Long-Term Safety and Efficacy of Oral Deucrictibant for Prophylaxis in Hereditary Angioedema: Results of the Phase 2 CHAPTER-1 Open-Label Extension Study

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Key takeaways

Final data from the completed Phase 2 CHAPTER-1 open-label extension (OLE) study provide further evidence on the long-term safety and efficacy of oral deucrictibant for the prevention of hereditary angioedema (HAE) attacks.

Safety	Efficacy		
Deucrictibant was generally well tolerated with one treatment-related TEAE of asymptomatic increased GGT	Up to ~34 months Attack rate reduced by week 1 and remained low for ~34 months for CHAPTER-1 RCT + OLE	0.12 Overall on-study mean attack rate during the OLE	0.06 Mean rate of "moderate and severe" attacks and of attacks treated with on-demand medication during the OLE

GGT, gamma-glutamyltransferase; OLE, open-label extension; RCT, randomized controlled trial; TEAE, treatment-emergent adverse event.

Background

- **Hereditary angioedema (HAE):** a bradykinin-mediated condition with painful swelling attacks affecting multiple locations in the body.[1]
- **Unmet need:** additional prophylactic treatments offering injectable-like efficacy™, a well-tolerated profile, and ease of administration.[2-5]
- **Deucrictibant:** a selective, investigational, orally administered bradykinin B2 receptor antagonist under development for prophylaxis and on-demand treatment of bradykinin-mediated attacks.[6-16]

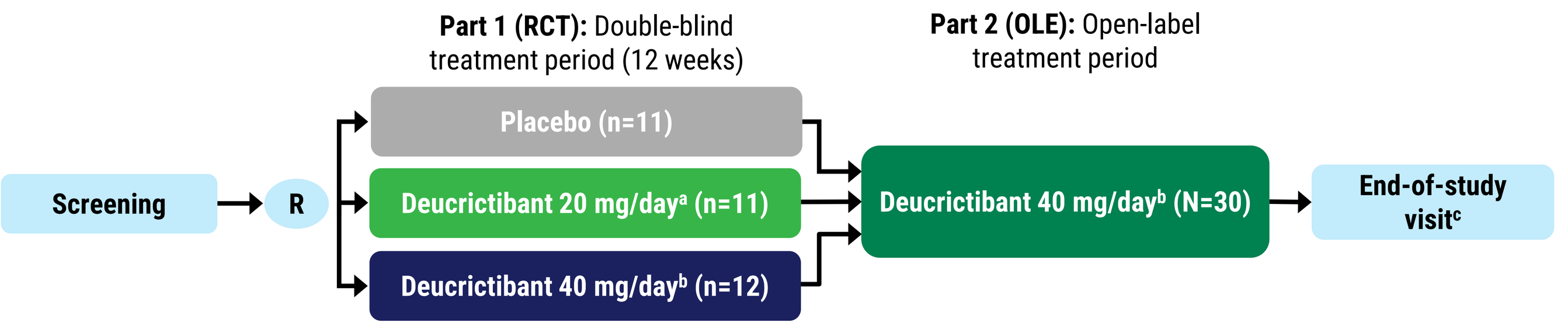
Objective

To evaluate the safety and efficacy of deucrictibant for long-term prophylaxis of HAE attacks in adults in the open-label extension (OLE) of the CHAPTER-1 study.[12]

Methods

- **CHAPTER-1 (NCT05047185)*:** a two-part, Phase 2 study.[12]
  - Part 1 randomized controlled trial (RCT) and Part 2 OLE are complete.
- **Eligibility:** adults diagnosed with HAE-1/2, not receiving other prophylactic treatments at screening, and with a pre-specified minimum number of attacks in the 3 months prior to screening.

Figure 1. CHAPTER-1 study design



IR, immediate-release; OLE, open-label extension; R, randomization; RCT, randomized controlled trial; XR, extended-release. n = number of participants randomized in each treatment group in the RCT. N = number of participants. [a]Deucrictibant IR capsule, 10 mg twice daily. [b]Deucrictibant IR capsule, 20 mg twice daily. [c]Twenty-one participants rolled over to the ongoing CHAPTER-4 (NCT06679881) OLE in which deucrictibant XR tablet is self-administered.[14]

Methods

- **Participants:** all 30 participants who completed the RCT continued into the OLE.
  - In the RCT, these 30 participants were randomized to deucrictibant 20 mg/day (n=11) or 40 mg/day (n=10), or placebo (n=9).
- **Key OLE objectives:** evaluate the long-term safety (primary objective) and efficacy of deucrictibant administered for prophylaxis against HAE attacks.

Results

Participants in the OLE

- Thirty participants in the OLE had received deucrictibant 40 mg/day for a mean (SD) treatment duration of 22.2 (8.1) months.
  - Maximum deucrictibant exposure during the entire study was 33.8 months.
- Twenty-one participants were on study at the time of CHAPTER-1 study end and all continued into the ongoing CHAPTER-4 (NCT06679881) in which deucrictibant extended-release (XR) 40 mg tablet is administered. None of the nine discontinuations in the CHAPTER-1 OLE were reported as due to reasons related to study drug.

Safety analysis

- Deucrictibant was generally well tolerated, with one treatment-related treatment-emergent adverse event (TEAE) reported: mild, asymptomatic increased gamma-glutamyltransferase (<2 upper limit of normal), which started during the RCT, resolved while continuing deucrictibant treatment during the OLE, and reoccurred by end of the OLE; alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase (ALP) levels were normal.
  - No treatment-related serious or severe TEAEs.
  - No TEAEs leading to study drug discontinuation, study withdrawal, or death.

Table 1. Adverse events in the OLE

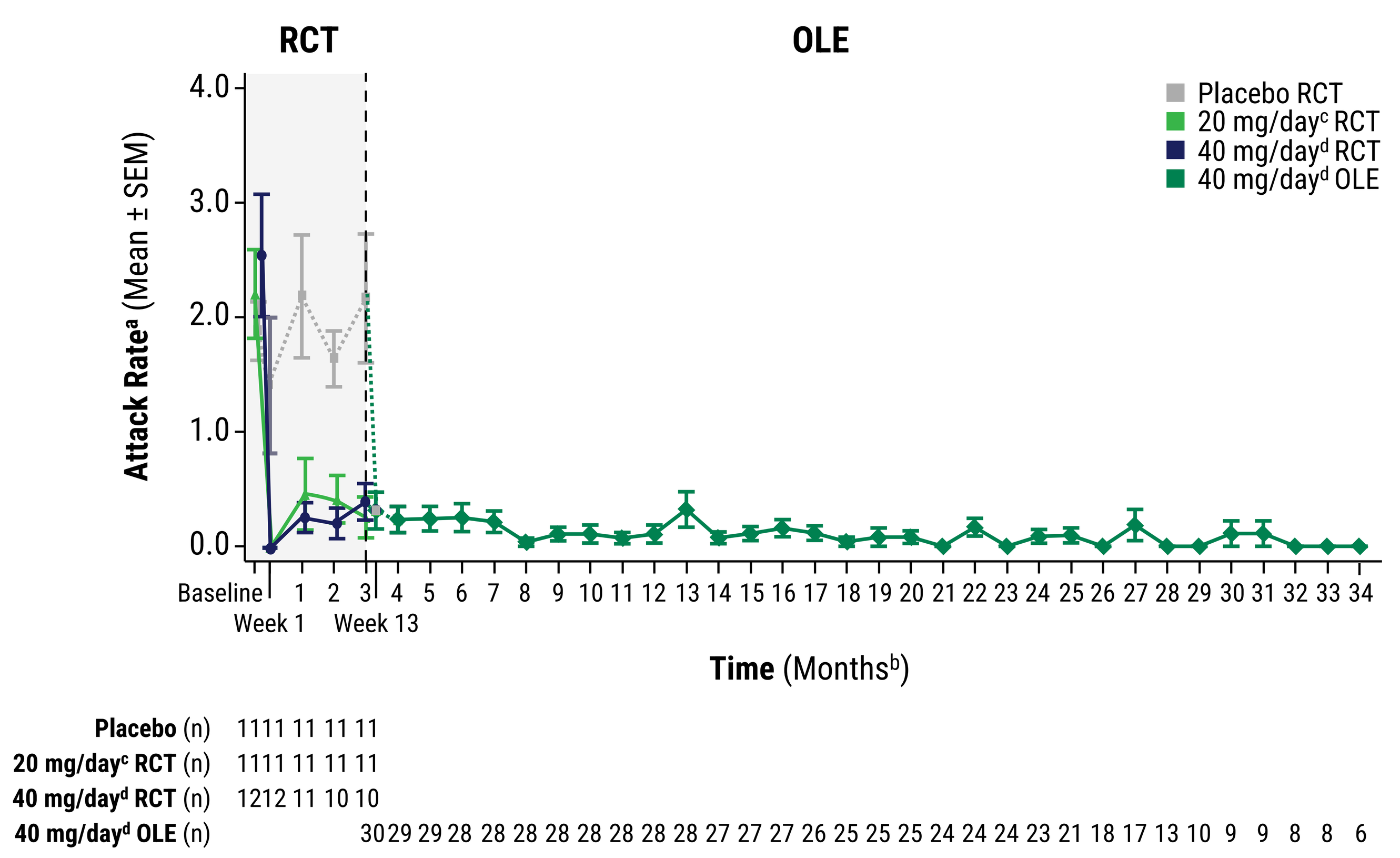
	Placebo to 40 mg/day[a] (N=9)		20 mg/day[b] to 40 mg/day[a] (N=11)		40 mg/day[a] to 40 mg/day[a] (N=10)		Total (N=30)	
	Participants, n (%)	Events, no.	Participants, n (%)	Events, no.	Participants, n (%)	Events, no.	Participants, n (%)	Events, no.
TEAEs	**8 (88.9)**	**40**	**8 (72.7)**	**45**	**8 (80.0)**	**25**	**24 (80.0)**	**110**
Treatment-related TEAEs	**0**	**0**	**0**	**0**	**1 (10.0)**	**1**	**1 (3.3)**	**1**
Gamma-glutamyltransferase increased	0	0	0	0	1 (10.0)	1	1 (3.3)	1
Serious TEAEs[c]	**0**	**0**	**1 (9.1)**	**2**	**1 (10.0)**	**1**	**2 (6.7)**	**3**
Tendon injury	0	0	0	0	1 (10.0)	1	1 (3.3)	1
Arthritis	0	0	1 (9.1)	1	0	0	1 (3.3)	1
Osteoarthritis	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. TEAE defined as adverse events that started or pre-existing adverse events that worsened during the period between the first study dose in OLE and 4 weeks after the last dose in OLE or the End of Study Visit, whichever was later. N = number of participants who received ≥1 dose of study treatment in the OLE. [a]Deucrictibant IR capsule, 20 mg twice daily. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Three serious TEAEs required reconstruction surgery, hip replacement, or knee replacement. These were not considered treatment-related.

Results

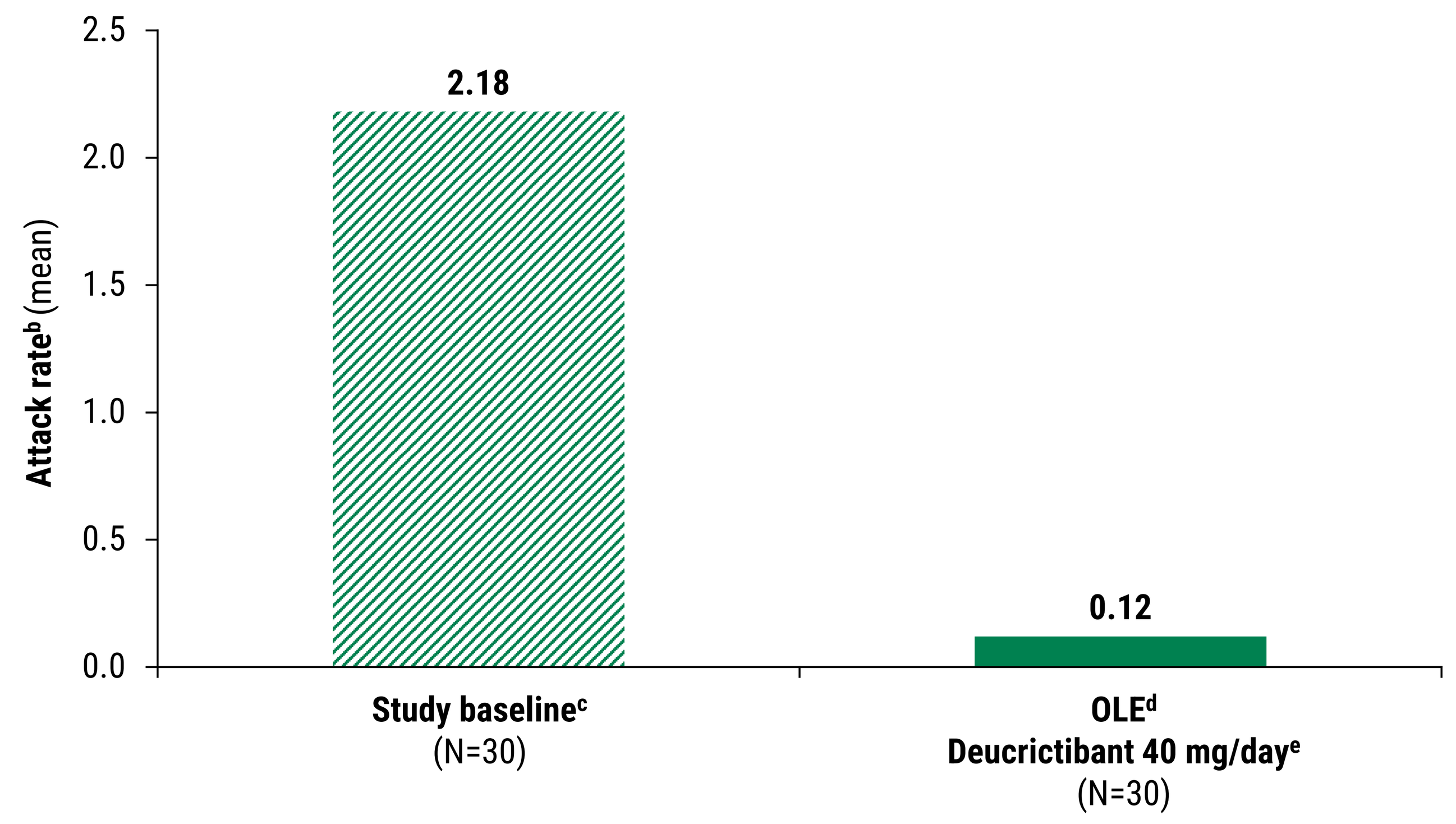
Efficacy analysis

Figure 2. Attack rate reduced by week 1 and week 13 and remained low for up to ~34 months



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.

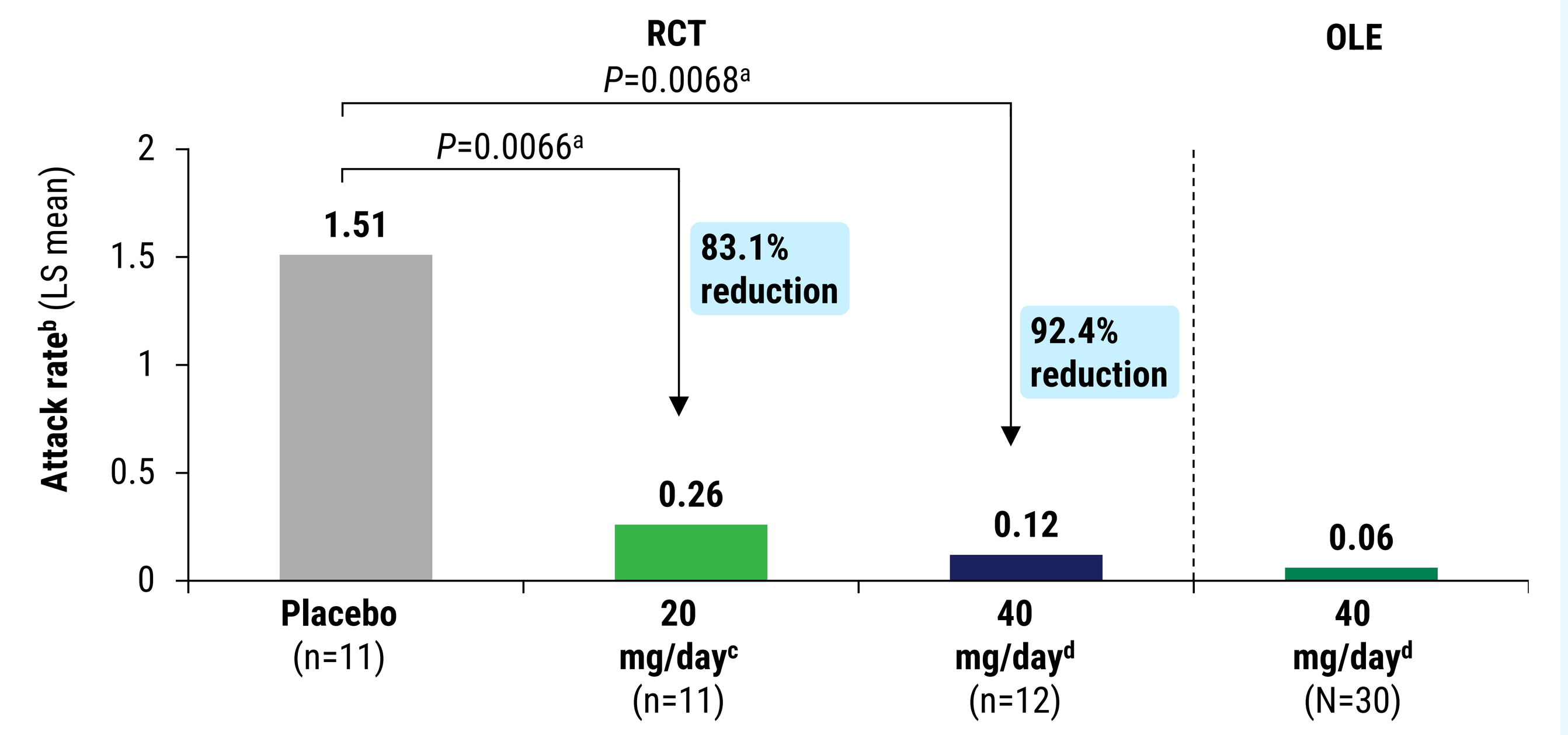
Figure 3. Average of 92.4% attack reduction from study baseline[a]



IR, immediate-release; OLE, open-label extension; RCT, randomized controlled trial. N = number of participants in the OLE. [a]92.4% is the average patient-level reduction from CHAPTER-1 RCT baseline and excludes one patient with 4 days of OLE treatment and no attacks. [b]Based on time-normalized number of attacks per 4 weeks. [c]Crude mean attack rate at baseline. [d]Crude mean attack rate in the OLE. [e]Deucrictibant IR capsule, 20 mg twice daily.

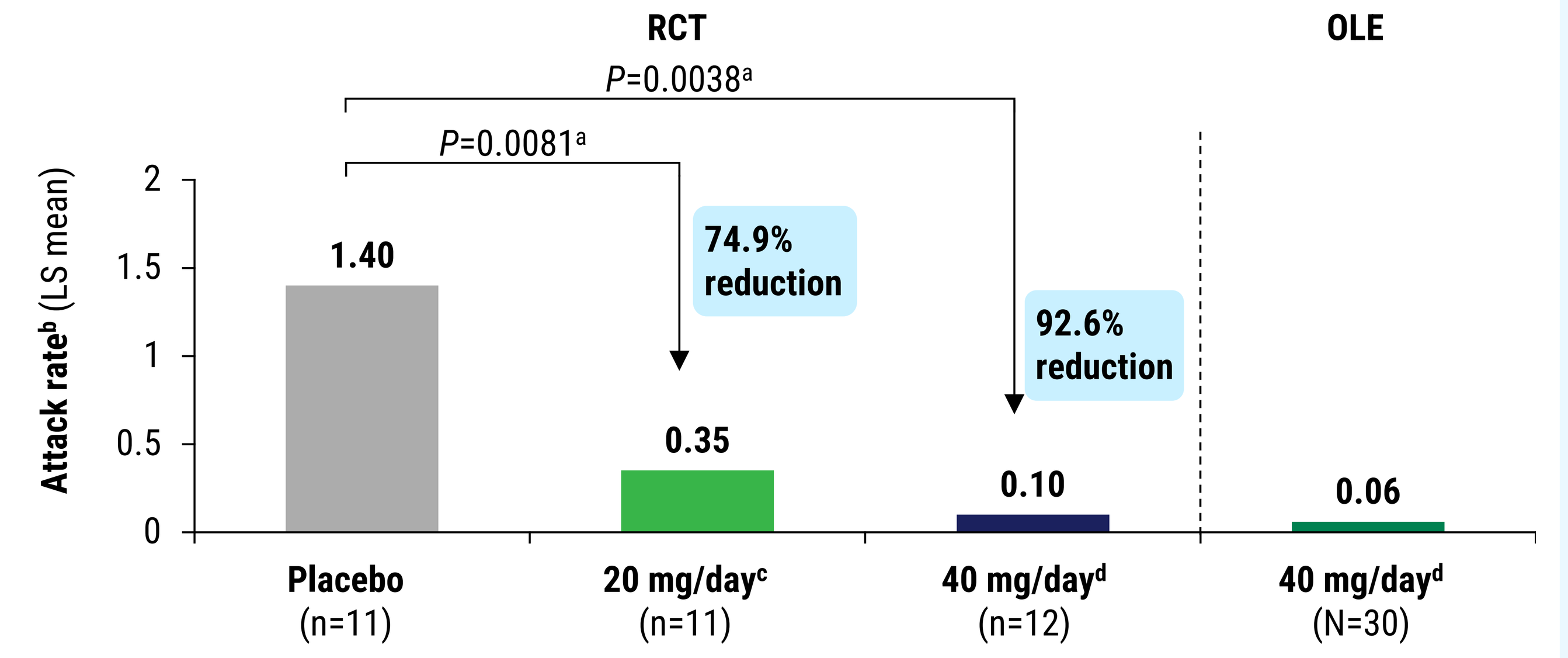
Results

Figure 4. "Moderate and severe" attack rate reduced in the RCT and 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. [a]The *P*-values in this figure are nominal. [b]Based on time-normalized number of attacks per 4 weeks. [c]Deucrictibant IR capsule, 10 mg twice daily. [d]Deucrictibant IR capsule, 20 mg twice daily.

Figure 5. On-demand treated attack rate reduced in the RCT and 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. [a]The *P*-values in this figure are nominal. [b]Based on time-normalized number of attacks per 4 weeks. [c]Deucrictibant IR capsule, 10 mg twice daily. [d]Deucrictibant IR capsule, 20 mg twice daily.

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

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COI: M.E.M.: AstraZeneca, Astria, BioCryst, Blueprint, Celldex, Cogent, CSL Behring, GSK, Ionis, Intellia, KalVista, Merck, Novartis, Pharming, Pharvaris, Regeneron, Takeda, Teva; **J.A.:** Astria, BioCryst, CSL Behring, Ionis, KalVista, Pharming, Pharvaris, Takeda; **F.A.:** BioCryst, CSL Behring, KalVista, Otsuka, Takeda; **M.C.:** BioCryst, CSL Behring, KalVista, Menarini, MSD, Novartis, Pharming, Pharvaris, Sobi, Takeda, UCB, Otsuka; **H.C.:** AstraZeneca (Alexion), CSL Behring, KalVista, Merck, Novartis, Pharming, Pharvaris, Roche, Sanofi, Sobi, Takeda; **N.C.:** BioCryst, CSL Vifor, GSK, Novartis, Pharming, Pharvaris, Takeda; **E.E.:** Biocryst, Dr. Falk Pharma, Novartis, Pharming, Pharvaris; **M.G.:** BioCryst, CSL Behring, Novartis; **S.G.:** Baxter, CSL Behring, Dyax, Grifols, Pharming/Swedish Orphan, Takeda, ViroPharma; **M.D.G.:** Biocryst, CSL Behring, Takeda; **P.G.:** BioCryst, CSL Behring, KalVista, Pharming, Takeda; **S.K-A:** BioCryst, Biotest, CSL Behring, Ionis, KalVista, Otsuka, Pharvaris, Takeda; **T.K.:** BioCryst, CSL Behring, KalVista, Otsuka, Pharvaris, Sanofi/Regeneron, Takeda; **M.M.:** Astria, BioCryst, CSL Behring, Intellia, KalVista, Novartis, Octapharma, Otsuka, Pharvaris, Takeda; **M.S.:** BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, Takeda; **M.D.T.:** none; **A.V.:** AstraZeneca, Berlin-Chemie/Menarini Group, CSL Behring, KalVista, Novartis, Pharming, Pharvaris, Sobi, Takeda; **H.J.W.:** BioCryst, BioMarin, CSL Behring, Genentech, GSK, Takeda; **W.H.Y.:** Aimmune Therapeutics, ALK Abello, AnaptysBio, Angioedema Centers of Reference and Excellence, Areteia, Aslan, AstraZeneca, Astria, BioCryst, Blueprint, Bristol Myers, Celgene, Celldex, CSL Behring, DBV Technologies, Dermira, Eli Lilly, Escient, Galderma, Genentech, GSK, Glenmark, Haleon, Hereditary Angioedema Canada, Incyte, Intellia, Ionis, Merck, Moderna, Novartis, Novavax, Pharvaris, Pharming, Providence, RAPT Therapeutics, Regeneron, Roche, Sanofi, Stallergenes, Takeda, Upstream Bio, VBI; **A.Z.:** Astria, BioCryst, CSL Behring, KalVista, Otsuka, Pharming, Pharvaris, Takeda; **R.C.:** employee of RC Consultancy and consultant to Pharvaris, holds stocks in Pharvaris; **S.M.:** employee of Mulders Clinical Consulting and consultant to Pharvaris; holds stocks in Pharvaris; **J.L., U.F., U.K, P.L.:** employees of Pharvaris, holds stocks in Pharvaris; **J.K.:** employee of JCK Consult and consultant to Pharvaris; holds stocks/stock options in Pharvaris; **A.L.:** employee of GrayMatters Consulting; consultant to Pharvaris; holds stocks/stock options in Pharvaris; advisor to Kosa Pharma; **E.A-P**: Astria, BioCryst, BioMarin, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Takeda; **M.A.R.:** Astria, BioCryst, BioMarin, Celldex, CSL Behring, Cycle Pharma, Grifols, Intellia, Ionis, KalVista, Novartis, Pharming, Pharvaris, Sanofi-Regeneron, Takeda.

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