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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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Conflict of Interest

Grants/research support, honoraria or consultation fees, sponsored speaker bureau

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CHAPTER-1 is a Pharvaris-sponsored clinical trial. ClinicalTrials.gov identifier: NCT05047185.

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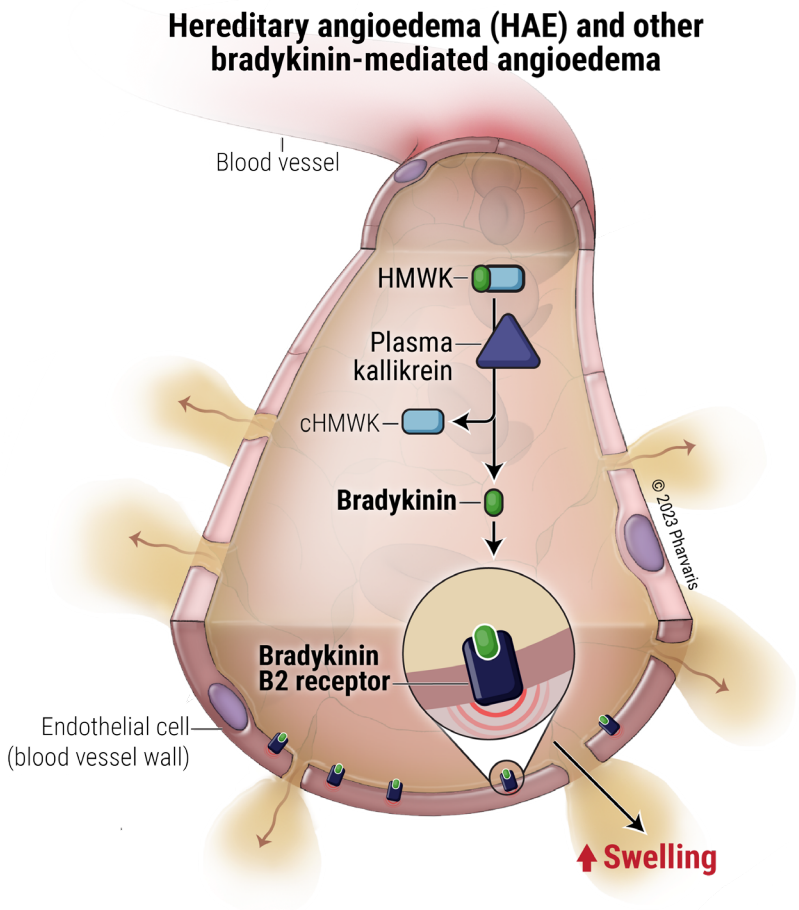
Hereditary angioedema (HAE) is a bradykinin-mediated condition with unmet medical needs



- Excess bradykinin is the main mediator of the clinical manifestations of bradykinin-mediated angioedema attacks, including HAE.[1,2]
- An unmet need remains for additional prophylactic treatments combining[3-6]:
  - Injectable-like efficacy
  - A well-tolerated profile
  - Ease of administration

cHMWK, cleaved HMWK; HAE, hereditary angioedema; HMWK, high-molecular-weight kininogen. **1**. Frank MM. *J Allergy Clin Immunol.* 2010;125:S262-71. **2**. Busse PJ, et al. *N Engl J Med*. 2020;382:1136-48. **3**. Bouillet L, et al. *Allergy Asthma Proc*. 2022;43:406-12. **4**. Betschel SD, et al. *J Allergy Clin Immunol Pract*. 2023;11:2315-25. **5**. Covella B, et al. *Future Pharmacol*. 2024;4:41-53. **6**. US Food and Drug Administration, Center for Biologics Evaluation and Research. The voice of the patient – hereditary angioedema. May 2018. https://www.fda.gov/media/113509/download. Accessed September 23, 2024.

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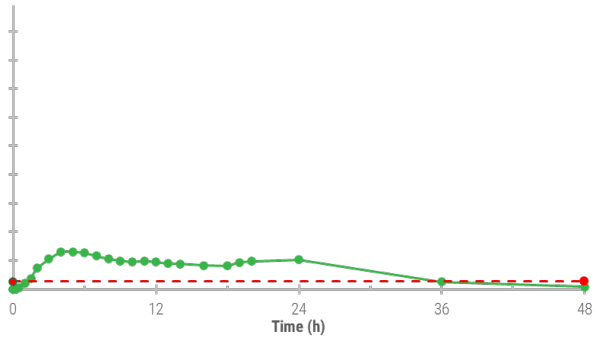
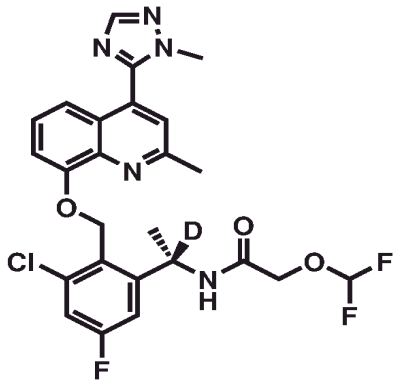
Two investigational oral therapies with the same active ingredient for the prophylactic and on-demand treatment of HAE attacks

DEUCRICTIBANT extended-release (XR) tablet

sustained absorption[1]



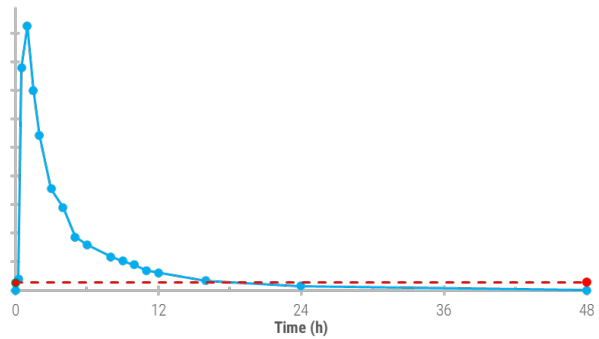
Maintains sustained therapeutic exposure over 24 hours[2] from day one, allowing for once-daily oral treatment to prevent HAE attacks[a]



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.** Crabbe 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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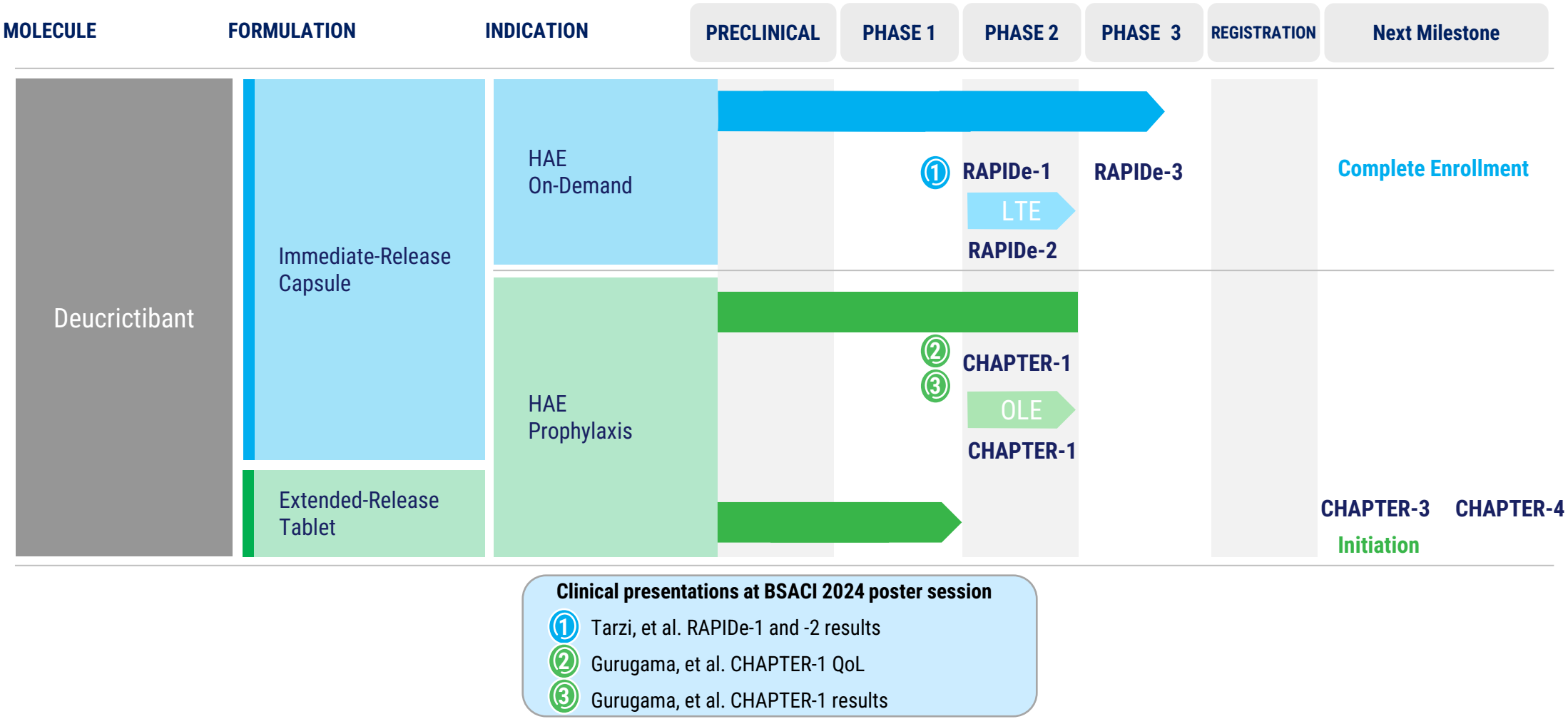
Deucrictibant development program in HAE



HAE, hereditary angioedema; LTE, long-term extension; OLE, open-label extension. **1**. RAPIDe-1. ClinicalTrials.gov identifier: NCT04618211. Accessed September 23, 2024. https://www.clinicaltrials.gov/study/NCT04618211. **2.** RAPIDe-2. ClinicalTrials.gov identifier: NCT05396105. Accessed September 23, 2024. https://www.clinicaltrials.gov/study/NCT05396105. **3**. RAPIDe-3. ClinicalTrials.gov identifier: NCT06343779. Accessed September 23, 2024. https://www.clinicaltrials.gov/study/NCT06343779. **4**. CHAPTER-1. ClinicalTrials.gov identifier: NCT05047185. Accessed September 23, 2024. https://www.clinicaltrials.gov/study/NCT05047185.

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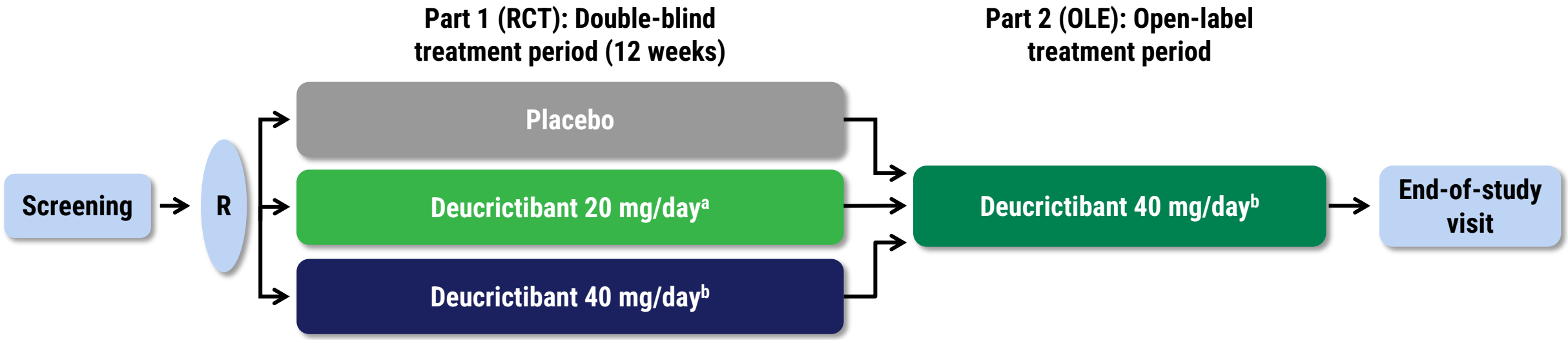
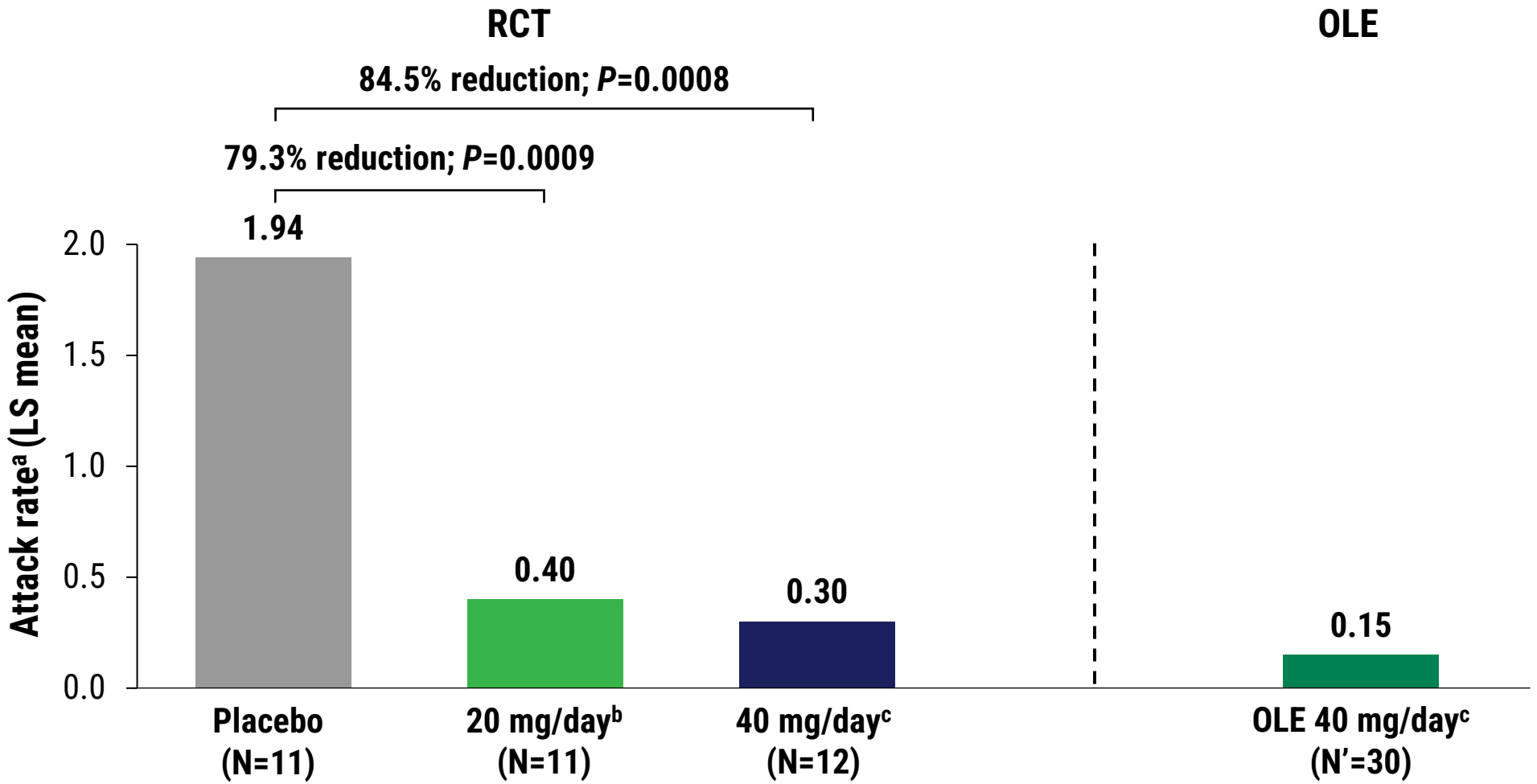
CHAPTER-1: Two-part, Phase 2 study of deucrictibant for long-term prophylaxis of HAE attacks



- Endpoints (RCT and OLE) included:
  - Time-normalized number of investigator-confirmed HAE attacks (**HAE attack rate**[c]) – primary endpoint in the RCT
  - Time-normalized number of **moderate and severe HAE attacks**
  - Time-normalized number of **HAE attacks treated with on-demand medication**
- All 30 participants who completed the RCT entered into the OLE.

HAE, hereditary angioedema; IR, immediate-release; OLE, open-label extension; R, randomization; RCT, randomized controlled trial. CHAPTER-1 is a Pharvaris-sponsored clinical trial. ClinicalTrials.gov identifier: NCT05047185. https://www.clinicaltrials.gov/study/NCT05047185. Accessed September 9, 2024. [a]Deucrictibant IR capsule, 10 mg twice daily. [b]Deucrictibant IR capsule, 20 mg twice daily. [c]Based on time normalized number of attacks per 4 weeks.

Attack rate was significantly reduced with 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.

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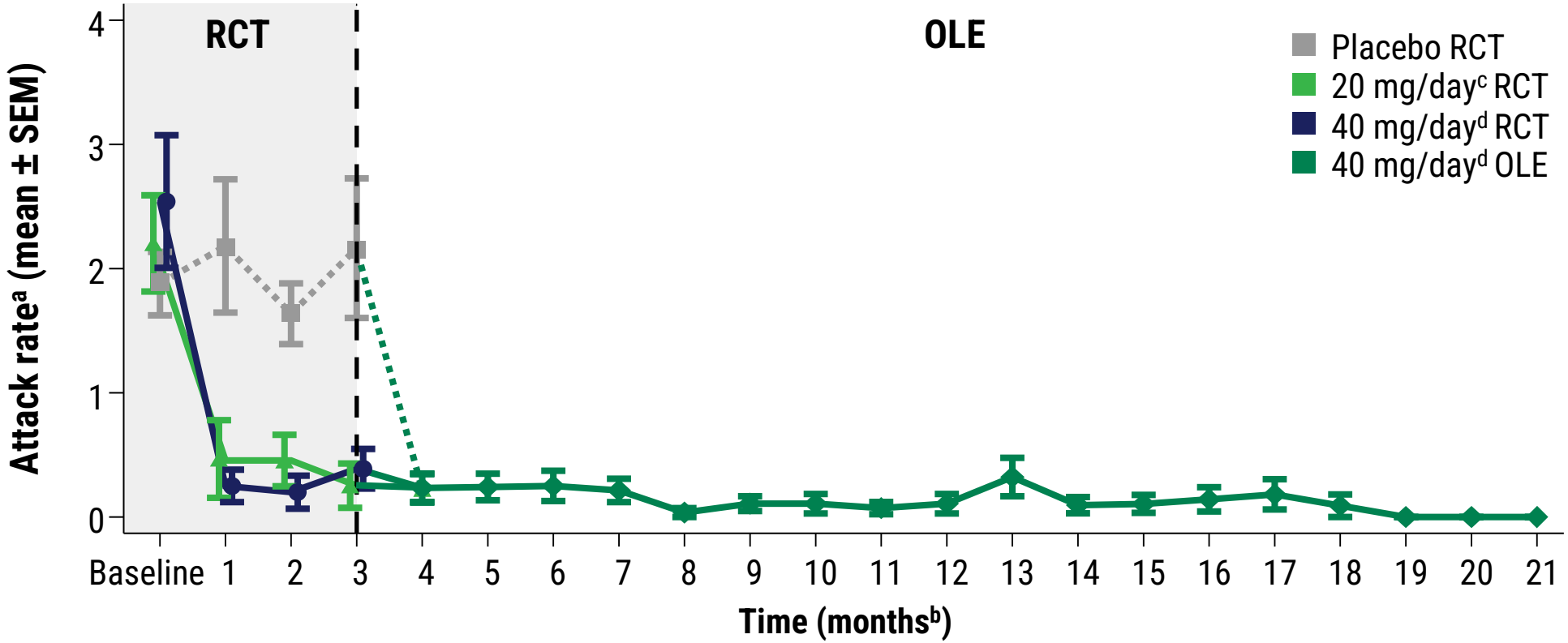
Reduced attack rate in the RCT remained low in the OLE



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.

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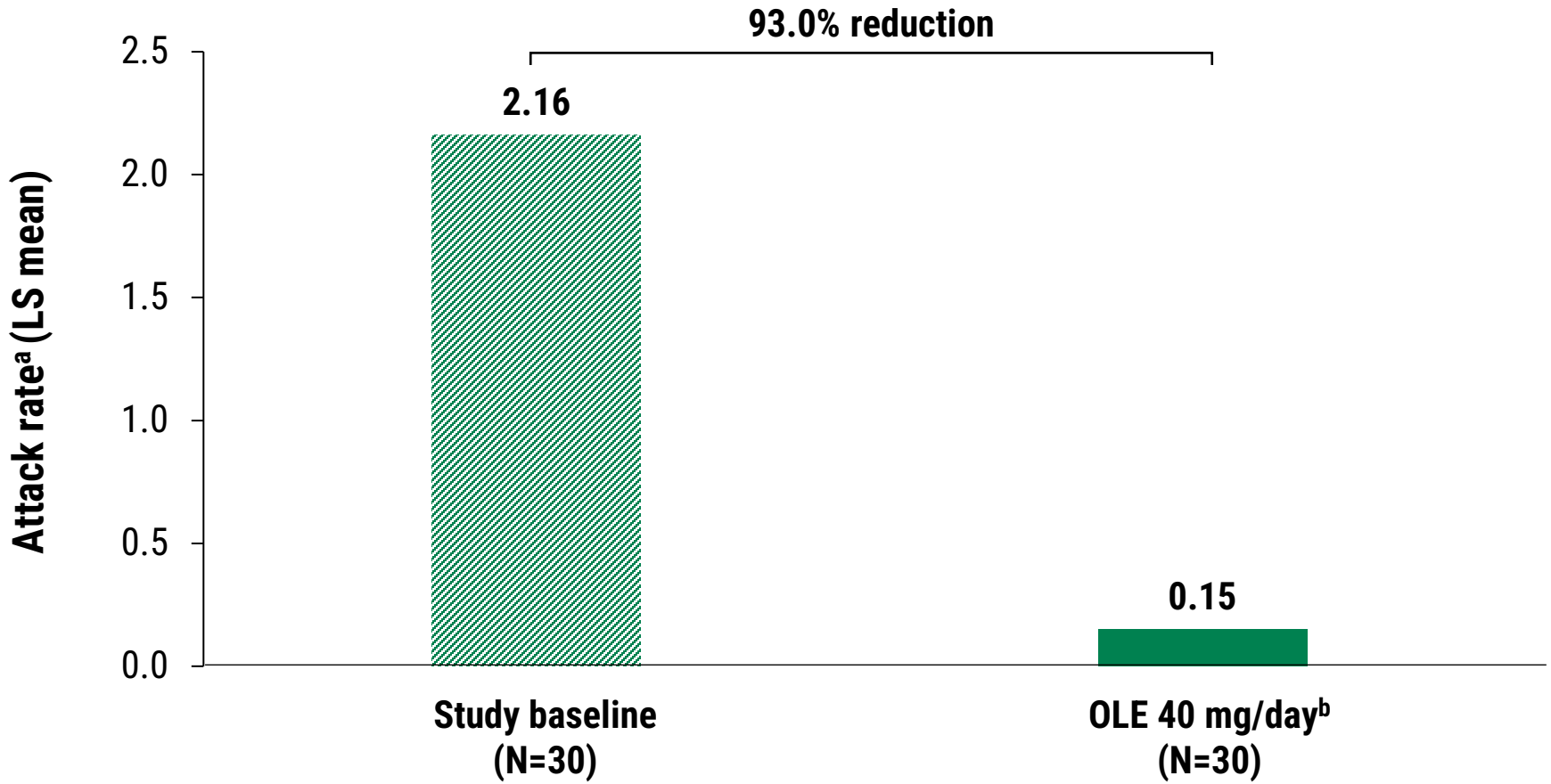
Deucrictibant reduced the attack rate in the OLE by 93% compared with RCT baseline



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.

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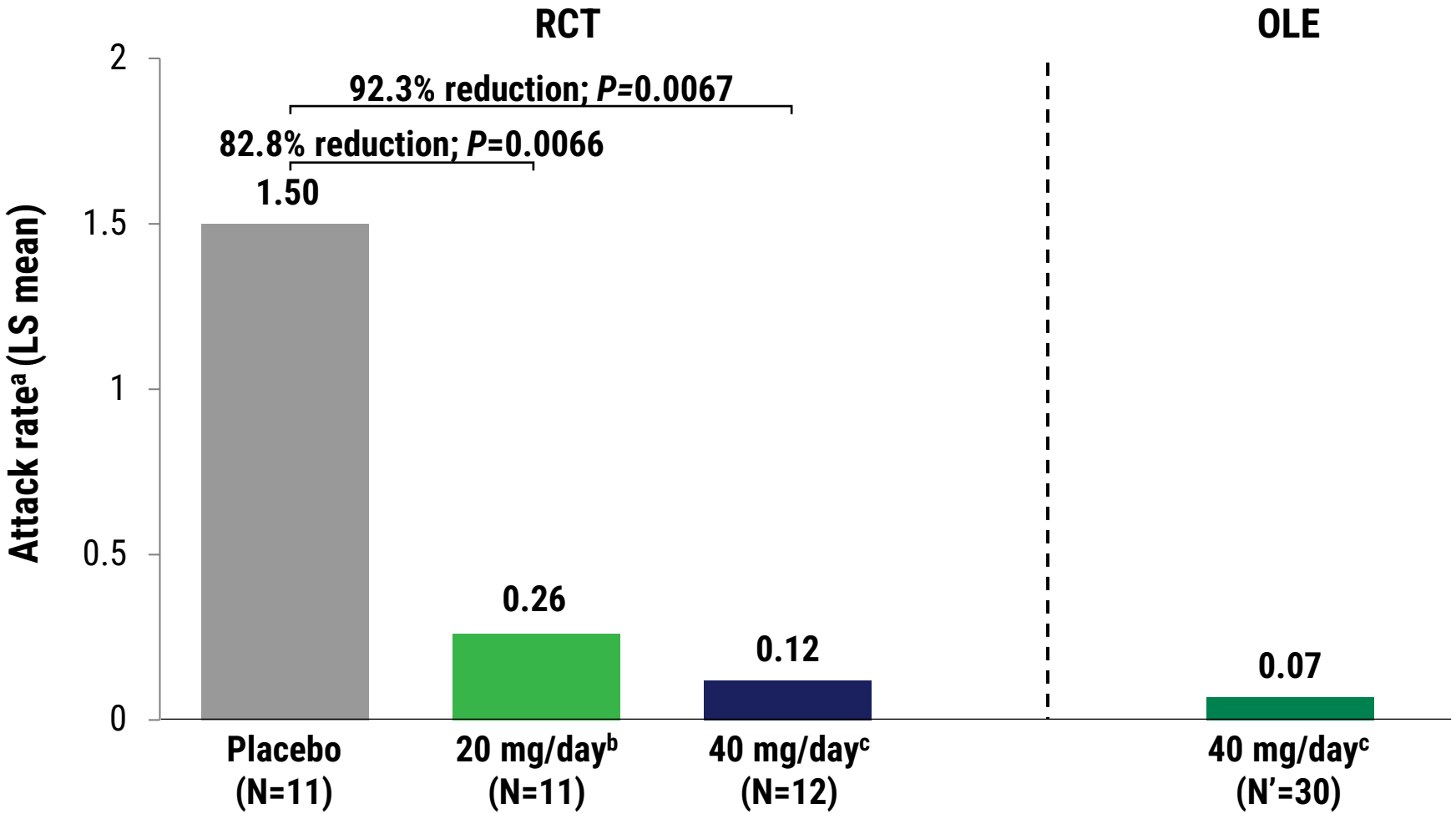
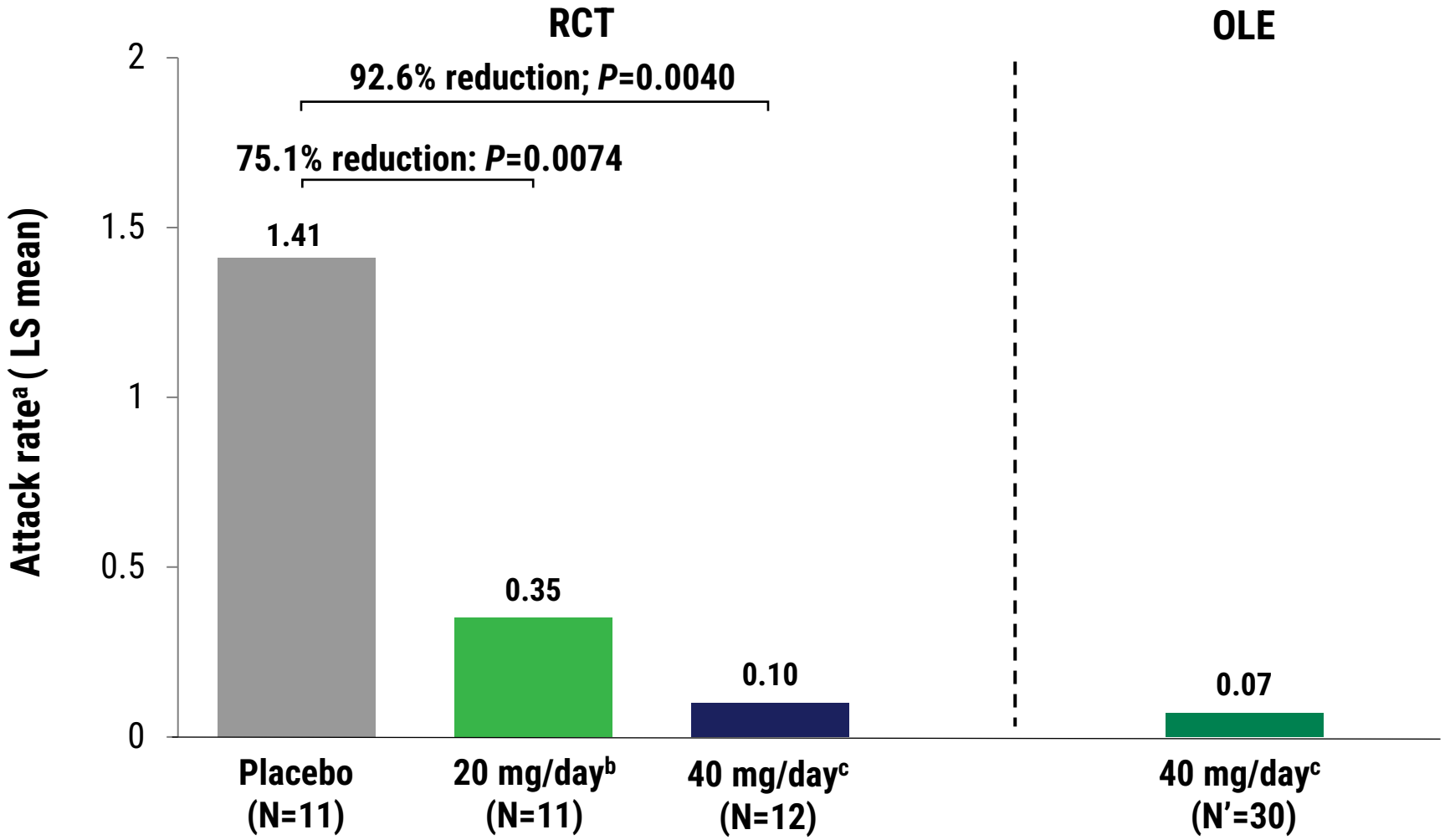
Reduced rate of “moderate and severe” attacks in the RCT remained low in the OLE



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.

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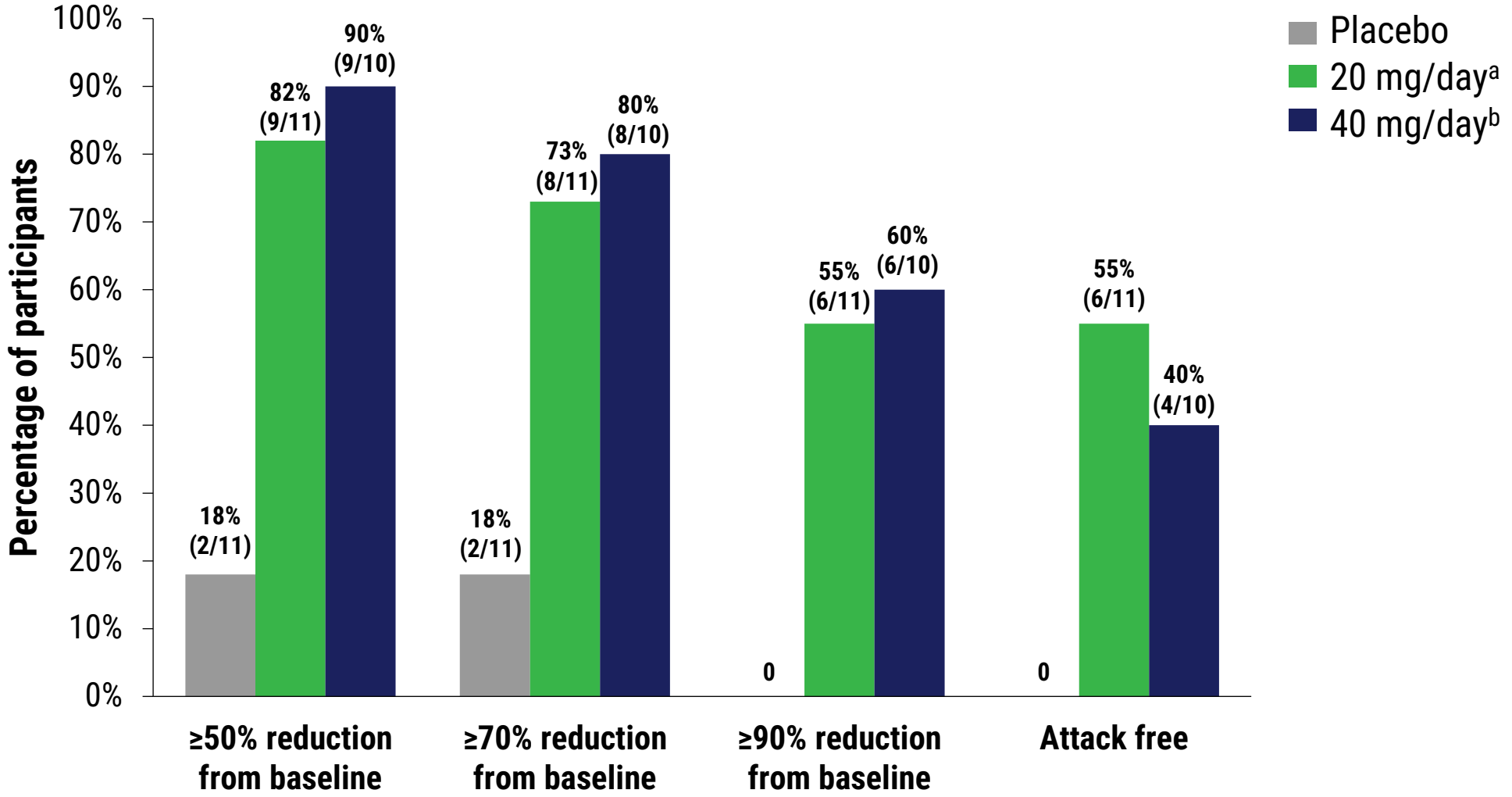
Deucrictibant substantially reduced attack rate from baseline



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.

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Deucrictibant was well tolerated at both doses

- All reported treatment-related treatment-emergent adverse events (TEAEs) were mild in severity in the RCT; this remained the same in the OLE, which had one reported TEAE (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 RCT	Placebo (N=11)		Deucrictibant			
			20 mg/day[a] (N=11)		40 mg/day[b] (N=12)	
	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; OLE, open-label extension; 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 reductions in the occurrence of “moderate and severe” HAE attacks, and of HAE attacks treated with on-demand medication.
- Results of this analysis provide evidence that during treatment with deucrictibant 40mg/day:
  - Following early-onset reduction in the RCT, 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 was comparable to that in participants initiating deucrictibant in the RCT.
  - Rate of “moderate and severe” attacks and attacks treated with on-demand medication were reduced in the RCT and remained low in the OLE.
- Results from the CHAPTER-1 RCT and its ongoing OLE study provide further evidence on the long-term efficacy and safety of deucrictibant for the 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 Sites’ staff who participated in the CHAPTER-1 trial.

HAE, hereditary angioedema. OLE, open-label extension; RCT, randomized controlled trial