Long-Term Safety and Efficacy of Prophylactic Oral Deucrictibant, a Bradykinin B2 Receptor Antagonist, in Hereditary Angioedema: Results of the CHAPTER-1 Open Label Extension Study

Marc A. Riedl[1]*, John Anderson[2], Francesco Arcoleo[3], Mauro Cancian[4], Hugo Chapdelaine[5], Niall Conlon[6], Efrem Eren[7], Mark Gompels[8], Sofia Grigoriadou[9], Maria D. Guarino[10], Padmalal Gurugama[11], Tamar Kinaciyan[12], Markus Magerl[13,14], Michael E. Manning[15], Marcin Stobiecki[16], Michael D. Tarzi[17], Anna Valerieva[18], H. James Wedner[19], William H. Yang[20], Andrea Zanichelli[21,22], Rafael Crabbé[23], Susan Mulders[24], Jonathan Levy[25], Ulrich Freudensprung[26], Umar Katbeh[26], Jochen Knolle[27], Anne Lesage[28], Peng Lu[26], Emel Aygören-Pürsün[29]

[1]University of California San Diego, Division of Allergy and Immunology, La Jolla, CA, USA; [2]AllerVie Health, Clinical Research Center of Alabama, Birmingham, AL, USA; [3]AOR Villa Sofia-Cervello, UOC di Patologia Clinica e Immunologia, Palermo, Italy; [4]University Hospital of Padua, Department of Systems Medicine, Padua, Italy; [5]Université de Montréal, CHU de Montréal, Montréal, QC, Canada; [6]St. James's Hospital and Trinity College, Wellcome Trust CRF, Dublin, Ireland; [7]University Hospital Southampton NHS Foundation Trust, Southampton, UK; [8]North Bristol NHS Trust, Bristol, UK; [9]Barts Health NHS Trust, Department of Immunology, London, UK; [10]Ospedale di Civitanova Marche, Civitanova Marche, Italy; [11]Cambridge University Hospitals NHS Foundation Trust, Department of Clinical Immunology, Cambridge, UK; [12]Medical University of Vienna, Department of Dermatology, Vienna, Austria; [13]Charité – Universitätsmedizin Berlin, Institute of Allergology, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [14]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany; [15]Allergy, Asthma and Immunology Associates, Ltd., Scottsdale, AZ, USA; [16]Jagiellonian University Medical College, Department of Clinical and Environmental Allergology, Krakow, Poland; [17]University Hospitals Sussex NHS Foundation Trust, Department of Respiratory Medicine, Brighton, UK; [18]Medical University of Sofia, Dept. of Allergology, Sofia, Bulgaria; [19]Washington University School of Medicine, Division of Allergy and Immunology, Department of Medicine, St. Louis, MO, USA; [20]Ottawa Allergy Research Corporation, Department of Medicine, University of Ottawa, Ottawa, ON, Canada; [21]Universita degli Studi di Milano, Dipartimento di Scienze Biomediche per la Salute, Milan, Italy; [22]I.R.C.C.S., Policlinico San Donato, Centro Angioedema, UO Medicina, Milan, Italy; [23]RC Consultancy, Bassins, Switzerland; [24]Mulders Clinical Consulting, Groesbeek, The Netherlands; [25]Pharvaris Inc., Lexington, MA, USA; [26]Pharvaris GmbH, Zug, Switzerland; [27]JCK Consult, Frankfurt, Germany; [28]GrayMatters Consulting, Schilde, Belgium; [29]University Hospital Frankfurt, Department for Children and Adolescents, Goethe University Frankfurt, Frankfurt, Germany

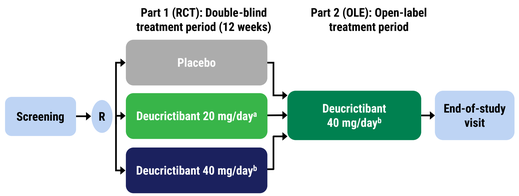
Introduction

- Excess bradykinin is the main mediator of the clinical manifestations of bradykinin-mediated angioedema, including hereditary angioedema (HAE), attacks.[1]
- 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.[2-5]
- Deucrictibant is a selective, orally administered bradykinin B2 receptor antagonist under development for prophylactic and on-demand treatment of HAE attacks.[3,6-12]
- CHAPTER-1 (NCT05047185)* is a two-part Phase 2 study evaluating the efficacy and safety of deucrictibant for long-term prophylaxis of HAE attacks.[12]
- In the double-blind placebo-controlled randomized controlled trial period (RCT; part 1), deucrictibant demonstrated[13]:
  - 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.

Methods

- In the ongoing open-label extension period (OLE; part 2), participants receive open-label treatment with deucrictibant 40 mg/day to evaluate long-term safety and efficacy of deucrictibant administered for prophylaxis against HAE attacks (**Figure 1**).

Figure 1. Study design



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.

- Eligible participants were aged ≥18 and ≤75 years, diagnosed with HAE-1/2, not receiving other prophylactic treatments at screening, and experienced ≥3 attacks within 3 months prior to screening or ≥2 attacks during screening (up to 8 weeks).
- Deucrictibant immediate-release (IR) capsule was dosed twice per day as a proof-of-concept for the once-daily deucrictibant extended-release (XR) tablet, which is the intended formulation of deucrictibant for prophylactic HAE treatment.[14]
- 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.

Results

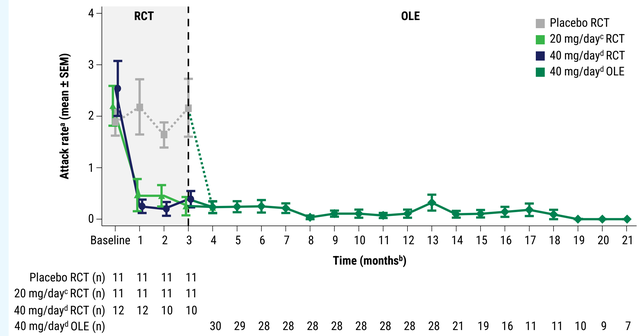
- This part 2 data snapshot (cutoff: 10 June 2024) included 30 participants in the OLE who received deucrictibant 40 mg/day with a mean (SD) treatment duration of 12.83 (5.03) months in the OLE.
- Mean age was 39.1 years at CHAPTER-1 part 1 baseline; 60.0% were female.
- Deucrictibant was well-tolerated, with one treatment-related treatment-emergent adverse event (TEAE) of tooth discoloration (**Table 1**).
- 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 (**Table 1**).
- Following early-onset reduction in attack rate with deucrictibant in the first month of the RCT, attack rate remained low during long-term (up to >1.5 years) deucrictibant 40 mg/day treatment in the OLE (**Figure 2**).

Table 1. Adverse events in the OLE

Adverse events	Placebo to 40 mg/day[a] (N=9) Participants, n (%)	Events, n	20 mg/day[b] to 40 mg/day[a] (N=11) Participants, n (%)	Events, n	40 mg/day[a] to 40 mg/day[a] (N=10) Participants, n (%)	Events, n	Total (N=30) 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. N = number of participants who received at least one dose of blinded study treatment in the OLE by the cutoff date of 10 June 2024. [a]Deucrictibant IR capsule, 20 mg twice daily. [b]Deucrictibant IR capsule, 10 mg twice daily.

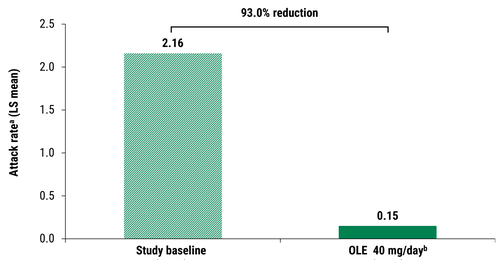
Figure 2. Reduced attack rate in the RCT remained low in the OLE



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.

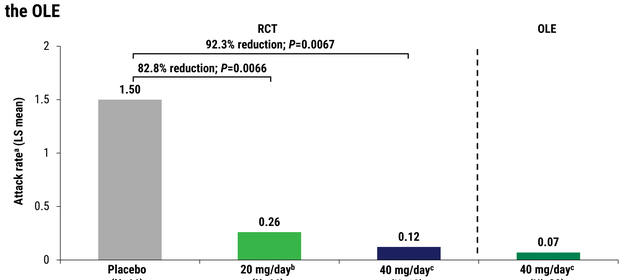
- Deucrictibant 40 mg/day reduced the attack rate in the OLE by 93.0% compared to CHAPTER-1 RCT study baseline (**Figure 3**).
- The reduced rate of "moderate and severe" attacks (**Figure 4**) and attacks treated with on-demand medication (**Figure 5**) remained low in the OLE.

Figure 3. Attack rate reduction in the OLE



IR, immediate release; LS, least squares; OLE, open-label extension. 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. [e]Based on time normalized number of attacks per 4 weeks. [b]Deucrictibant IR capsule, 20 mg twice daily.

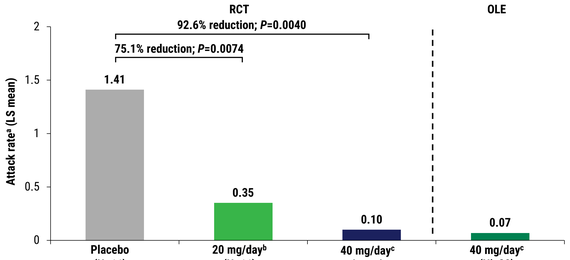
Figure 4. Reduced rate of "moderate and severe" attacks in the RCT remained low in the OLE



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. [e]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.

Results

Figure 5. 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. [e]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.

Conclusions

- **In the current analysis of the ongoing Phase 2 CHAPTER-1 open-label extension study, deucrictibant 40 mg/day was well-tolerated, with no new 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.**
  - **Rate of moderate and severe attacks, and attacks treated with on-demand medication remained low.**
- **Results of the ongoing CHAPTER-1 open-label extension 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.**

References

1. Busse PJ, et al. *N Engl J Med*. 2020;382:1136-48. **2.** Bouillet L, et al. *Allergy Asthma Proc*. 2022;43:406-12. **3.** Betschel SD, et al. *J Allergy Clin Immunol Pract*. 2023;11:2315-25. **4.** Center for Biologics Evaluation and Research. The voice of the patient – hereditary angioedema. US Food and Drug Administration; May 2018. Accessed August 16, 2024. https://www.fda.gov/media/113509/download; **5.** Covella B, et al. *Future Pharmacol*. 2024;4:41-53. **6.** Lesage A, et al. *Front Pharmacol*. 2020;11:916. **7.** Lesage A, et al. *Int Immunopharmacol*. 2022;105:108523. **8.** https://clinicaltrials.gov/study/NCT04618211. Accessed August 16, 2024. **9.** https://www.clinicaltrials.gov/study/NCT05396105. Accessed August 16, 2024. **10.** https://clinicaltrials.gov/study/NCT06343779. Accessed August 16, 2024. **11.** Maurer M, et al. Presented at: AAAAI; February 25–28, 2022; Phoenix, AZ, USA. **12.** https://www.clinicaltrials.gov/study/NCT05047185. Accessed August 16, 2024. **13.** Aygören-Pürsün, et al. Presented at EAACI 2024; May 31–June 3, 2024; Valencia, Spain. **14.** Groen K, et al. Presented at ACAAI 2022. November 10–14, 2022; Louisville, KY, USA.

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

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.[2,5-11]
- CHAPTER-1 (NCT05047185) 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[12]:
  - 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.

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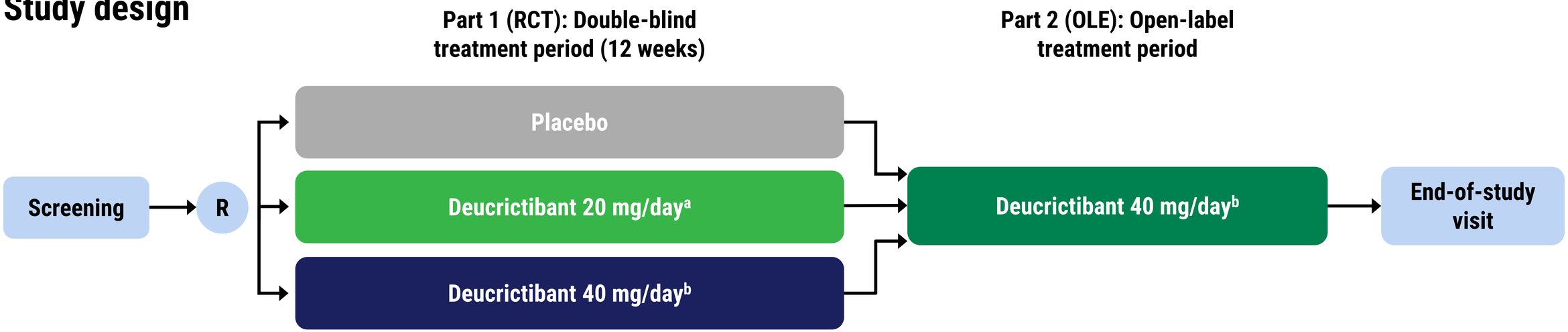
This presentation includes data for an investigational product not yet approved by regulatory authorities.

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 long-term safety and efficacy of deucrictibant administered for prophylaxis against HAE attacks.

Study design



- 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.

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

Deucrictibant was well-tolerated with no new safety signals

- This data snapshot (cutoff: 10 June 2024) included 30 participants in the OLE who received deucrictibant 40 mg/day with a mean (SD) treatment duration of 12.83 (5.03) months in the OLE.
- Deucrictibant was well-tolerated, with one treatment-related treatment-emergent adverse event (TEAE) of tooth discoloration.
- No treatment-related serious or severe TEAEs and no treatment-related TEAEs in laboratory parameters, vital signs, or ECG findings.
- No TEAEs leading to treatment discontinuation, study withdrawal, or death.

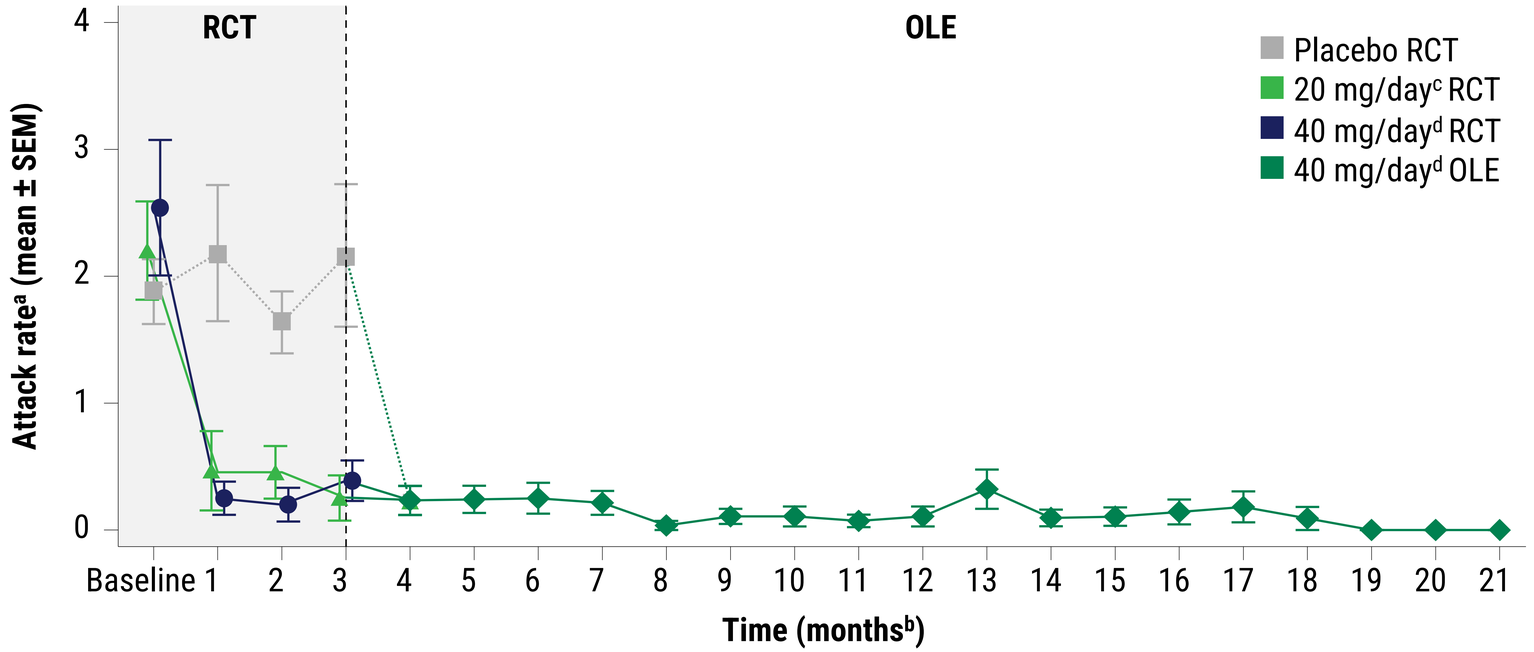
Adverse events in the OLE

Adverse events	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**

ECG, electrocardiogram, IR, immediate release; OLE, open-label extension; TEAE, treatment emergent adverse event. N = number of participants who received at least one dose of blinded study treatment in the OLE by the cutoff date of 10 June 2024. [a]Deucrictibant IR capsule, 20 mg twice daily. [b]Deucrictibant IR capsule, 10 mg twice daily.

Reduced attack rate in the RCT remained low in the OLE

- Following early-onset reduction in attack rate with deucrictibant in the first month of the RCT, attack rate remained low during long-term (up to >1.5 years) deucrictibant 40 mg/day treatment in the OLE.



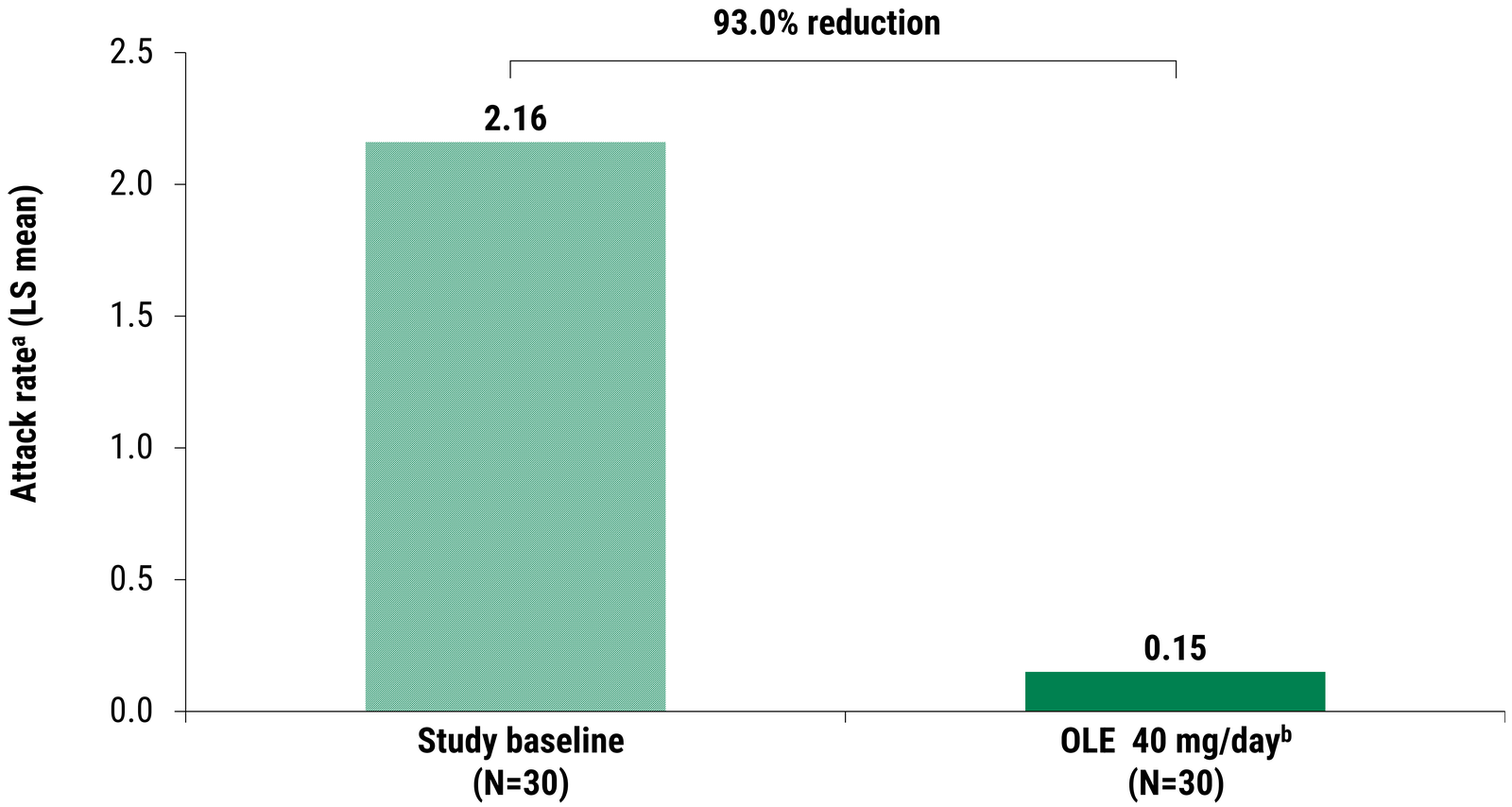
Placebo RCT (n)	11	11	11	11																	
20 mg/day[c] RCT (n)	11	11	11	11																	
40 mg/day[d] RCT (n)	12	12	10	10																	
40 mg/day[d] OLE (n)					30	29	28	28	28	28	28	28	28	28	21	19	16	11	11	10	9	7

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.

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

93% attack rate reduction in the OLE

- Deucrictibant 40 mg/day reduced the attack rate in the OLE by 93.0% compared to CHAPTER-1 RCT study baseline.



IR, immediate release; LS, least squares; OLE, open-label extension. 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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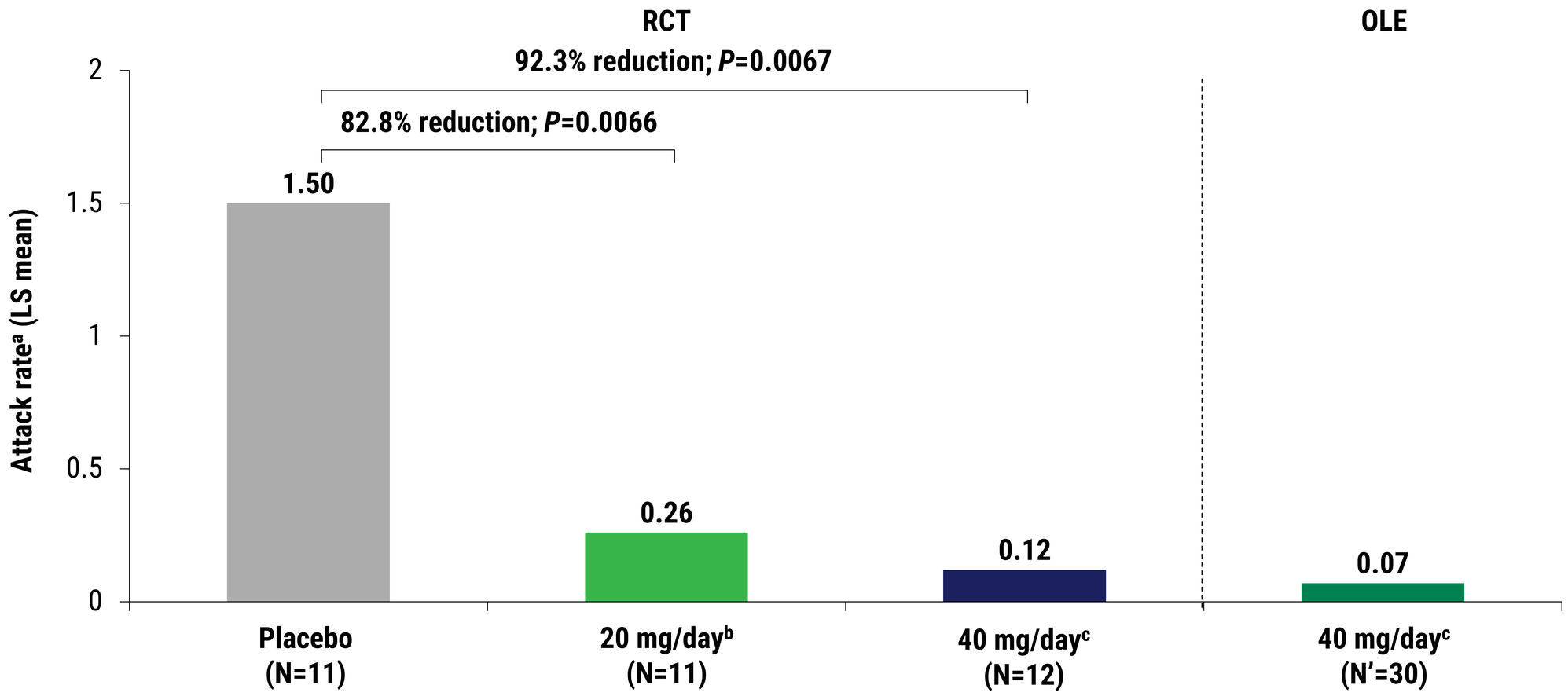
Reduced rate of "moderate and severe" attacks in the RCT remained low in the OLE



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.

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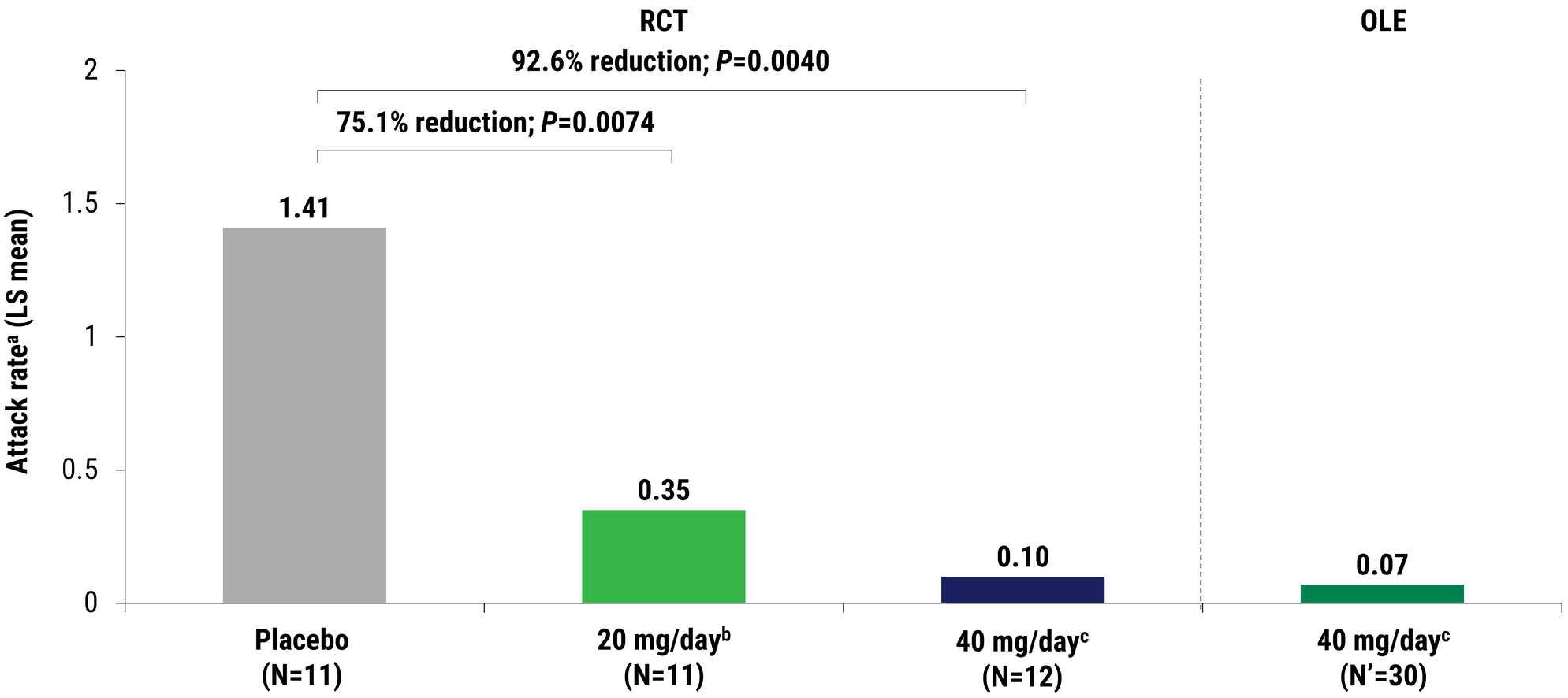
Reduced rate of on-demand–treated attacks in the RCT remained low in the OLE



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.

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

Conclusions

- In the current analysis of the ongoing Phase 2 CHAPTER-1 OLE study, deucrictibant 40 mg/day was well-tolerated, with no new 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.
  - Rate of moderate and severe attacks, and attacks treated with on-demand medication remained low.
- 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 participated in the CHAPTER-1 trial.

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