2024.
- Aygören-Pürsün, et al. Presented at EAACI 2024; May 31–June 3, 2024; Valencia, Spain.
- Green K, et al. Presented at ACAAI 2022. November 10–14, 2022; Louisville, KY, USA.

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