

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

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Key takeaways

Final data from the completed open-label extension (OLE) of the Phase 2 CHAPTER-1 study investigating daily oral deucricitbant administration provide first evidence of the long-term safety and efficacy of bradykinin B2 receptor antagonism for prophylaxis against bradykinin-mediated angioedema attacks.

Safety	Efficacy
<p>Deucricitbant was generally well tolerated with no safety signals observed in laboratory parameters, vital signs, or ECG findings</p>	<p>Up to ~34 months Attack rate reduced by week 1 and remained low for up to ~34 months</p>
<p>Approximately half of participants were attack-free during the OLE</p>	<p>0.12 Overall on-study mean monthly attack rate during the OLE</p>

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

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 efficacyTM, a well-tolerated profile, and ease of administration.^{2,5}
- Oral deucricitbant:** a selective bradykinin B2 receptor antagonist under development for prophylaxis and on-demand treatment of bradykinin-mediated attacks.⁶⁻¹⁴

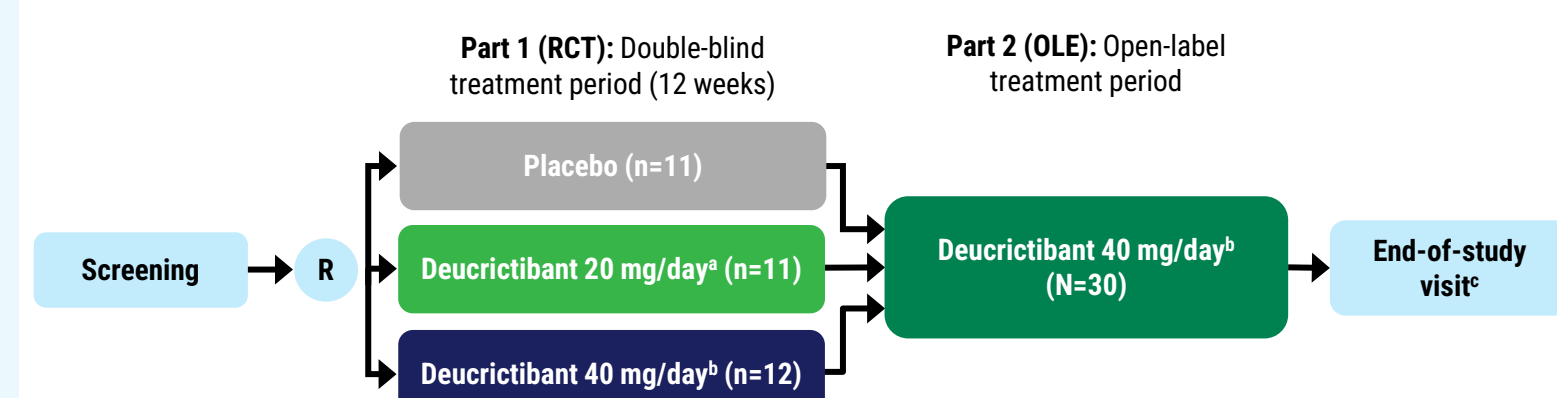
Objective

To evaluate the safety and efficacy of deucricitbant for long-term prophylaxis of HAE attacks in adults in the open-label extension (OLE) of the CHAPTER-1 study.¹³

Methods

- CHAPTER-1 (NCT05047185)*:** a two-part, Phase 2 study.¹³
 - Part 1 randomized controlled trial (RCT) and Part 2 OLE were completed.
- 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. n = number of participants randomized in each treatment group in the RCT. N = number of participants. *Deucricitbant IR capsule, 10 mg twice daily. †Deucricitbant IR capsule, 20 mg twice daily. ‡Twenty-one participants rolled over to the ongoing CHAPTER-4 open-label study (NCT06679881)¹² in which deucricitbant extended-release tablet is self-administered.

- Participants:** all 30 participants who completed the RCT continued into the OLE.
 - In the RCT, these 30 participants were randomized to deucricitbant 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 deucricitbant for prophylaxis against HAE attacks.

Results

Participants in the OLE

- Thirty participants in the OLE received deucricitbant 40 mg/day for a mean (SD) treatment duration of 22.2 (8.1) months.
 - Maximum deucricitbant 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 open-label study (NCT06679881)¹² in which deucricitbant extended-release (XR) tablet, 40 mg, is self-administered. None of the nine discontinuations in the CHAPTER-1 OLE were reported as treatment-related or associated with an adverse event.

Safety analysis

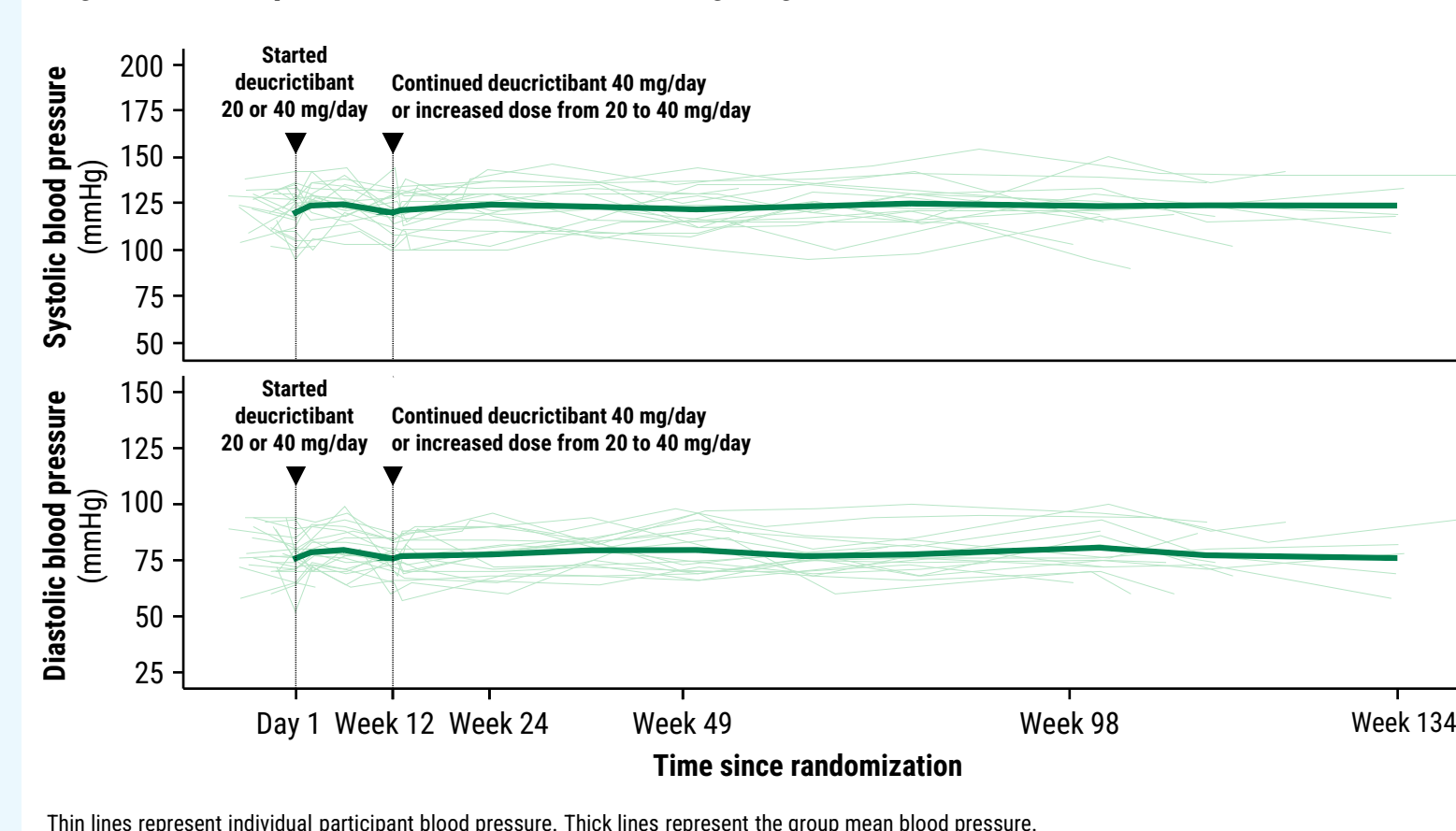
- Deucricitbant was generally well tolerated, with one treatment-related treatment-emergent adverse event (TEAE) reported: mild, asymptomatic increased gamma-glutamyltransferase (<2 upper limit of normal).
- No clinically significant abnormalities in laboratory parameters, vital signs, or electrocardiogram findings.
- No treatment-related severe or serious TEAEs were reported.
- 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, n	Participants, n (%)	Events, n	Participants, n (%)	Events, n	Participants, n (%)	Events, n
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 ^c	0	0	0	0	1 (10.0)	1	1 (3.3)	1
Serious TEAEs^d	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; RCT, randomized controlled trial; 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. ^aDeucricitbant IR capsule, 20 mg twice daily. ^bDeucricitbant IR capsule, 10 mg twice daily. ^cStarted during the RCT, resolved while continuing deucricitbant treatment during the OLE, and recurred by end of the OLE; alanine aminotransferase, aspartate aminotransferase, bilirubin, and alkaline phosphatase levels were normal. ^dThree serious TEAEs required reconstruction surgery, hip replacement, or knee replacement. These were not considered treatment-related.

Figure 2. Blood pressure remained stable during long-term treatment with deucricitbant

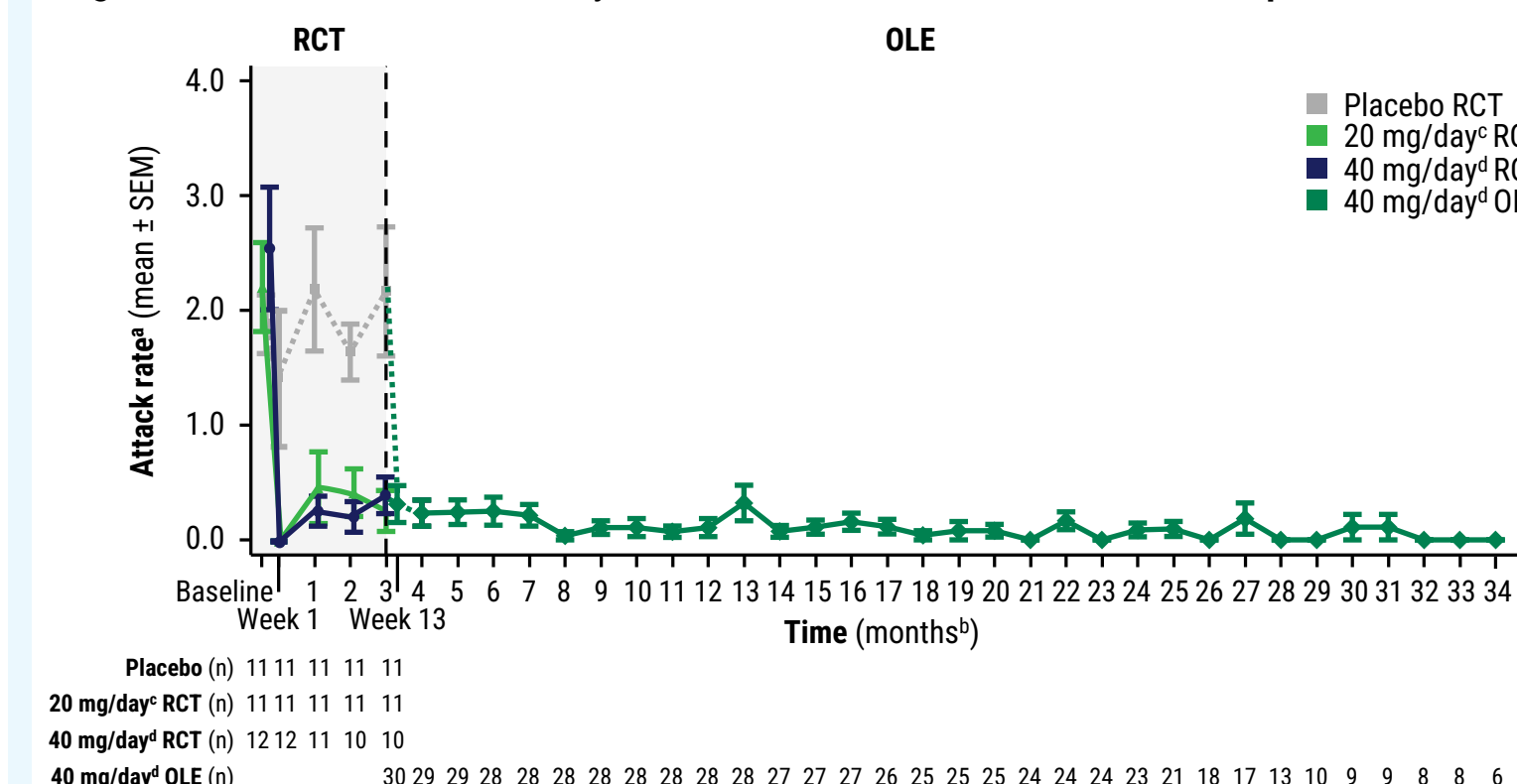


Thin lines represent individual participant blood pressure. Thick lines represent the group mean blood pressure.

Results

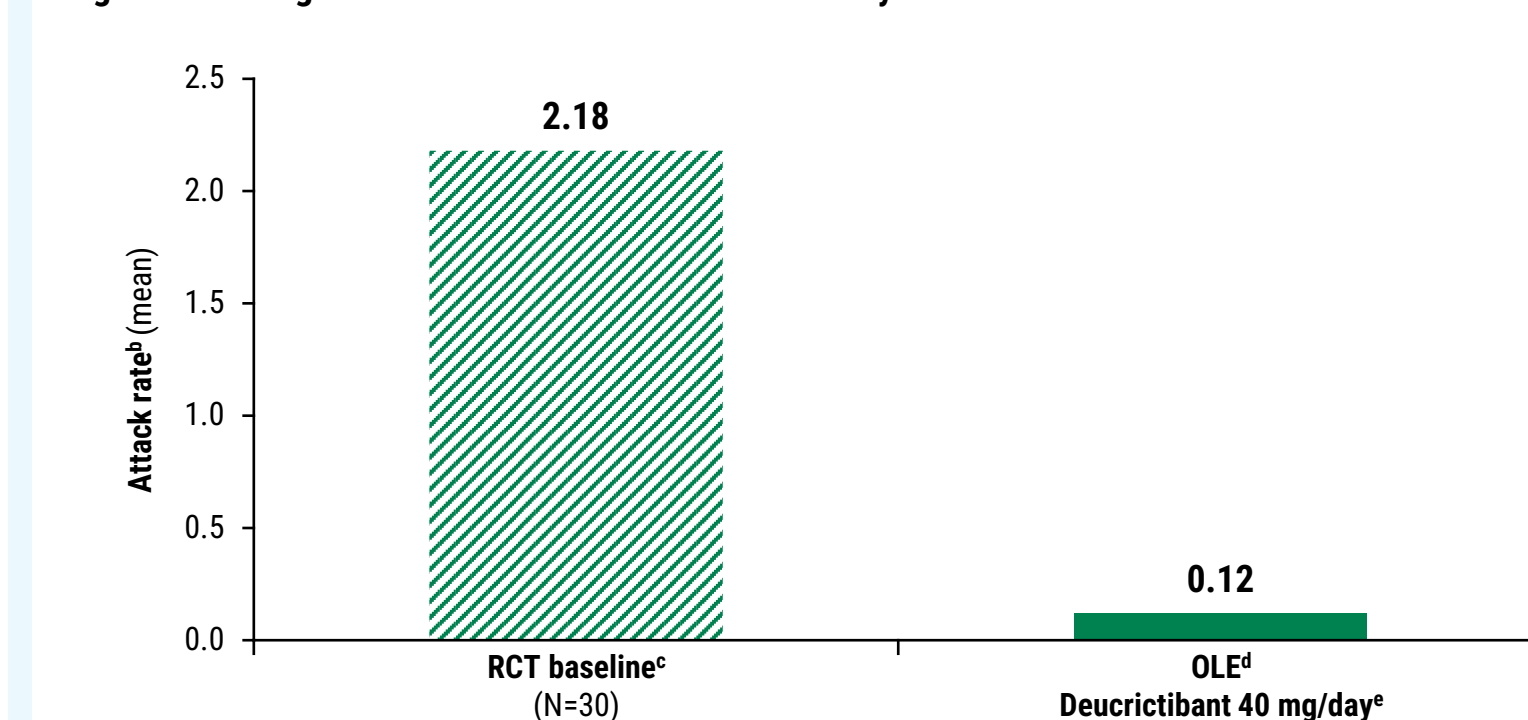
Efficacy analysis

Figure 3. Attack rate was reduced by week 1 and week 13 and remained low for up to ~34 months



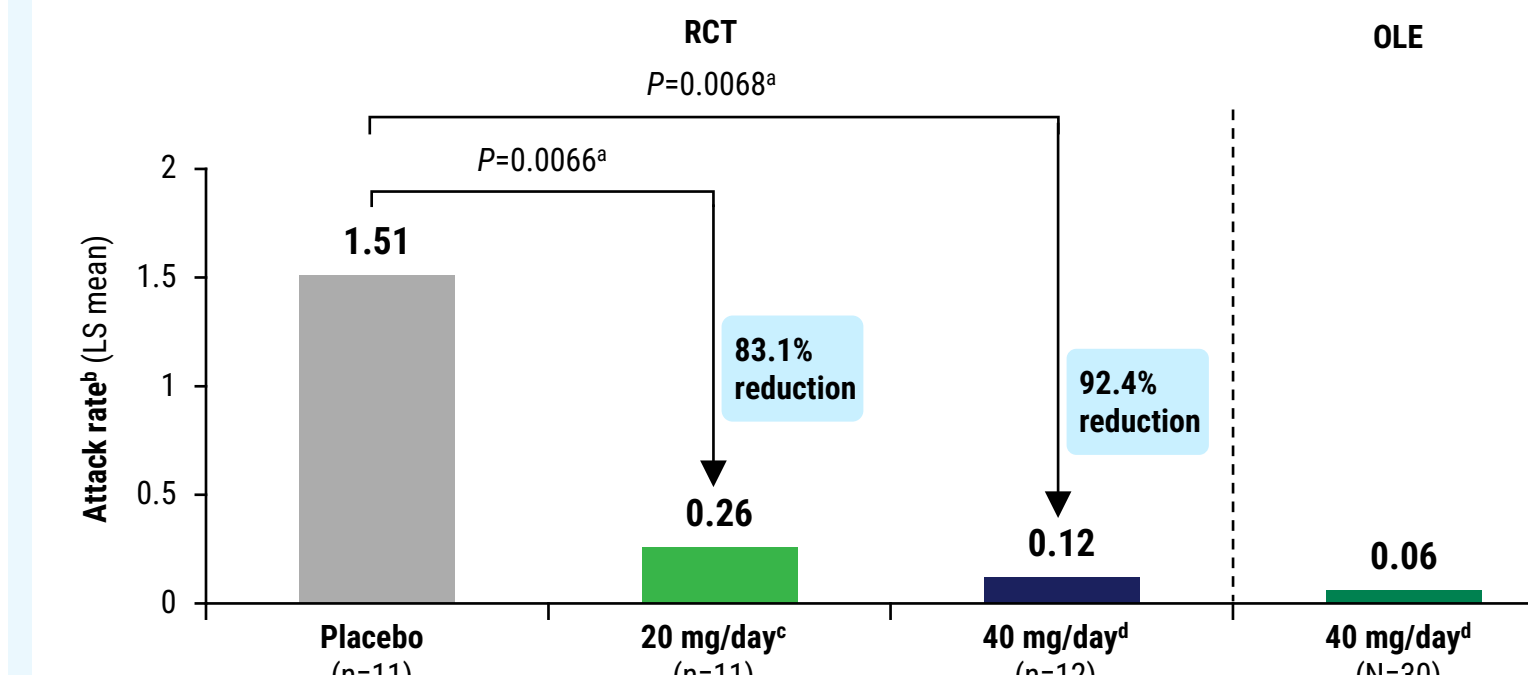
IR, immediate-release; OLE, open-label extension; RCT, randomized controlled trial; SEM, standard error of the mean. n = number of participants analyzed at each timepoint. ^aBased on time-normalized number of attacks per 4 weeks. ^b1 month = 4 weeks. ^cDeucricitbant IR capsule, 10 mg twice daily. ^dDeucricitbant IR capsule, 20 mg twice daily.

Figure 4. 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. ^a92.4% is the average participant-level reduction from CHAPTER-1 RCT baseline and excludes one participant with 4 days of OLE treatment and no attacks. ^bBased on time-normalized number of attacks per 4 weeks. ^cCrude mean attack rate at baseline. ^dCrude mean attack rate in the OLE. ^eDeucricitbant IR capsule, 20 mg twice daily.

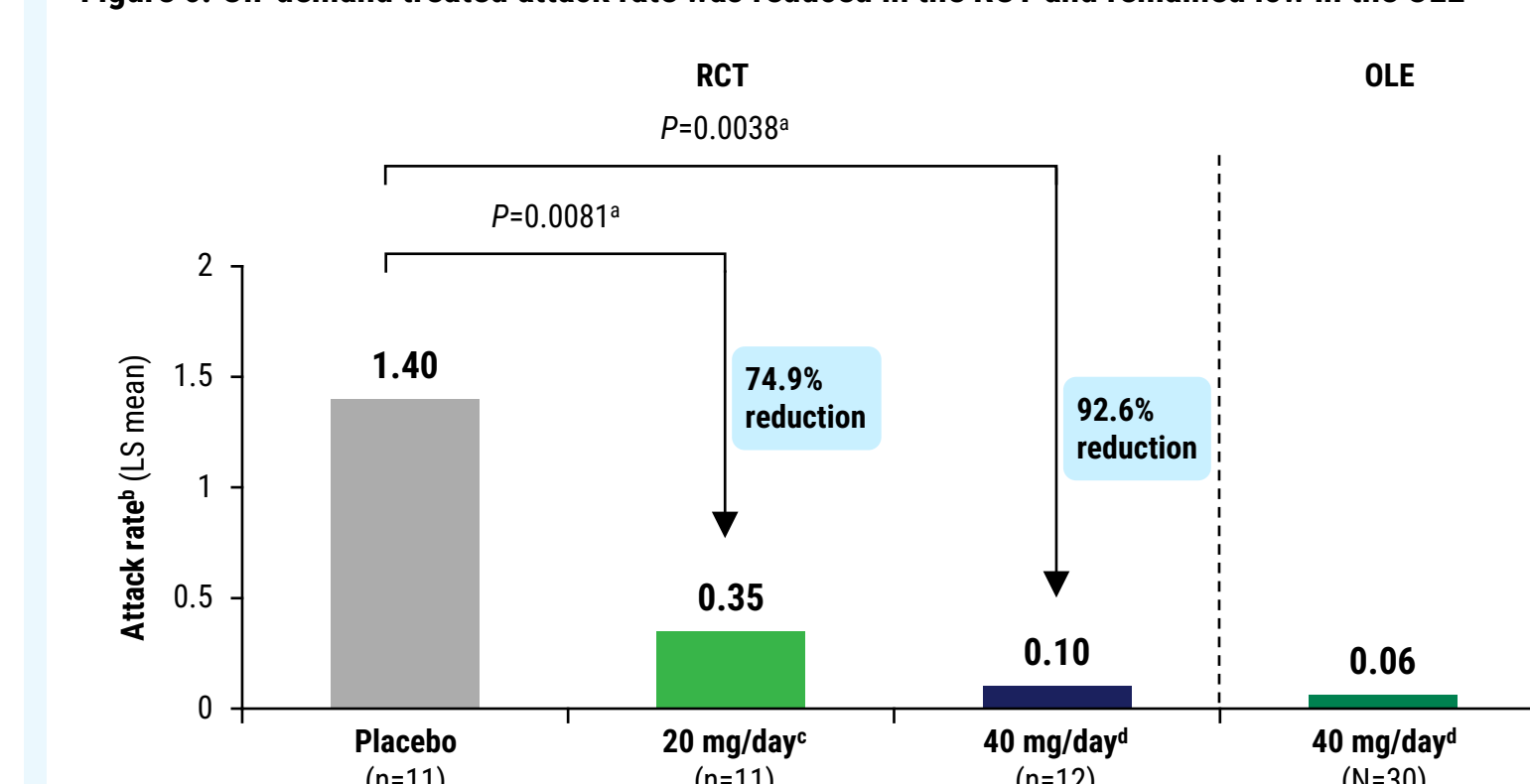
Figure 5. Moderate-to-severe attack rate was reduced in the RCT and remained low in the OLE



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. ^aThe P-values in this figure are nominal. ^bBased on time-normalized number of attacks per 4 weeks. ^cDeucricitbant IR capsule, 10 mg twice daily. ^dDeucricitbant IR capsule, 20 mg twice daily.

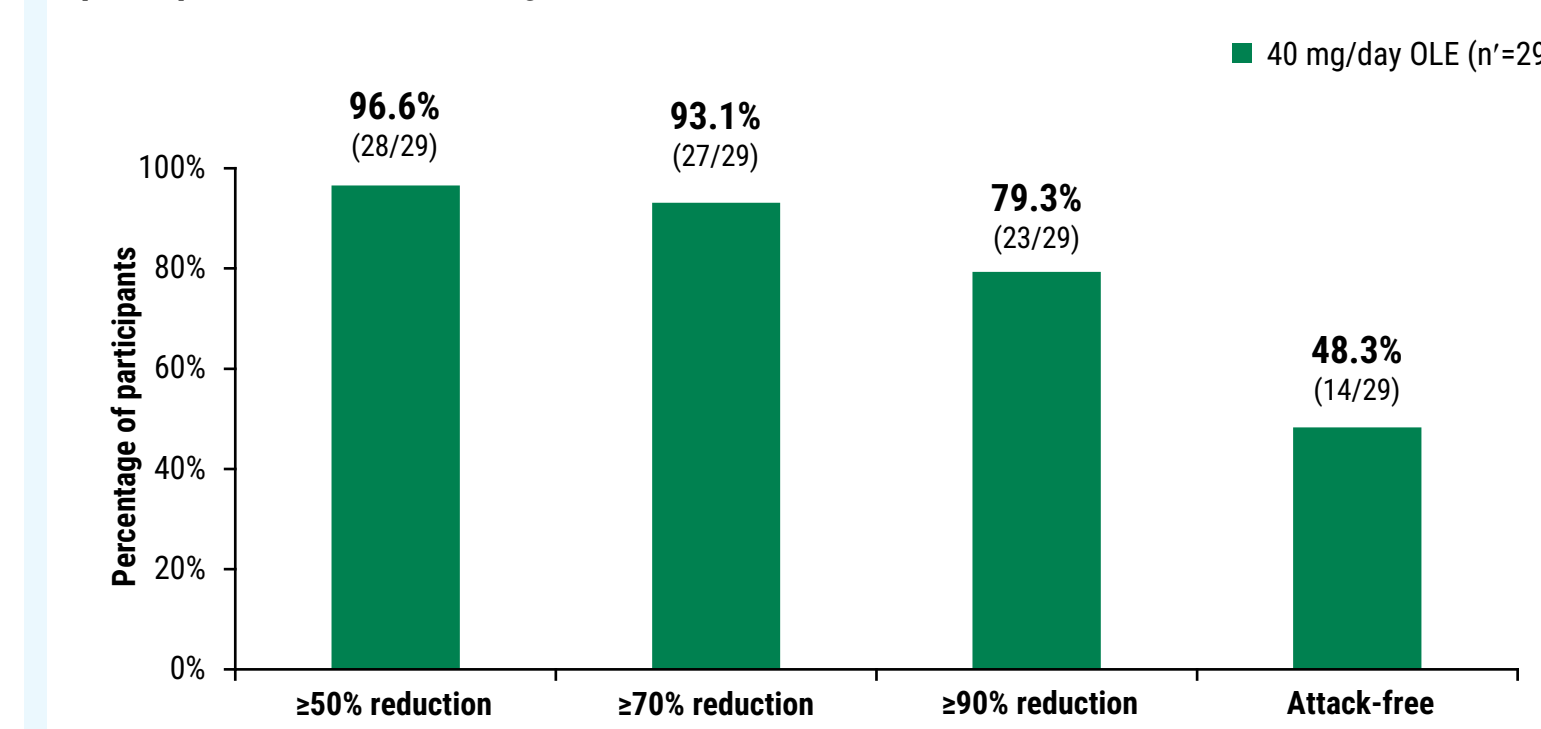
Results

Figure 6. On-demand treated attack rate was 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. ^aThe P-values in this figure are nominal. ^bBased on time-normalized number of attacks per 4 weeks. ^cDeucricitbant IR capsule, 10 mg twice daily. ^dDeucricitbant IR capsule, 20 mg twice daily.

Figure 7. Attack rate reduced relative to RCT study baseline with approximately half of participants attack-free during the OLE



IR, immediate-release; OLE, open-label extension; RCT, randomized controlled trial. ^aParticipants with ≥4 weeks of treatment in the OLE receiving 40 mg/day (deucricitbant IR capsule, 20 mg twice daily).

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COI: J.A.: Astra, BioCryst, CSL Behring, Ionis, KalVista, Pharming, Pharvaris, Takeda; F.A.: BioCryst, CSL Behring, KalVista, Otsuka, Takeda; M.C.: ADARx, BioCryst, Chiesi, CSL Behring, Gentili, KalVista, Menarini, MSD, NeoPharmed, Novartis, Otsuka, Pharming, Pharvaris, Sobi, Takeda, UCB; 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, Biotech, CSL Behring, Ionis, KalVista, Otsuka, Pharvaris, Takeda; T.K.: ADARx, Astra, BioCryst, CSL Behring, KalVista, Otsuka, Pharvaris, Sanofi/Regeneron, Takeda; M.M.: Argo, Astra, BioCryst, CSL Behring, Intellia, KalVista, Novartis, Octapharma, Otsuka, Pharvaris, Takeda; M.E.M.: AstraZeneca, Astra, BioCryst, Blueprint, Celldex, Cogent, CSL Behring, GSK, Intellia, Ionis, KalVista, Merck, Novartis, Pharming, Pharvaris, Regeneron, Takeda, Teva; M.S.: BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, Takeda; M.D.T.: none to report; A.V.: AstraZeneca, Astra, Berlin-Chemie/Menarini Group, CSL Behring, Ewopharma, Ionis, KalVista, Novartis, Organon, Pharming, Pharvaris, Sobi, Stallergenes Greer, Takeda, Teva; H.J.W.: BioCryst, BioMarin, CSL Behring, Genentech, GSK, Takeda; W.H.Y.: Aimme Therapeutics, ALK Abello, AnaptysBio, Angioedema Centers of Reference and Excellence, Areteia, Aslan, AstraZeneca, Astra, 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.: Astra, BioCryst, CSL Behring, Intellia, 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, hold 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.: Astra, BioCryst, BioMarin, CSL Behring, Intellia, KalVista, Otsuka, Pharming, Pharvaris, Takeda; M.A.R.: ADARx, Astra, BioCryst, BioMarin, Celldex, CSL Behring, Cycle Pharma, Grifols, Intellia, Ionis, KalVista, Novartis, Pharming, Pharvaris, Sanofi-Regeneron, Takeda.

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