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Long-Term Safety and Efficacy of Oral Deucrictibant for Hereditary Angioedema Prophylaxis: The CHAPTER-1 Open-Label Extension Study

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Conflicts of interest disclosure

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Introduction

- 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.[1-4]
- Deucrictibant is a selective, orally-administered bradykinin B2 receptor antagonist under development for prophylactic and on-demand treatment of HAE attacks.[2,5-13]
- CHAPTER-1 is a two-part Phase 2 study evaluating the efficacy and safety of deucrictibant for long-term prophylaxis of HAE attacks.[11]
- In the double-blind placebo-controlled randomized controlled trial period (RCT; part 1), deucrictibant demonstrated[14]:
  - 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

HAE, hereditary angioedema. **1.** Bouillet L, et al. *Allergy Asthma Proc*. 2022;43:406-12. **2**. Betschel SD, et al. *J Allergy Clin Immunol Pract*. 2023;11:2315-25. **3.** Center for Biologics Evaluation and Research. The voice of the patient – hereditary angioedema. US Food and Drug Administration; May 2018. Accessed November 20, 2024. https://www.fda.gov/media/113509/download;
4. Covella B, et al. *Future Pharmacol*. 2024;4:41-53. **5.** Lesage A, et al. *Front Pharmacol*. 2020;11:916. **6.** Lesage A, et al. *Int Immunopharmacol*. 2022;105:108523. **7.** https://clinicaltrials.gov/study/NCT04618211. Accessed November 20, 2024. **8.** https://www.clinicaltrials.gov/study/NCT05396105. Accessed November 20, 2024. **9**. https://clinicaltrials.gov/study/NCT06343779. Accessed November 20, 2024.
10. Maurer M, et al. Presented at: AAAAI; February 25–28, 2022; Phoenix, AZ, USA. **11.** https://www.clinicaltrials.gov/study/NCT05047185. Accessed November 20, 2024.
12. https://clinicaltrials.gov/study/NCT06669754. Accessed November 20, 2024. **13.** https://clinicaltrials.gov/study/NCT06679881. Accessed November 20, 2024. **14.** Aygören-Pürsün, et al. Presented at EAACI 2024; May 31–June 3, 2024; Valencia, Spain.

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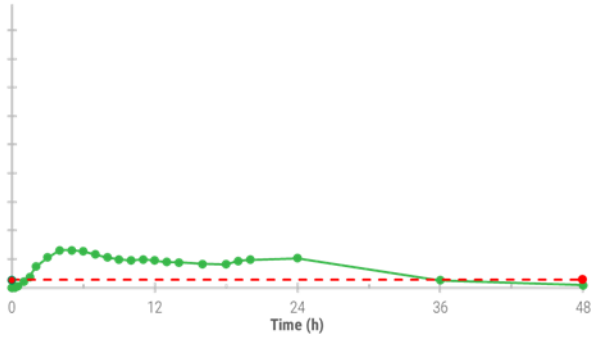
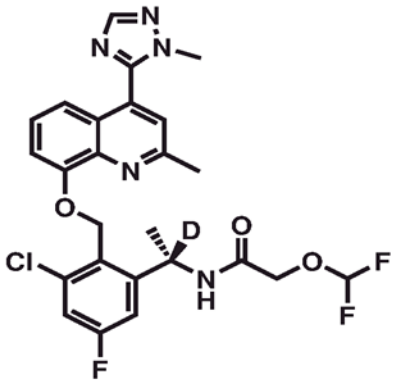
Deucrictibant under development for the prophylactic and on-demand treatment of HAE attacks

DEUCRICTIBANT extended-release (XR) tablet

sustained absorption[1]



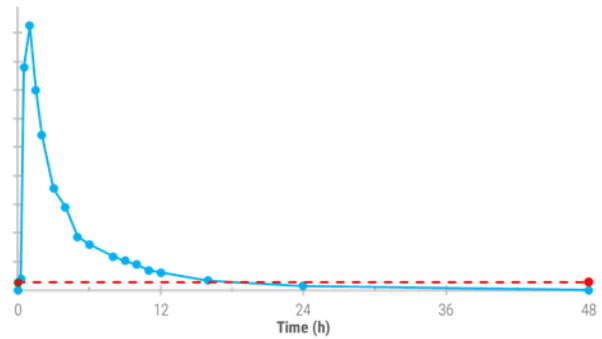
Maintains sustained therapeutic exposure over 24 hours[2] from day one, allowing for once-daily oral treatment to prevent HAE attacks[a]



deucrictibant

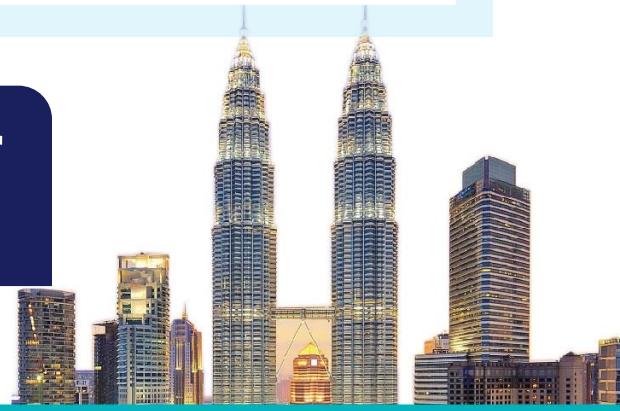
DEUCRICTIBANT immediate-release (IR) capsule

rapid absorption[3]



Rapidly reaches therapeutic exposure within 15-30 minutes[4], making it suitable for on-demand oral treatment of HAE attacks[a]

Two oral products with the same active ingredient for the prevention and treatment of HAE attacks



HAE, hereditary angioedema. [a]Aspirational; to be confirmed with clinical data from Phase 3 studies. **1.** Company data: single-dose cross-over PK study in healthy volunteers (n=14) under fasting conditions. **2.** Lesage A, et al. Presented at IDDST; May 22-24, 2024. **3.** Crabbé R, et al. Presented at AAAAI; Feb 26-Mar 1, 2021. **4.** Maurer M, et al. Presented at AAAAI; Feb 24-27, 2023; San Antonio, TX, USA.

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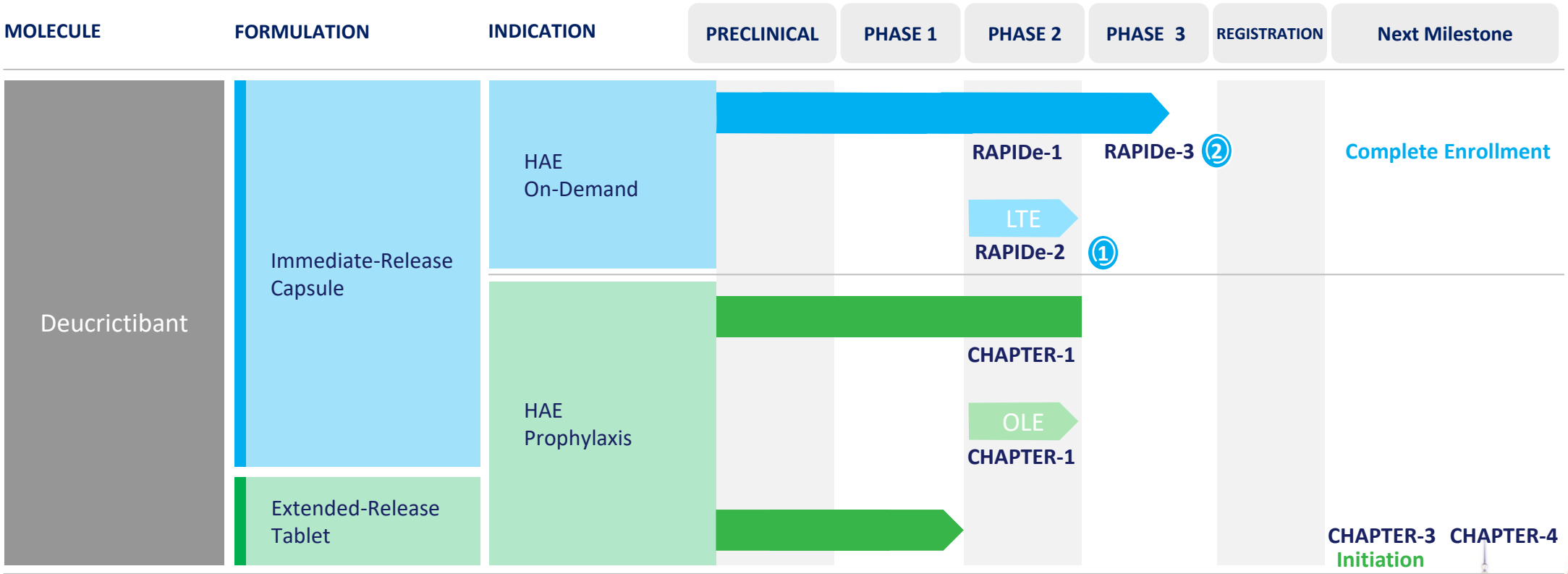
Deucrictibant development program in HAE



Presentations at APAAACI 2024 poster session

1	Li et al. Propensity score matching: RAPIDe-2 vs. mixed methods results	December 15, 8.00 AM – 6.00 PM
2	Li et al. RAPIDe-3 study design	December 15, 8.00 AM – 6.00 PM

HAE, hereditary angioedema; LTE, long-term extension; OLE, open-label extension; RCT, randomized controlled trial. RAPIDe-1: ClinicalTrials.gov identifier: NCT04618211. Accessed November 11, 2024. https://www.clinicaltrials.gov/study/NCT04618211. RAPIDe-2: ClinicalTrials.gov identifier: NCT05396105. Accessed November 11, 2024. https://www.clinicaltrials.gov/study/NCT05396105. RAPIDe-3: ClinicalTrials.gov identifier: NCT06343779. Accessed November 11, 2024. https://www.clinicaltrials.gov/study/NCT06343779. CHAPTER-1: ClinicalTrials.gov identifier: NCT05047185. Accessed November 11, 2024. https://www.clinicaltrials.gov/study/NCT05047185. CHAPTER-3: ClinicalTrials.gov identifier: NCT06669754. Accessed November 11, 2024. https://clinicaltrials.gov/study/NCT06669754. CHAPTER-4: ClinicalTrials.gov identifier: NCT06679881. Accessed November 11, 2024. https://clinicaltrials.gov/study/NCT06679881.

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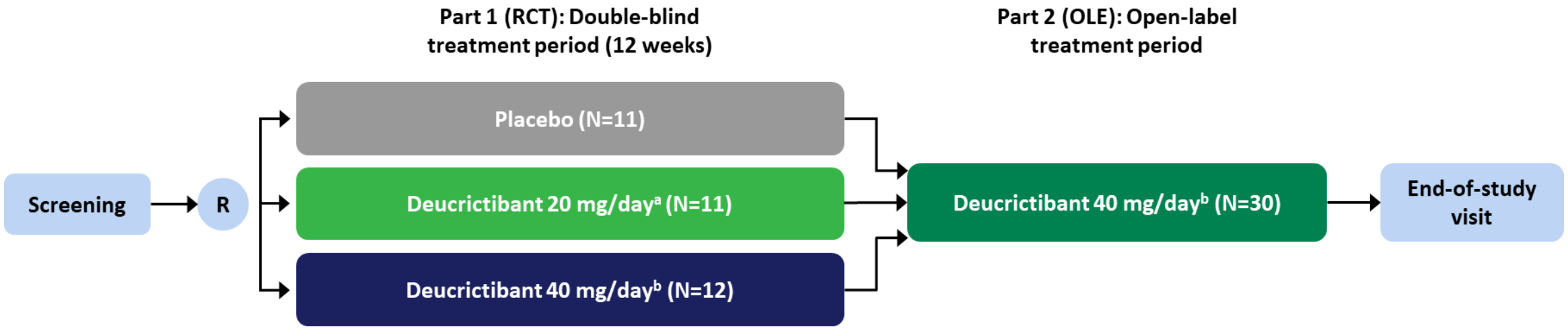
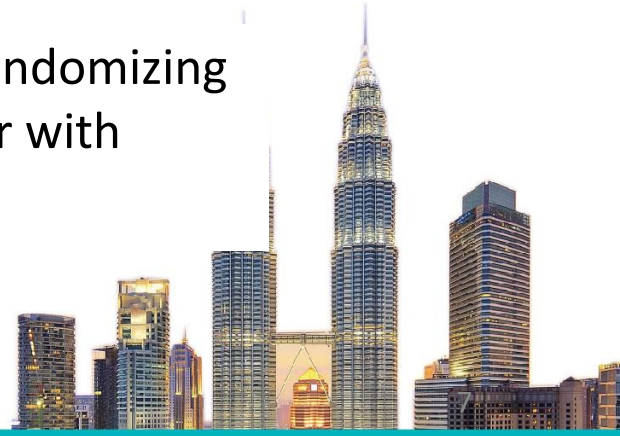
CHAPTER-1 OLE objectives and study design

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



- 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.



HAE, hereditary angioedema; 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 was well tolerated with no safety signals

- Deucrictibant was well tolerated, with one treatment-related treatment-emergent adverse event (TEAE) of tooth discoloration.
- 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.

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	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 (defined as adverse event occurring during time window from first study drug administration).
N = number of participants who received ≥1 dose of study treatment in the OLE by the cutoff date (10 June 2024). [a]Deucrictibant IR capsule, 20 mg twice daily. [b]Deucrictibant IR capsule, 10 mg twice daily.

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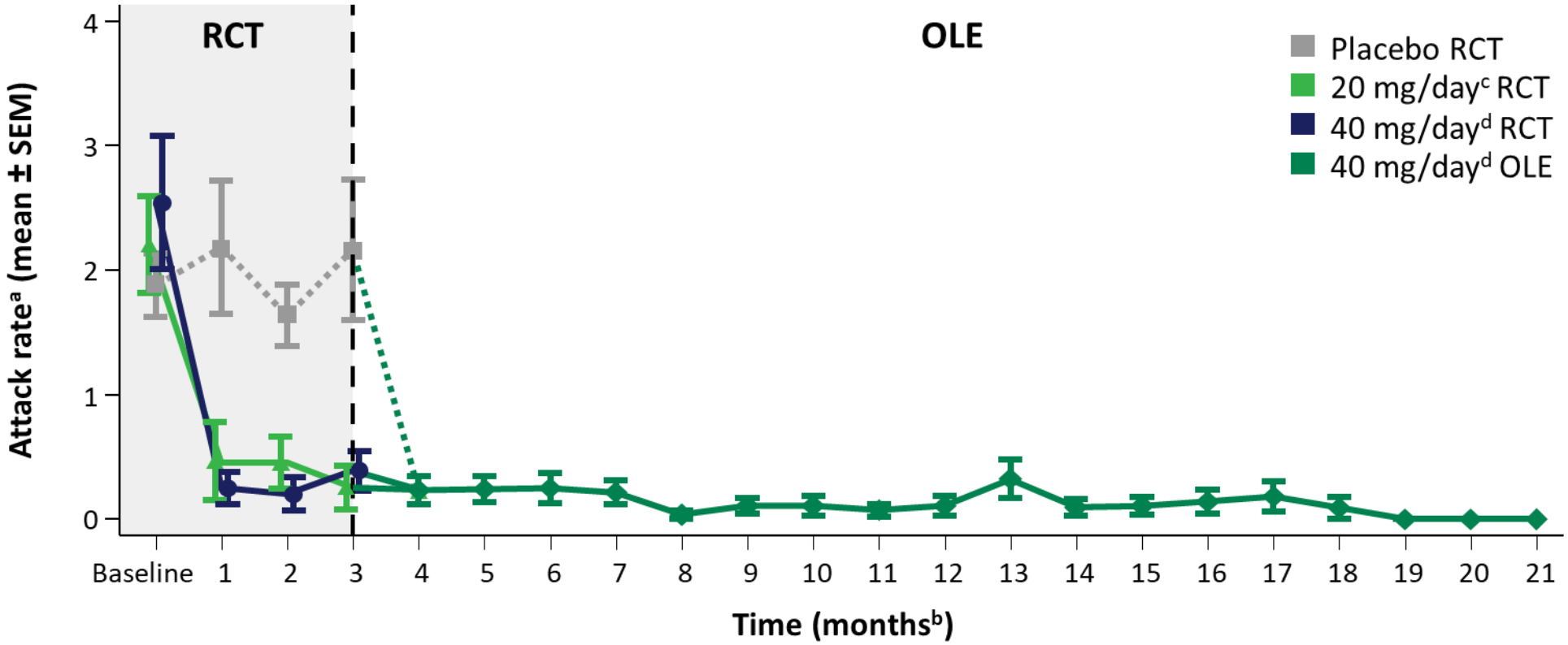
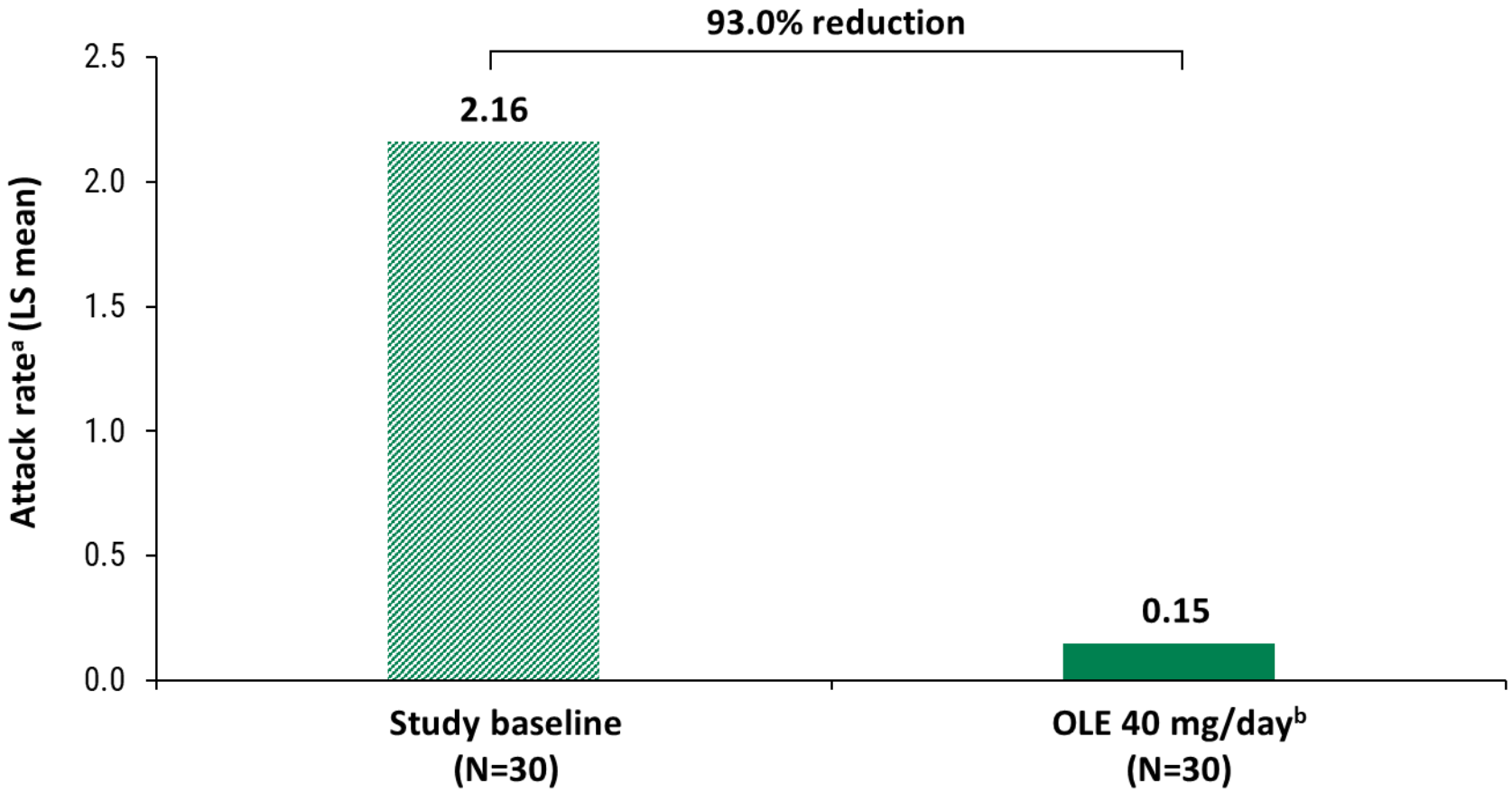
Reduced attack rate in the RCT remained low in the OLE



Placebo RCT (n)	11	11	11	11																	
20 mg/day[c] RCT (n)	11	11	11	11																	
40 mg/day[d] RCT (n)	12	12	10	10																	
40 mg/day[d] OLE (n)					30	29	28	28	28	28	28	28	28	28	21	19	16	11	11	10	9	7

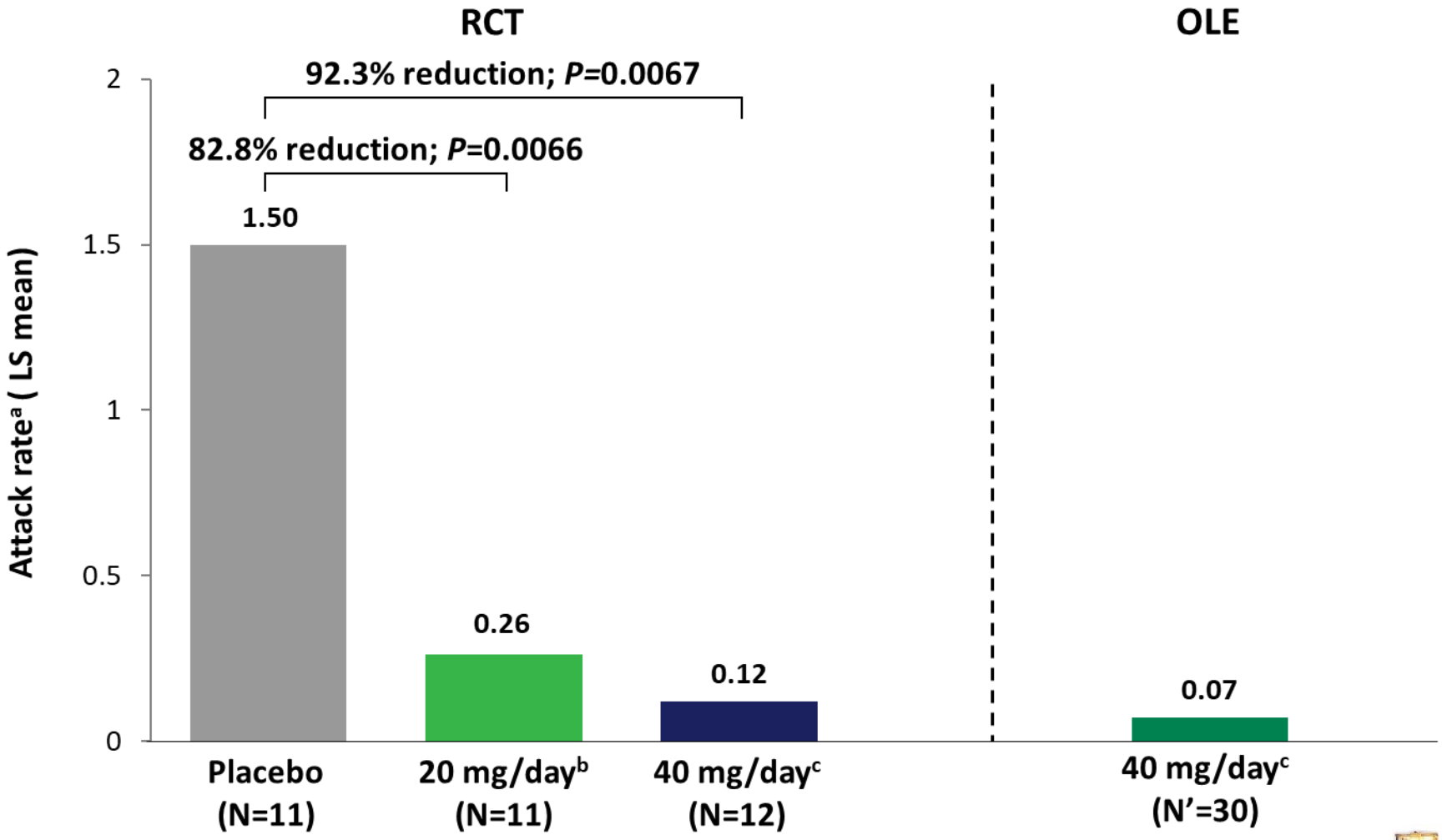
IR, immediate release; OLE, open-label extension; RCT, randomized controlled trial; SEM, standard error of the mean. (n) = number of patients analyzed at each timepoint. [a]Based on time normalized number of attacks per 4 weeks. [b]1 month = 4 weeks. [c]Deucrictibant IR capsule, 10 mg twice daily. [d]Deucrictibant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

Deucrictibant reduced the attack rate in the OLE by 93% compared with RCT baseline



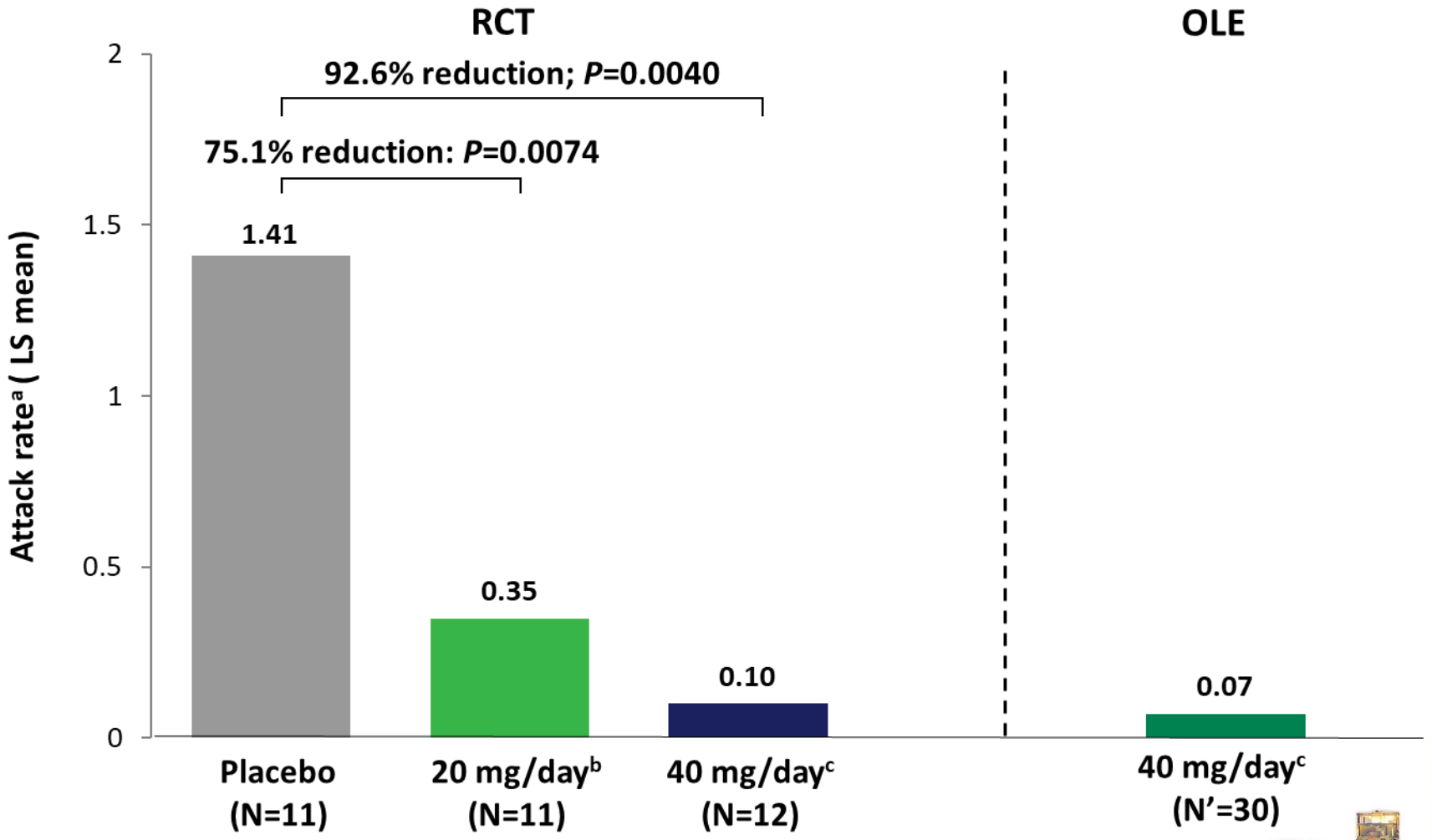
IR, immediate release; LS, least squares; OLE, open-label extension; RCT, randomized controlled trial. N = number of participants in the OLE. LS mean estimates of attack rate are based on Poisson regression models adjusted for baseline attack rate and time on treatment. No multiplicity adjustment was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

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



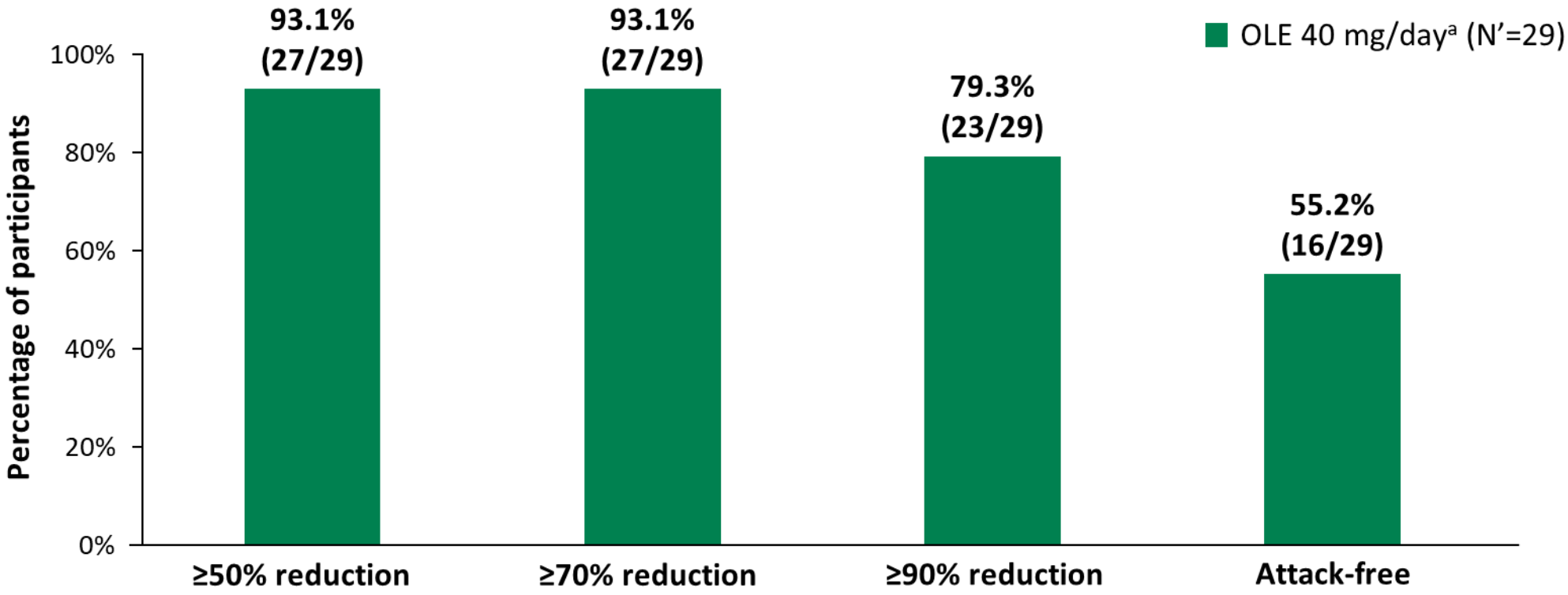
IR, immediate release; LS, least squares; OLE, open-label extension; RCT, randomized controlled trial. N = number of participants randomized in each treatment group in the RCT. N' = number of participants in the OLE. LS mean estimates of attack rate are based on Poisson regression models adjusted for 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.

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.

Substantial attack rate reduction in the OLE relative to study baseline

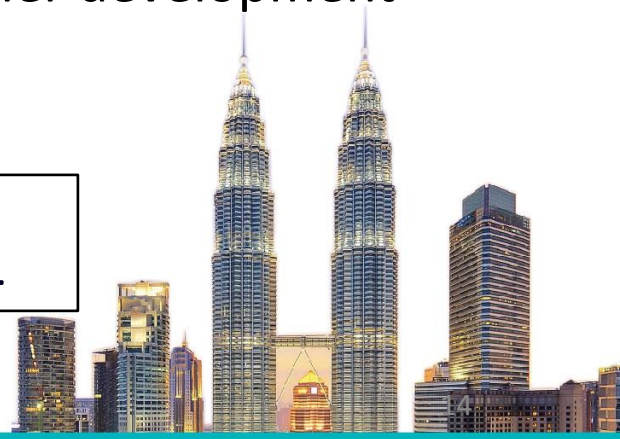


IR, immediate-release; OLE, open-label extension. N' = participants with ≥4 weeks of treatment in the OLE. [a]Deucrictibant IR capsule, 20 mg twice daily.

Conclusions

- In the current analysis of the ongoing Phase 2 CHAPTER-1 OLE study, deucrictibant 40 mg/day was well tolerated, with no safety signals observed.
- Results of this analysis provide evidence that during treatment with deucrictibant 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 deucrictibant 40 mg/day in the OLE comparable to that in participants initiating deucrictibant in the RCT was observed.
  - Rates of “moderate and severe” attacks and attacks treated with on-demand medication remained low.
  - Approximately 80% of participants achieved ≥90% reduction in attack rate relative to RCT study baseline and 55.2% were attack-free in the OLE.
- Results of the ongoing CHAPTER-1 OLE 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.

The Authors and the Sponsor would like to thank all the people with HAE as well as all study site staff who have participated in the CHAPTER-1 trial.



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