Efficacy and Safety of Oral Deucrictibant, a Potent Bradykinin B2 Receptor Antagonist, in Prophylaxis of Hereditary Angioedema Attacks: Results of CHAPTER-1 Phase 2 Trial

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

Conflicts of interest disclosure

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M.A.R.: Astria, BioCryst, Biomarin, CSL Behring, Cycle Pharma, Fresenius-Kabi, Grifols, Ionis, Ipsen, KalVista, Ono Pharma, Pfizer, Pharming, Pharvaris, RegenxBio, Sanofi-Regeneron, Takeda; **J.A.**: BioCryst, BioMarin, CSL Behring, Cycle Pharmaceuticals, KalVista, Pharming, Pharvaris, Takeda; **F.A.**: CSL Behring, Takeda; **M.C.**: BioCryst, CSL Behring, KalVista, Menarini, MSD, Novartis, Pharming, Pharvaris, Shire/Takeda, Sobi, UCB; **H.C.**: AstraZeneca (Alexion), CSL Behring, KalVista, Merck, Novartis, Pharming, Pharvaris, Roche, Sanofi, Sobi, Takeda; **N.C.**: Novartis, Takeda; **E.E.**: none; **M.G.**: BioCryst, CSL Behring, Novartis; **S.G.**: Baxter, CSL Behring, Dyax, Grifols, Jerini/Shire, Pharming/Swedish Orphan, Viropharma; **M.D.G.**: CSL Behring; **P.G.**: BioCryst, CSL Behring, KalVista, Pharming, Shire, Takeda; **T.K.**: BioCryst, CSL Behring, KalVista, Novartis, Sanofi-Regeneron, Pharvaris, Shire/Takeda; **M.M.**: BioCryst, CSL Behring, Intellia, KalVista, Novartis, Octapharma, Pharming, Pharvaris, Shire/Takeda; **M.E.M.**: Allakos, Amgen, AstraZeneca, BioCryst, Blueprint, CSL Behring, Cycle, Genentech, GSK, KalVista, Merck, Novartis, Pharming, Pharvaris, Sanofi/Regeneron, Takeda; **M.S.**: BioCryst, CSL Behring, KalVista, Pharming, Shire/Takeda; **M.D.T.**: none**; A.V.**: AstraZeneca, Berlin-Chemie/Menarini Group, CSL Behring, Novartis, Pharming, Pharvaris, Shire/Takeda, Sobi, Teva; **H.J.W.**: BioCryst, BioMarin, CSL Behring, Genentech, GSK, Takeda; **W.H.Y.**: Aimmune, ALK, Amgen, AnaptysBio, Aslan Therapeutics, AstraZeneca, BioCryst, Celgene, CSL Behring, DBV Technologies, Dermira, Eli Lilly, Galderma, Genentech/Roche, Glenmark, GSK, Haleon, Incyte Biosciences, Ionis, Merck, Novartis, Novavax, Pharming, Pharvaris, Providence, Regeneron, Sanofi Genzyme, Shire/Takeda, VBI; **A.Z.**: BioCryst, CSL Behring, KalVista, Pharming, Takeda; **R.C.**: employee of CG Consultancy and consultant to Pharvaris, holds stocks in Pharvaris; **S.M.**: employee of Mulders Clinical Consulting and consultant to Pharvaris, holds stocks in Pharvaris; **M.R.**, **L.Z.**: employees of Pharvaris, hold stock/stock options in Pharvaris; **J.K.**: employee of JCK Consult and consultant to Pharvaris, holds stocks/stock options in Pharvaris; **A.L.**: employee of GrayMatters Consulting and consultant to Pharvaris, holds stocks/stock options in Pharvaris; advisor to Kosa Pharma; **P.L.**: employee of Pharvaris, holds stock/stock options in Pharvaris; **E.A-P.**: Astria, BioCryst, Biomarin, Centogene, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Shire/Takeda.

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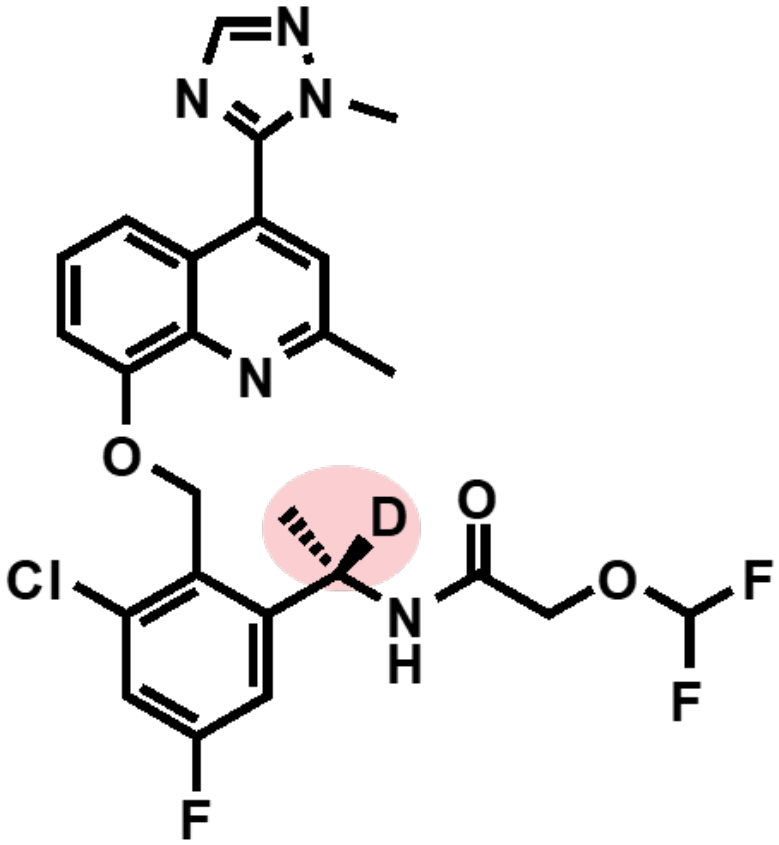
CHAPTER-1 is a Pharvaris-sponsored clinical trial. ClinicalTrials.gov identifier: NCT05047185.

Deucrictibant is an orally bioavailable, selective, highly potent, competitive antagonist of bradykinin B2 receptor



- Antagonist of bradykinin B2 receptor (-*tibant* stem[1])
- 2.4-fold lower molecular weight than icatibant
- Metabolic soft spot stabilized by introduction of a *deu*terium atom
  - Optimized for metabolic stability and exposure in humans
- Pure antagonist at bradykinin B2 receptor
  - No intrinsic agonism observed for deucrictibant[2]

    (Intrinsic agonism of icatibant hypothesised to underly the injection site reactions at high concentrations[2])

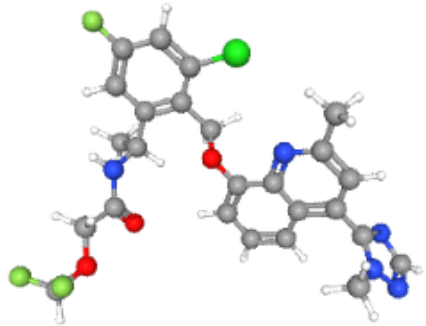
Figure from: Lesage A, et al. *Front Pharmacol*. 2020;11:916. Lesage A, et al. *Int Immunopharmacol*. 2022;105:108523.

1. World Health Organization. Guidance on the use of international nonproprietary names (INNs) for pharmaceutical substances. 2017. https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/who-pharm-s-nom-1570.pdf. Accessed February 21, 2024. **2**. European Medicines Agency. CHMP assessment report for Firazyr®. 2008. https://www.ema.europa.eu/en/documents/assessment-report/firazyr-epar-public-assessment-report_en.pdf. Accessed February 21, 2024.

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

Deucrictibant
Immediate-release capsule

Rapid absorption

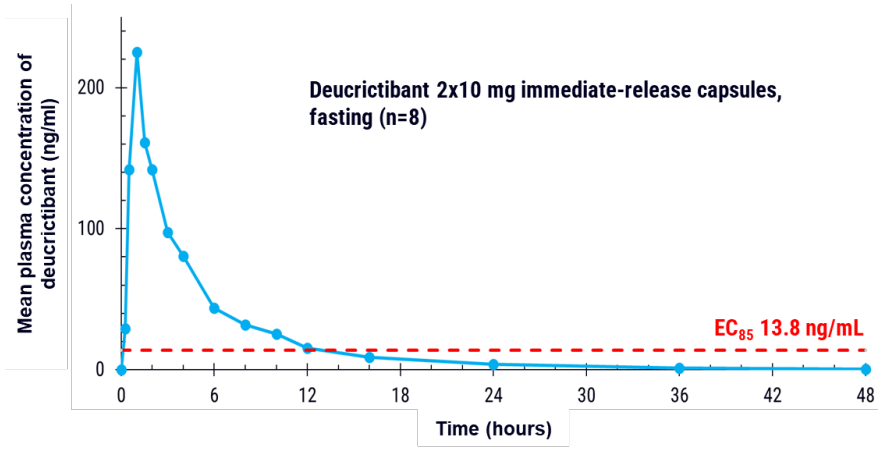


Deucrictibant
Extended-release tablet

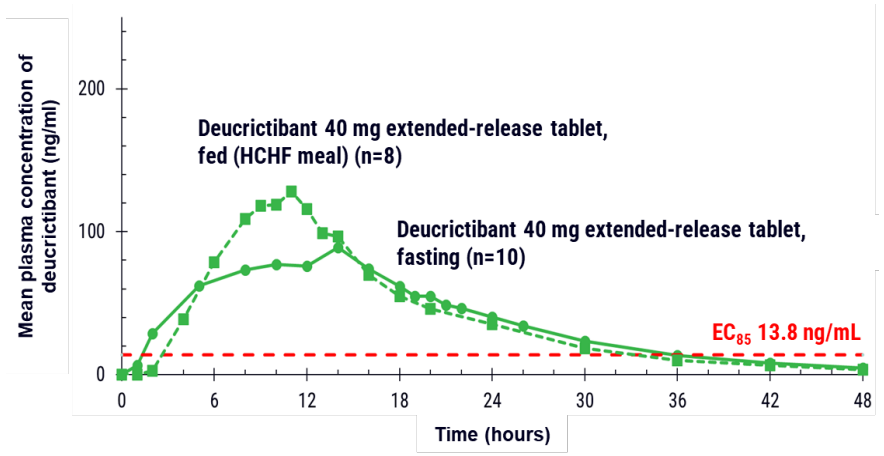
Sustained absorption

Deucrictibant

Aim to provide rapid and reliable symptom relief, through rapid exposure of attack-mitigating therapy in a convenient, small oral dosage form*

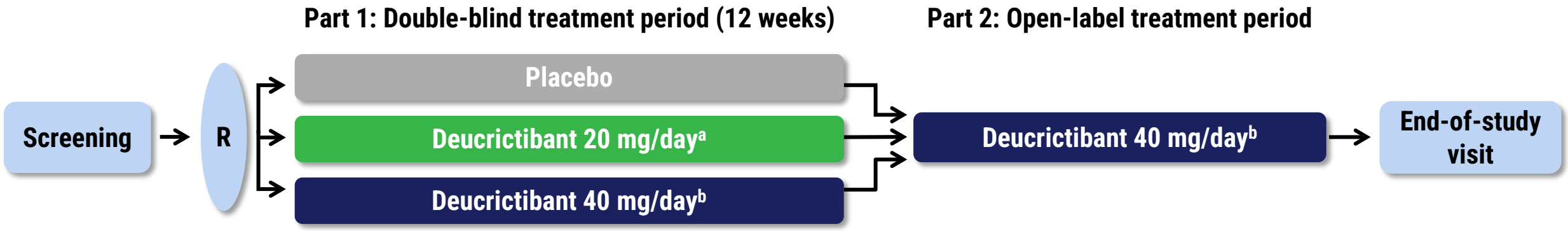


Aim to provide sustained exposure of attack-preventing therapy in a convenient, small oral dosage form*



HAE, hereditary angioedema; HCHF, high-calorie high-fat. Adapted from: Groen K, et al. Presented at ACAAI 2022. November 10–14, 2022; Louisville, KY, USA. *Aspirational; to be confirmed with clinical data.

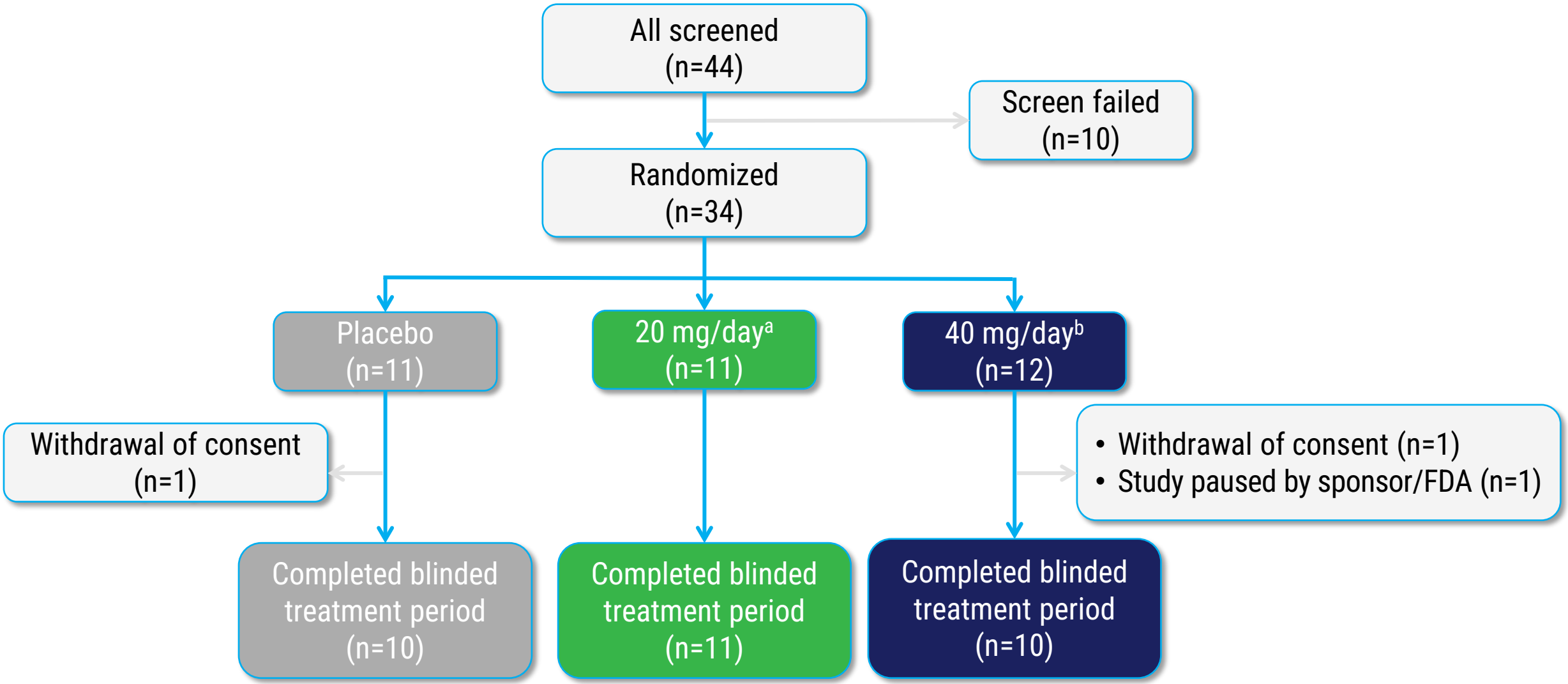
CHAPTER-1: Two-part, Phase 2 study of deucrictibant for long-term prophylaxis of HAE attacks



- Primary endpoint:
  - Time-normalized number of investigator-confirmed HAE attacks (**monthly[c] HAE attack rate**)
- Secondary endpoints:
  - Time-normalized number of **moderate and severe HAE attacks**
  - Time-normalized number of **HAE attacks treated with on-demand medication**

HAE, hereditary angioedema; IR, immediate-release; R, randomization. CHAPTER-1 is a Pharvaris-sponsored clinical trial. ClinicalTrials.gov identifier: NCT05047185. https://www.clinicaltrials.gov/study/NCT05047185. Accessed January 9, 2024. [a]Deucrictibant IR capsule, 10 mg twice daily. [b]Deucrictibant IR capsule, 20 mg twice daily. [c]1 month = 4 weeks.

Participant disposition



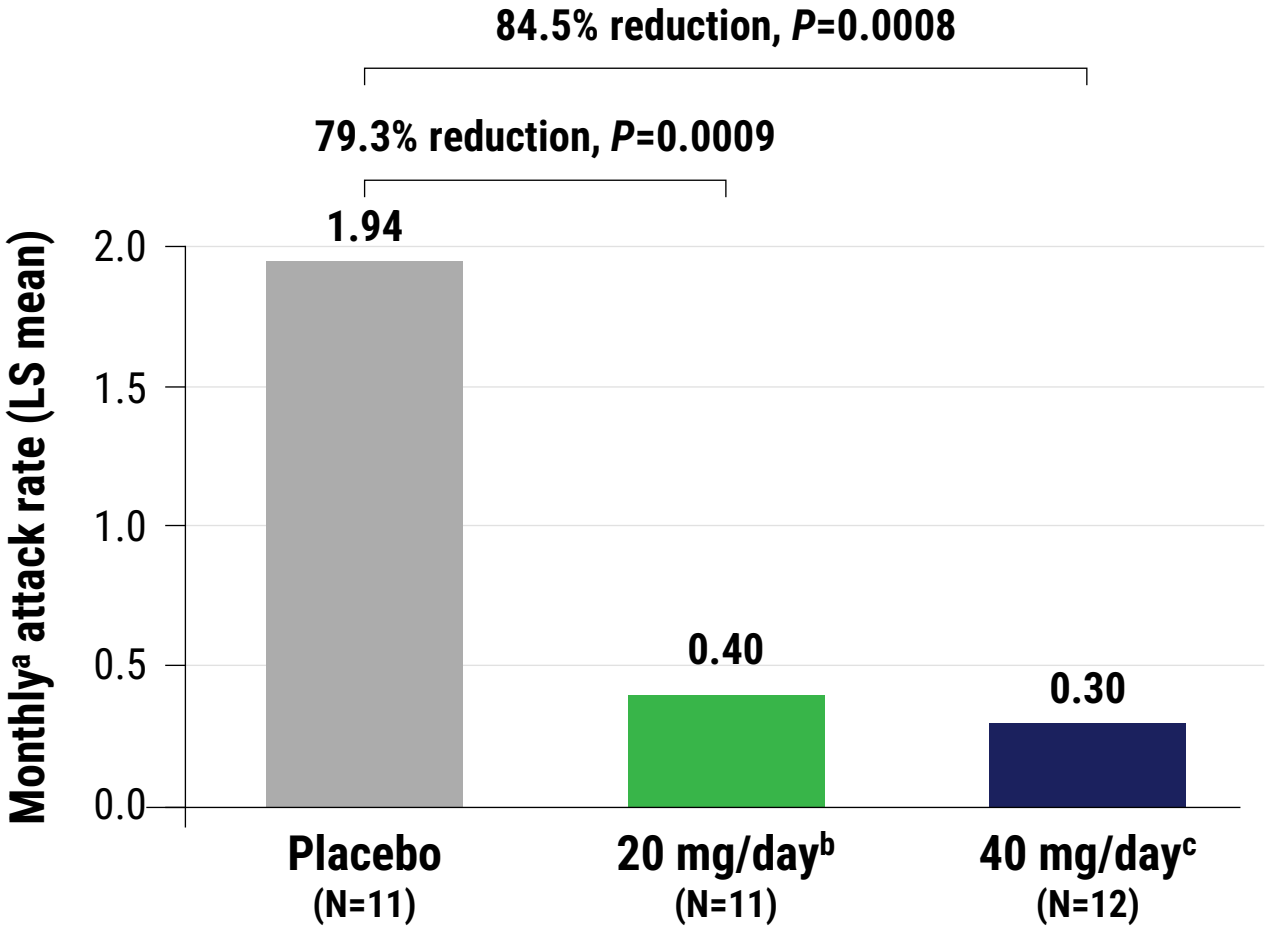
IR, immediate-release. n = number of participants. [a]Deucrictibant IR capsule, 10 mg twice daily. [b]Deucrictibant IR capsule, 20 mg twice daily.

Balanced demographics and baseline characteristics

	Placebo (N=11)	20 mg/day[b] (N=11)	40 mg/day[c] (N=12)	All (N=34)
Age (years), mean	41.4	38.4	40.8	40.2
Sex: M/F, n	3/8	6/5	4/8	13/21
Race: White, n (%)	11 (100)	11 (100)	12 (100)	34 (100)
BMI (kg/m^2), mean	26.7	29.5	25.4	27.1
HAE type, n				
Type 1	10	9	12	31
Type 2	1	2	0	3
Baseline monthly[a] HAE attack rate				
Mean	1.9	2.1	2.5	2.2
Median (min, max)	1.7 (0.7, 3.7)	1.7 (1.0, 5.3)	1.7 (1.0, 6.7)	1.7 (0.7, 6.7)
Randomized baseline monthly[a] HAE attack rate categories, n (%)				
1 to <2 attacks	6 (54.5)	7 (63.6)	7 (58.3)	20 (58.8)
2 to <3 attacks	3 (27.3)	1 (9.1)	1 (8.3)	5 (14.7)
≥3 attacks	2 (18.2)	3 (27.3)	4 (33.3)	9 (26.5)

BMI, body mass index; HAE, hereditary angioedema; IR, immediate-release. N = number of randomized participants. [a]1 month = 4 weeks. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 20 mg twice daily.

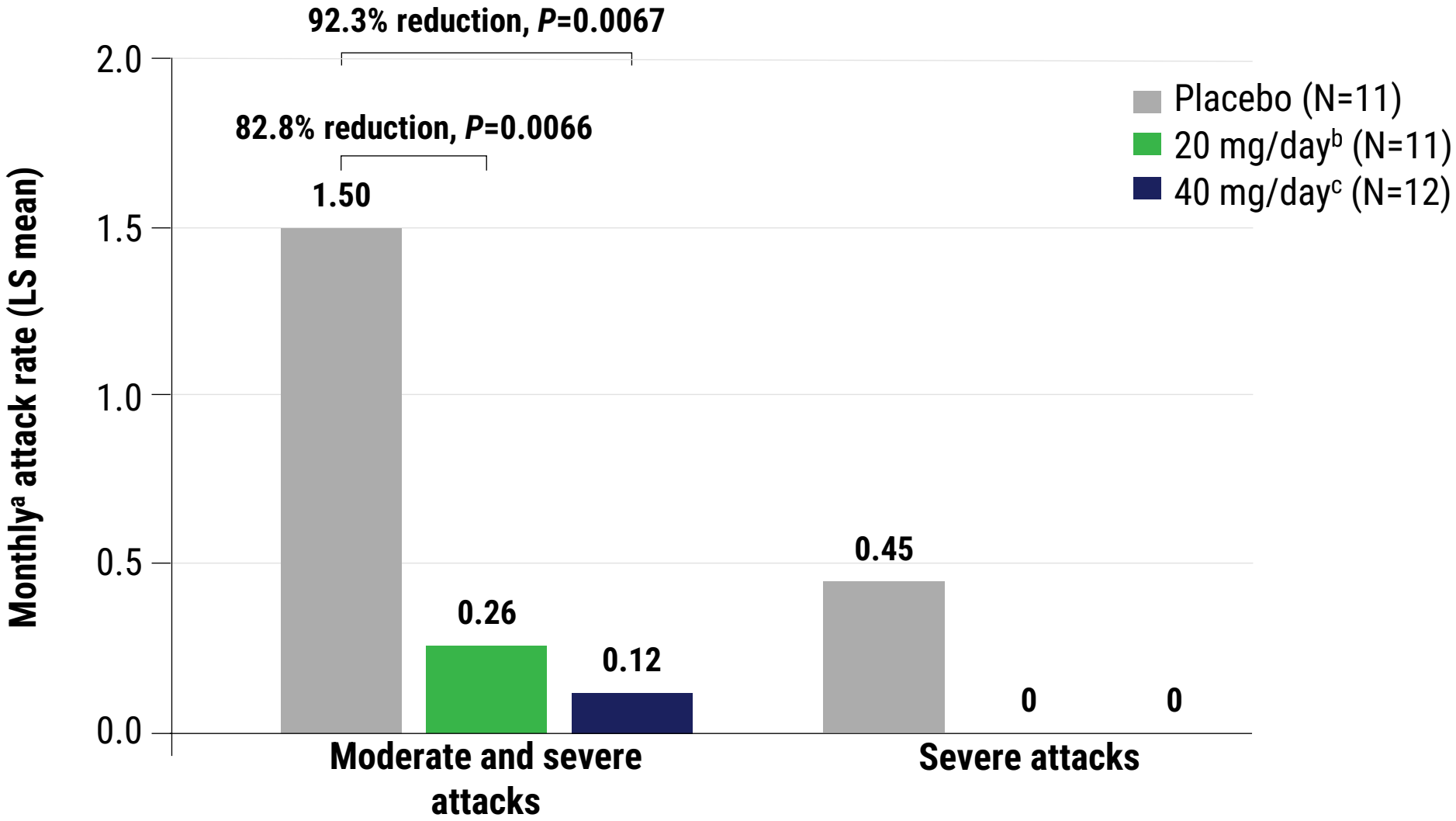
Primary endpoint:
Deucrictibant significantly reduced the monthly attack rate



	Placebo (N=11)	Deucrictibant IR capsule 20 mg/day[b] (N=11)	Deucrictibant IR capsule 40 mg/day[c] (N=12)
Monthly[a] attack rate			
Baseline (BL), median	1.67	1.67	1.74
On study, median	2.15	0	0.15
Change from BL, median	0.33	−1.34	−1.59
% change from BL	17%	−100%	−96%
Model-based inference			
LS mean	1.94	0.40	0.30
% reduction vs placebo	–	79.3%	84.5%
P value	–	0.0009	0.0008

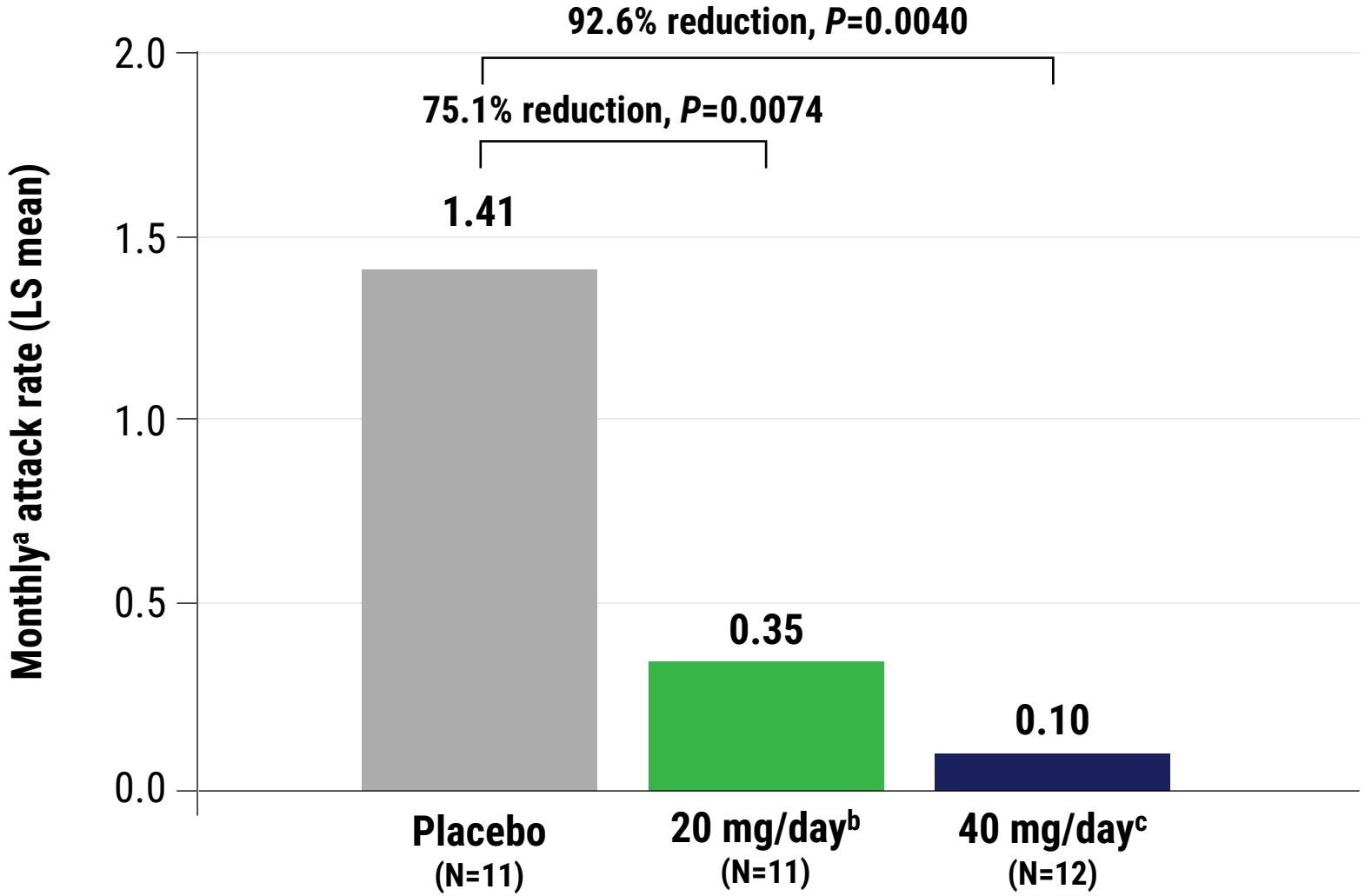
IR, immediate-release; LS, least squares. N = number of randomized participants. Model-based inferences are based on a Poisson regression model adjusted for baseline attack rate and time on treatment. No multiplicity adjustment was applied. [a]1 month = 4 weeks . [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 20 mg twice daily.

Deucrictibant reduced occurrence of moderate and severe attacks



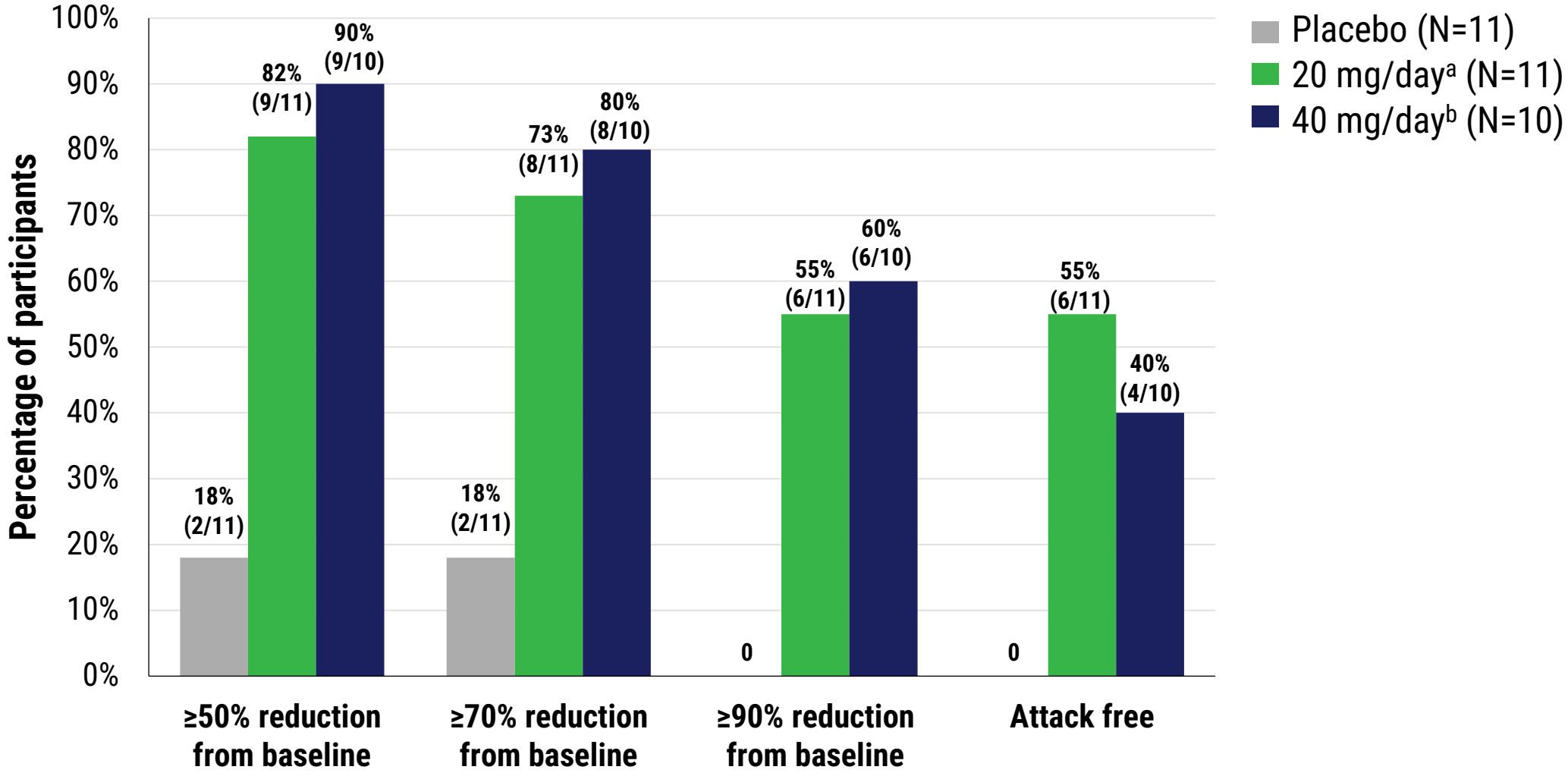
IR, immediate-release; LS, least squares. N = number of randomized participants. The *P* values in this figure are nominal.
[a]1 month = 4 weeks. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 20 mg twice daily.

Deucrictibant reduced occurrence of attacks treated with on-demand medication



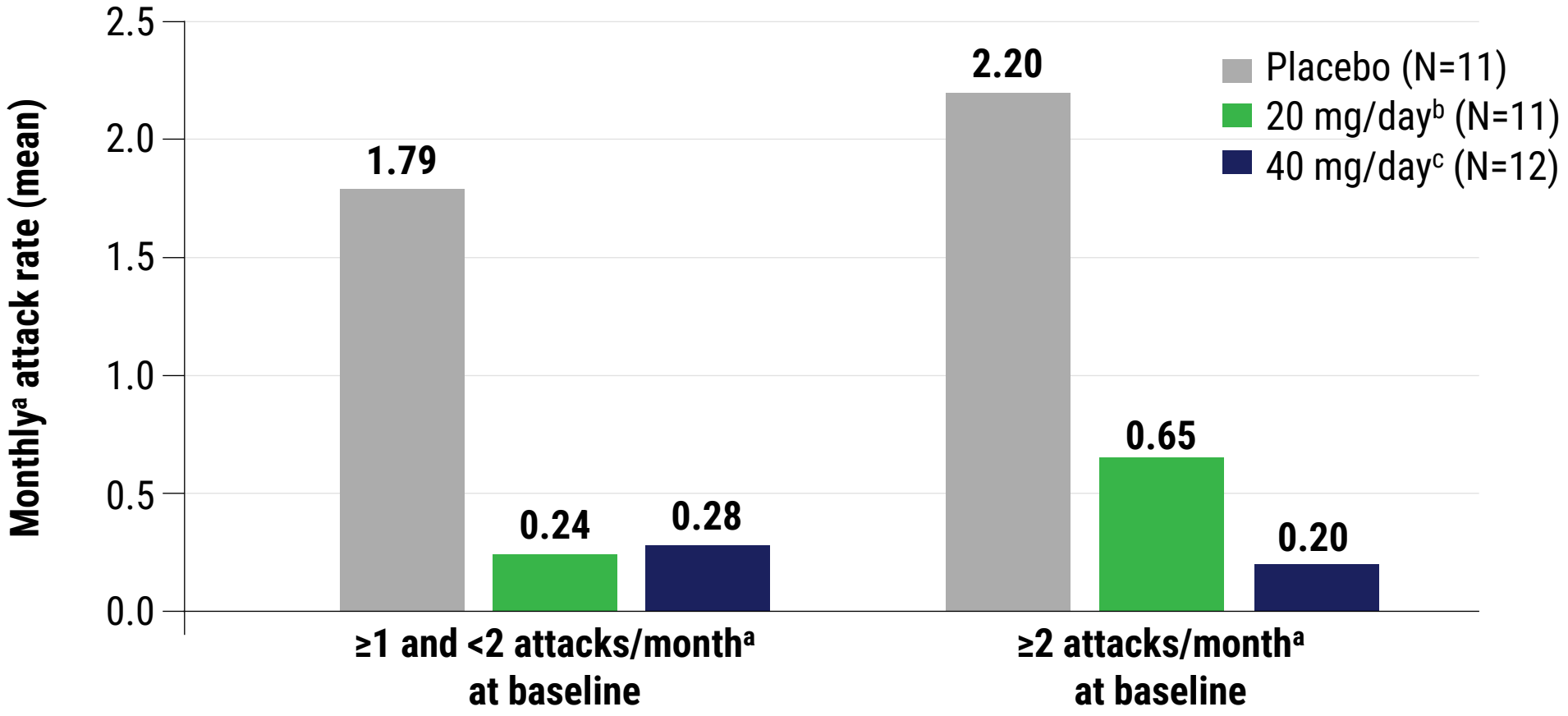
IR, immediate-release; LS, least squares. N = number of randomized participants. The *P* values in this figures are nominal.
[a]1 month = 4 weeks. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 20 mg twice daily.

Deucrictibant substantially reduced attack rate from baseline



IR, immediate-release. N = number of randomized participants. Results based on participants with at least 4 weeks of treatment. [a]Deucrictibant IR capsule, 10 mg twice daily. [b]Deucrictibant IR capsule, 20 mg twice daily.

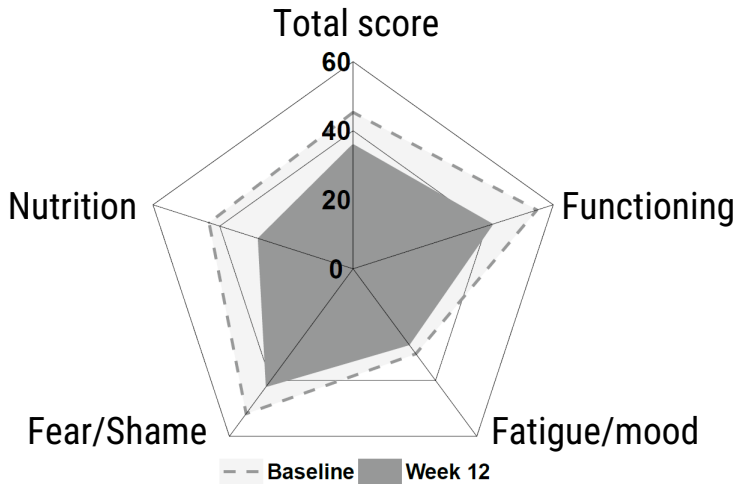
Deucrictibant reduced monthly attack rate regardless of baseline attack rate



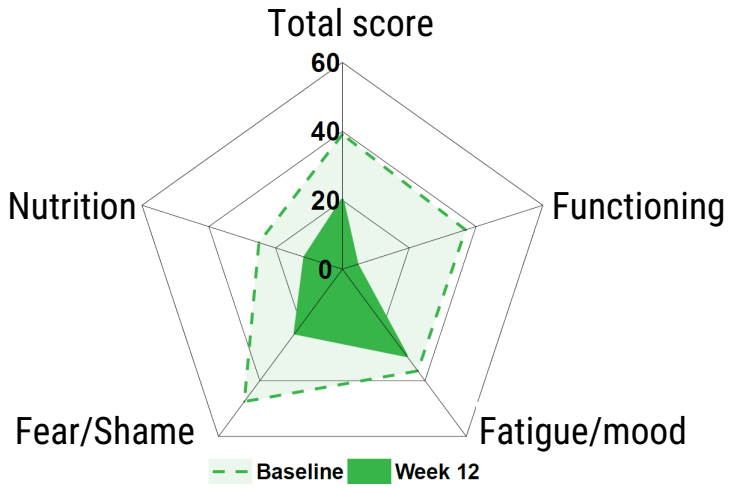
N = number of randomized participants. [a]1 month = 4 weeks. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 20 mg twice daily.

AE-QoL: Deucrictibant improved health-related quality of life

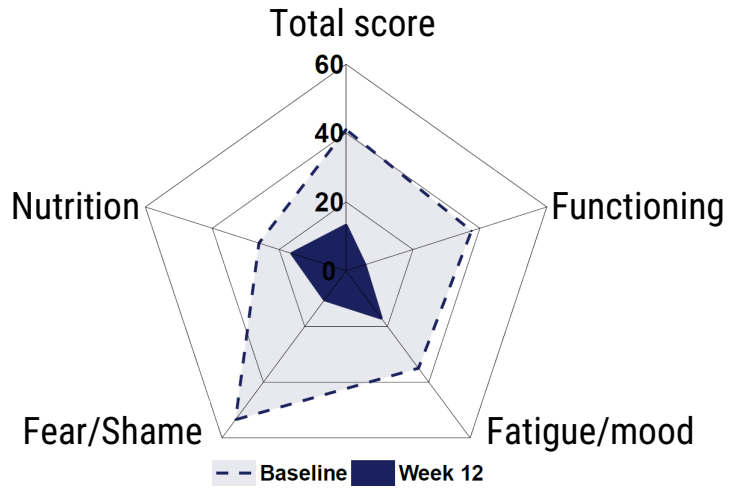
Placebo



20 mg/day[a]



40 mg/day[b]



		Deucrictibant IR capsule	
AE-QoL total score	**Placebo**	**20 mg/day[a]**	**40 mg/day[b]**
Baseline	**N=11**	**N=10**	**N=12**
Mean (SD)	45.3 (18.5)	39.1 (22.0)	41.1 (15.5)
Median (Q1, Q3)	42.6 (29.4, 57.4)	37.5 (16.2, 55.9)	40.4 (31.6, 49.3)
Week 12	**N'=8**	**N'=10**	**N'=10**
Mean (SD)	35.7 (19.6)	20.2 (15.6)	13.2 (6.9)
Median (Q1, Q3)	37.5 (19.1, 49.3)	18.4 (7.4, 33.8)	12.5 (10.3, 17.7)

AE-QoL, Angioedema Quality of Life questionnaire; IR, immediate-release; SD, standard deviation. N = number of randomized participants with AE-QoL data at baseline. N' = number of participants with AE-QoL data at week 12.
[a]Deucrictibant IR capsule, 10 mg twice daily. [b]Deucrictibant IR capsule, 20 mg twice daily.

Deucrictibant was well tolerated at both doses

- All reported treatment-related treatment-emergent adverse events (TEAEs) were mild in severity

Adverse events	Placebo (N=11)		Deucrictibant IR capsule			
			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; TEAE, treatment-emergent adverse event. N = number of participants who received at least 1 dose of blinded study treatment. [a]Deucrictibant IR capsule, 10 mg twice daily. [b]Deucrictibant IR capsule, 20 mg twice daily.

Conclusions

- Prophylactic treatment with deucrictibant significantly reduced the occurrence of HAE attacks
- Primary endpoint was met: 84.5% (*P*=0.0008) reduction in monthly attack rate vs placebo[a]
  - 92.3% reduction in occurrence of moderate and severe attacks[a]
  - 92.6% reduction in occurrence of attacks treated with on-demand medication[a]
  - Consistent reduction in the occurrence of HAE attacks regardless of baseline attack rate
- Both doses of deucrictibant were well tolerated
- These data 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. [a]40 mg/day deucrictibant treatment group.