Long-Term Safety, Efficacy and Sustained Therapeutic Exposure of Oral Deucrictibant for Prophylaxis in Hereditary Angioedema: Data Snapshot Results of the CHAPTER-1 Open-Label Extension and Results of a Pharmacokinetics Study in Healthy Volunteers

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Key takeaways

The Phase 2 CHAPTER-1 open-label extension (OLE) study provides further evidence on the long-term safety and efficacy of oral deucrictibant for the prevention of hereditary angioedema (HAE) attacks.
Results of a Phase 1 pharmacokinetic study in healthy volunteers supports the once-daily administration in Phase 3 trials investigating the efficacy and safety of deucrictibant extended-release (XR) tablet for prophylaxis of HAE attacks.

Phase 2 long-term extension study | **Deucrictibant extended-release (XR) tablet**

- **Deucrictibant was generally well tolerated with one treatment-related TEAE of tooth discoloration**
- **1.5 YEARS** — **Reduced attack rate in the RCT remained low ≥1.5 years in the OLE**
- **93.1% reduction** — **in attack rate in the OLE compared with baseline**
- **24h** — **Sustained exposure through ≥24 hours supports once-daily dosing for HAE attack prevention**

HAE, hereditary angioedema; 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 both prophylactic and on-demand treatment of bradykinin-mediated attacks.[5-15]
- **Deucrictibant formulations:** in the prophylaxis CHAPTER-1 trial, deucrictibant was administered as immediate-release (IR) capsule formulation, dosed twice daily, as a proof-of-concept for the once-daily deucrictibant XR tablet, which is the intended commercial formulation of deucrictibant for prophylactic HAE treatment.[16]

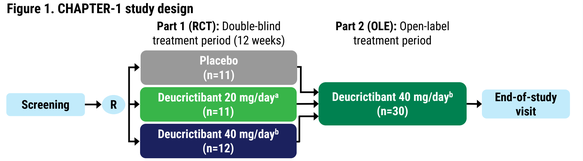
Objectives

- To evaluate the safety and efficacy of deucrictibant for long-term prophylaxis of HAE attacks in adults in the CHAPTER-1* OLE study.[12]
- To characterize the single-dose pharmacokinetics of deucrictibant XR tablet (40 mg) and deucrictibant IR capsule (2 x 20 mg) in healthy volunteers in a Phase 1, open-label, randomized, two-period, crossover study (PHA022121-C020*).

Methods

- **CHAPTER-1 (NCT05047185)*:** a two-part, Phase 2 study.[12] Eligible participants included adults diagnosed with HAE-1/2, not receiving other prophylactic treatments at screening, and with a minimum number of attacks. 30 participants completed the randomized controlled trial (RCT) and entered the OLE.

Figure 1. CHAPTER-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.

- **PHA022121-C020*:** healthy volunteers received, in randomized order, a single oral dose of deucrictibant XR tablet (40 mg) or deucrictibant IR capsule (2 x 20 mg taken simultaneously) under fasting conditions.

Results – CHAPTER-1 OLE

Participants in the OLE

- At data cutoff (10 June 2024), 30 participants in the OLE had received deucrictibant 40 mg/day for a mean (SD) treatment duration of 12.8 (5.0) months.
  - Maximum exposure to deucrictibant: 20.8 months in the OLE; 23.7 months in the entire study.

Safety analysis

- Deucrictibant was generally well tolerated with one treatment-related treatment-emergent adverse event (TEAE) of tooth discoloration reported.

Table 1. Adverse events in the OLE

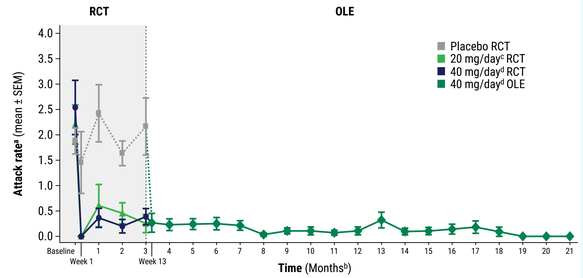
	Placebo to 40 mg/day[a] (N=9)		20 mg/day[b] to 40 mg/day[a] (N=11)		40 mg/day[a] to 40 mg/day[a] (N=10)		Total (N=30)	
	Participants, n (%)	Events, n	Participants, n (%)	Events, n	Participants, n (%)	Events, n	Participants, n (%)	Events, n
TEAEs	**5 (55.6)**	**25**	**7 (63.6)**	**31**	**6 (60.0)**	**16**	**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. 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 is later. N = number of participants who received ≥1 dose of 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.

Efficacy analysis

- RCT: Deucrictibant reduced the attack rate by week 1.
- OLE: Low attack rate sustained through ≥1.5 years.

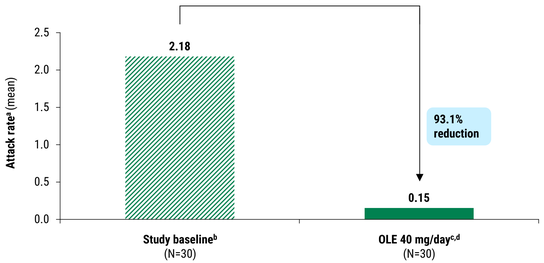
Figure 2. Attack rate reduced by week 1 in the RCT remained low through ≥1.5 years in the OLE



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.

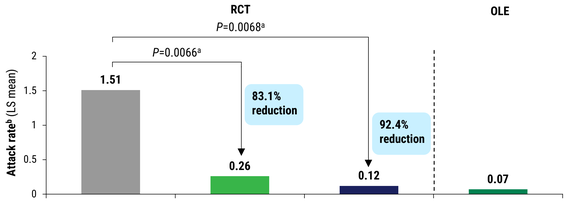
Results – CHAPTER-1 OLE

Figure 3. Attack rate reduced in the OLE compared with study baseline



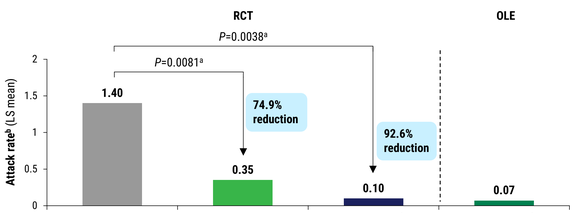
IR, immediate-release; OLE, open-label extension. N = number of participants in the OLE. [a]Based on time normalized number of attacks per 4 weeks. [b]Baseline attack rate is raw (unadjusted) mean. [c]OLE attack rate is least squares mean. No multiplicity adjustment was applied. [d]Deucrictibant IR capsule, 20 mg twice daily.

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.

Results – PHA022121-C020

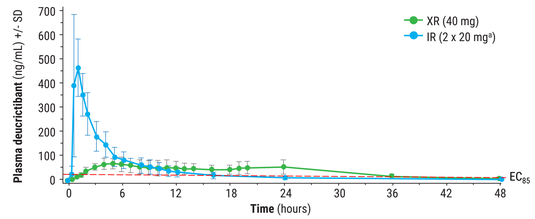
- This analysis included 14 participants with evaluable PK data for both XR and IR formulations.

Table 2. Summary of PK characteristics

PK parameter	Deucrictibant XR tablet (N=14[a])	Deucrictibant IR capsule (N=14[b])
C_{max}, ng/mL	87.2 (25.5)	547 (193)
t_{max}, hours, median (range)	5.03 (3.98–24.00)	1.00 (0.50–1.50)
C_{12h}, ng/mL	47.3 (27.7)	31.1 (19.9)
C_{24h}, ng/mL	51.6 (29.7)	7.47 (6.88)
AUC_{12h}, ng·h/mL	571 (188)	1509 (527)
AUC_{24h}, ng·h/mL	1124 (416)	1703 (660)
AUC_{last}, ng·h/mL	1609 (668)	1794 (742)
AUC_{inf}, ng·h/mL	1547 (699)	1799 (745)
t_{last}, hours, median (range)	47.64 (47.25–48.00)	47.55 (23.98–48.00)
$t_{1/2}$, hours	5.72 (1.70)	5.10 (1.28)
CL/F, L/hours	31.5 (14.7)	26.5 (12.7)
V_z/F, L	245 (129)	179 (52.1)

Mean ± standard deviation unless otherwise noted. AUC_{0h}, area under the concentration–time curve from time of drug administration to x hours; AUC_{inf}, area under the plasma concentration–time curve extrapolated to infinity; AUC_{last}, area under the plasma concentration–time curve to the last measurable plasma concentration; CL/F, oral clearance; C_{max}, maximum plasma concentration; C_{0h}, plasma concentration at x hours post-dose; IR, immediate-release; L, liter; PK, pharmacokinetic; $t_{1/2}$, terminal elimination half-life; t_{last}, time of last measurable concentration; t_{max}, actual sampling time to reach the maximum observed analyte concentration; V_z/F, volume of distribution during the terminal phase; XR, extended-release. [a]n=12 for AUC_{inf}, $t_{1/2}$, V_z/F, and CL/F. [b]n=15 for C_{max} and t_{max}.

Figure 6. Linear plasma concentration-time profiles



EC_{85}, effective concentration estimated to provide 85% maximal response; IR, immediate-release; SD, standard deviation; XR, extended-release. Error bars represent standard deviation. [a]Single oral dose of 2 x 20 mg deucrictibant IR capsule.

- Mean plasma concentration at 24 hours post-dose (C_{24h}) of deucrictibant XR was approximately four-fold higher than the effective concentration estimated to provide 85% maximal response (EC_{85}; 13.8 ng/mL).
  - C_{24h} of deucrictibant XR was higher than EC_{85} in 12/14 participants and higher than the effective concentration estimated to provide 50% maximal response (EC_{50}; 2.4 ng/mL) in all participants.
- Compared with IR capsule, XR tablet showed:
  - 84% lower mean values for C_{max} (547 vs. 87.2 ng/mL)
  - A longer median t_{max} (1 vs. 5.03 hours)
  - Mean $t_{1/2}$ of deucrictibant was comparable for the XR tablet and IR soft capsules: 5.72 and 5.10 hours, respectively.
- The efficacy and safety of deucrictibant XR tablet for once-daily prophylaxis of HAE attacks is currently being investigated in a Phase 3 trial.

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

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. Covella B, et al. *Future Pharmacol*. 2024;4:41-53. 4. Center for Biologics Evaluation and Research. The voice of the patient – hereditary angioedema. US Food and Drug Administration; May 2018. https://www.fda.gov/media/115509/download. Accessed September 2, 2025. 5. Betschel SD, et al. *J Allergy Clin Immunol Pract*. 2023;11:2315-25. 6. Lesage A, et al. *Front Pharmacol*. 2020;11:916. 7. Lesage A, et al. *Int Immunopharmacol*. 2022;105:108523. 8. RAPIDe-1. https://clinicaltrials.gov/study/NCT04618211. Accessed September 2, 2025. 9. RAPIDe-2. https://www.clinicaltrials.gov/study/NCT05396105. Accessed September 2, 2025. 10. RAPIDe-3. https://clinicaltrials.gov/study/NCT06343779. Accessed September 2, 2025. 11. Maurer M, et al. Presented at: AAAAI; February 24–27, 2023; San Antonio, TX, USA. 12. CHAPTER-1. https://www.clinicaltrials.gov/study/NCT05047185. Accessed September 2, 2025. 13. CHAPTER-3. https://clinicaltrials.gov/study/NCT06669754. Accessed September 2, 2025. 14. CHAPTER-4. https://clinicaltrials.gov/study/NCT06679881. Accessed September 2, 2025. 15. Aygören-Pürsün, et al. Presented at: EAACI; May 31–June 3, 2024; Valencia, Spain. 16. Zanichelli A, et al. Presented at: 14th C1-Inhibitor Deficiency and Angioedema Workshop 2025. May 29–June 1, 2025; Budapest, Hungary.

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- **Deucrictibant:** a selective, investigational, orally administered bradykinin B2 receptor antagonist under development for both prophylactic and on-demand treatment of bradykinin-mediated attacks.[5-15]
- **Deucrictibant formulations:** in the prophylaxis CHAPTER-1 trial, deucrictibant was administered as immediate-release (IR) capsule formulation, dosed twice daily, as a proof-of-concept for the once-daily deucrictibant extended-release (XR) tablet, which is the intended commercial formulation of deucrictibant for prophylactic HAE treatment.[16]

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**. Covella B, et al. *Future Pharmacol*. 2024;4:41-53. **4**. Center for Biologics Evaluation and Research. The voice of the patient – hereditary angioedema. US Food and Drug Administration; May 2018. https://www.fda.gov/media/113509/download; Accessed September 2, 2025. **5**. Betschel SD, et al. *J Allergy Clin Immunol Pract*. 2023;11:2315-25. **6**. Lesage A, et al. *Front Pharmacol*. 2020;11:916. **7.** Lesage A, et al. *Int Immunopharmacol*. 2022;105:108523. **8**. RAPIDe-1. https://clinicaltrials.gov/study/NCT04618211. Accessed September 2, 2025. **9**. RAPIDe-2. https://www.clinicaltrials.gov/study/NCT05396105. Accessed September 2, 2025. **10**. RAPIDe-3. https://clinicaltrials.gov/study/NCT06343779. Accessed September 2, 2025. **11**. Maurer M, et al. Presented at: AAAAI; February 24–27, 2023; San Antonio, TX, USA. **12**. CHAPTER-1. https://www.clinicaltrials.gov/study/NCT05047185. Accessed September 2, 2025. **13.** CHAPTER-3. https://clinicaltrials.gov/study/NCT06669754. Accessed September 2, 2025. **14.** CHAPTER-4. https://clinicaltrials.gov/study/NCT06679881. Accessed September 2, 2025. **15**. Aygören-Pürsün, et al. Presented at: EAACI; May 31–June 3, 2024; Valencia, Spain. **16**. Zanichelli A, et al. Presented at: 14th C1-Inhibitor Deficiency and Angioedema Workshop 2025. May 29–June 1, 2025; Budapest, Hungary.

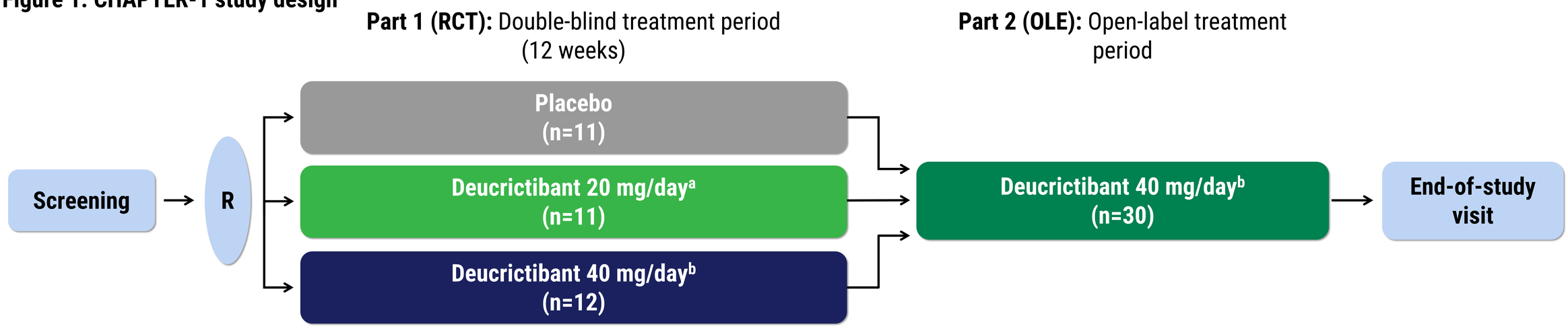
This presentation includes data for an investigational product not yet approved by regulatory authorities.

Methods and objectives

CHAPTER-1 (NCT05047185)*: a two-part, Phase 2 study.[12] Eligible participants included adults diagnosed with HAE-1/2, not receiving other prophylactic treatments at screening, and with a pre-specified minimum number of attacks.

- **Objective:** evaluate the safety and efficacy of deucrictibant for long-term prophylaxis of HAE attacks in adults in the CHAPTER-1* OLE study.[12]

Figure 1. CHAPTER-1 study design



PHA022121-C020*: healthy volunteers received, in randomized order, a single oral dose of deucrictibant XR tablet (40 mg) or deucrictibant IR capsule (2 x 20 mg taken simultaneously) under fasting conditions.

- **Objective:** characterize the single-dose pharmacokinetics of deucrictibant XR tablet (40 mg) and deucrictibant IR capsule (2 x 20 mg) in healthy volunteers in a Phase 1, open-label, randomized, two-period, crossover study (PHA022121-C020*).

HAE, hereditary angioedema; IR, immediate-release; OLE, open-label extension; R, randomization; RCT, randomized controlled trial; XR, extended-release. [a]Deucrictibant IR capsule, 10 mg twice daily. [b]Deucrictibant IR capsule, 20 mg twice daily.

12. CHAPTER-1. https://www.clinicaltrials.gov/study/NCT05047185. Accessed September 2, 2025. *CHAPTER-1 is a Pharvaris-sponsored clinical trial. ClinicalTrials.gov identifier: NCT05047185. The PHA022121-C020 study was funded and sponsored by Pharvaris.

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

Results – CHAPTER-1 OLE

Participants in the OLE

- At data cutoff (10 June 2024), 30 participants in the OLE had received deucrictibant 40 mg/day for a mean (SD) treatment duration of 12.8 (5.0) months.
  - Maximum exposure to deucrictibant: 20.8 months in the OLE; 23.7 months in the entire study.

Safety analysis

- Deucrictibant was generally well tolerated with one treatment-related treatment-emergent adverse event (TEAE) of tooth discoloration reported.

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	**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**

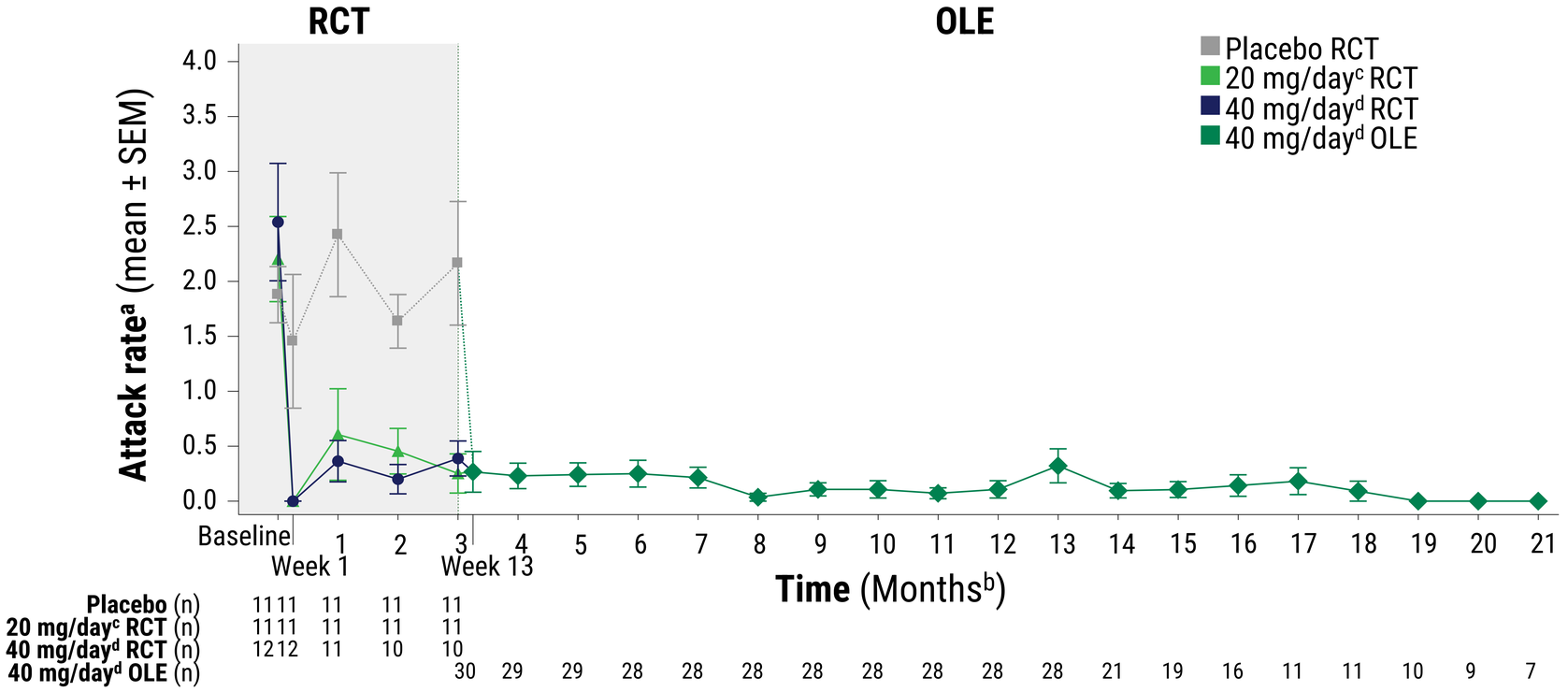
IR, immediate-release; OLE, open-label extension; TEAE, treatment-emergent adverse event. TEAE defined as adverse events that started or pre-existing adverse events that worsened during the period between the first study dose in OLE and 4 weeks after the last dose in OLE or the End of Study Visit, whichever is later. N = number of participants who received ≥1 dose of 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.

Results – CHAPTER-1 OLE

Efficacy analysis

- RCT: Deucrictibant reduced the attack rate by week 1.
- OLE: Low attack rate sustained through ≥1.5 years.

Figure 2. Attack rate reduced by week 1 in the RCT remained low through ≥1.5 years 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.

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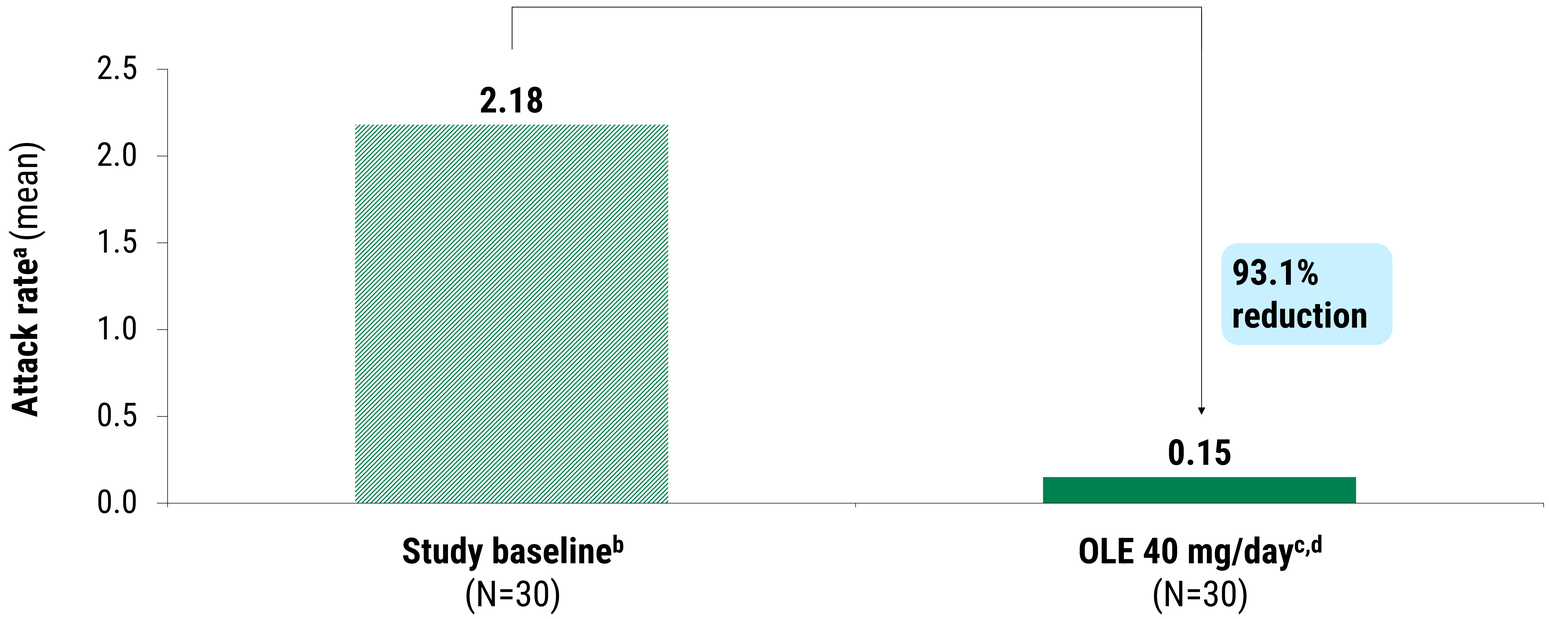
Results – CHAPTER-1 OLE

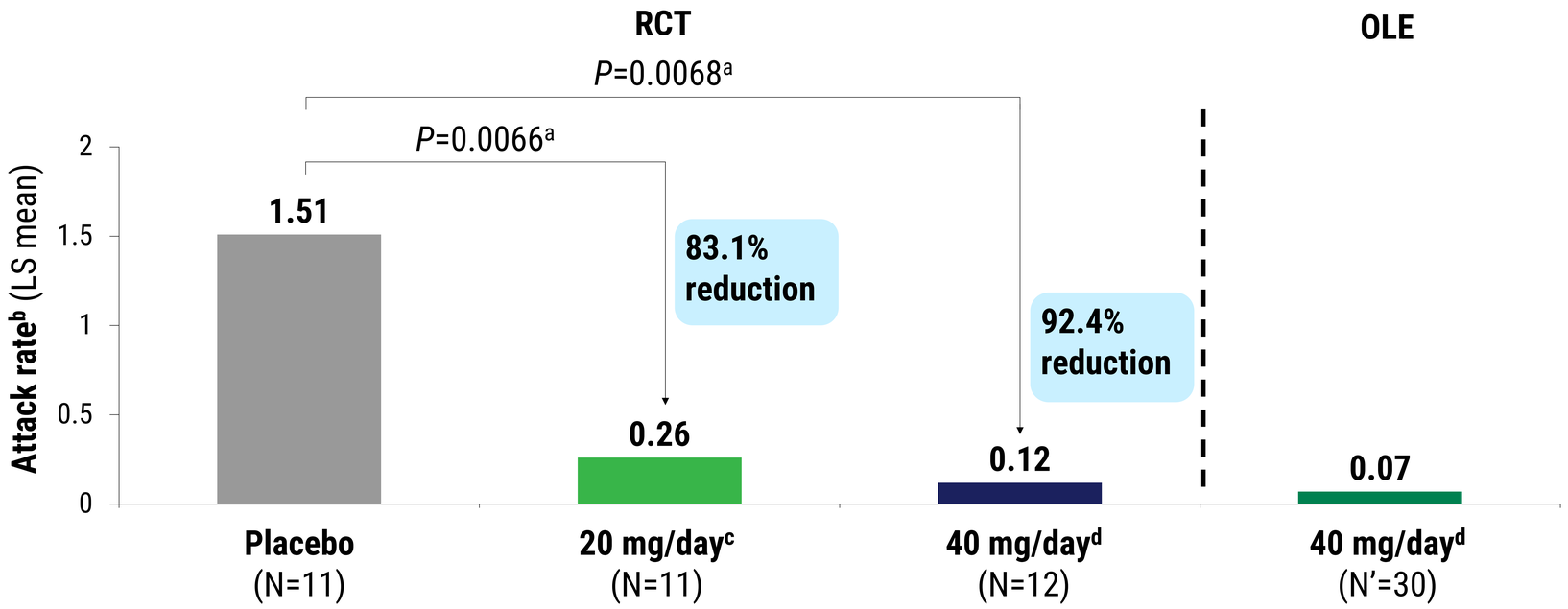
Figure 3. Attack rate reduced in the OLE compared with study baseline



IR, immediate-release; OLE, open-label extension. N = number of participants in the OLE. [a]Based on time normalized number of attacks per 4 weeks. [b]Baseline attack rate is raw (unadjusted) mean. [c]OLE attack rate is least squares mean. No multiplicity adjustment was applied. [d]Deucrictibant IR capsule, 20 mg twice daily.

Results – CHAPTER-1 OLE

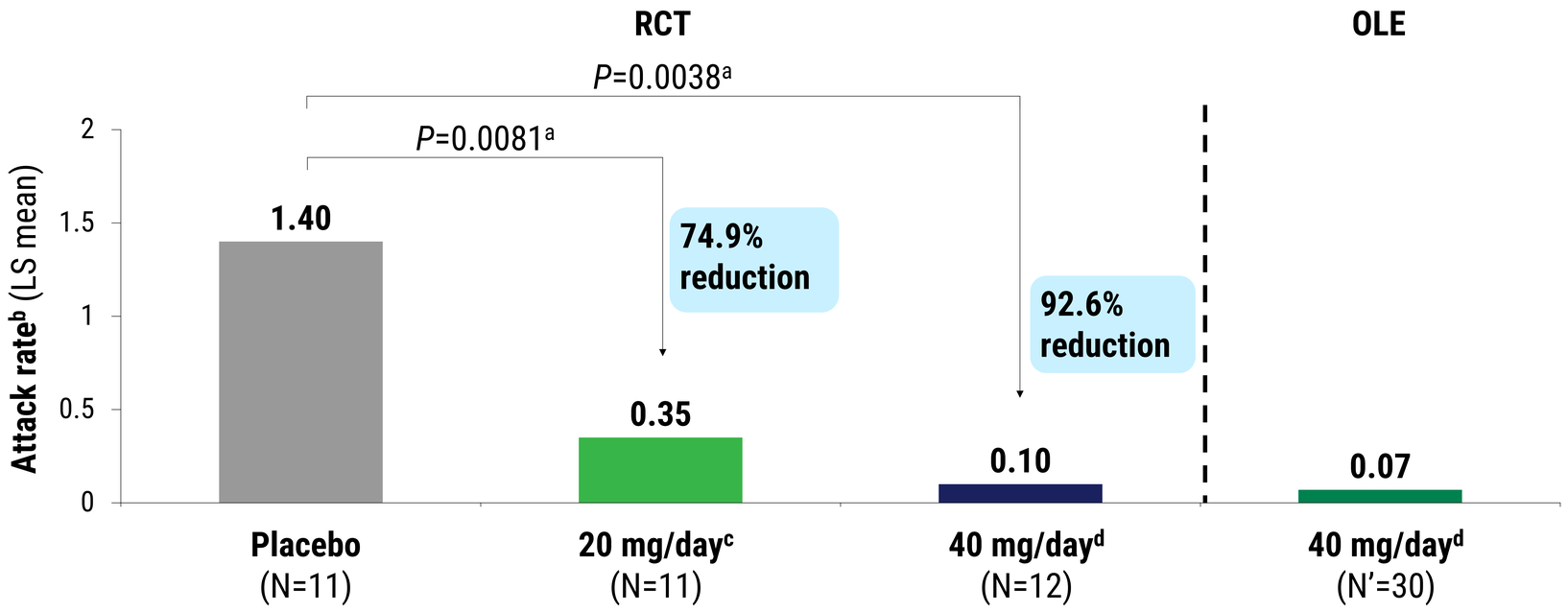
Figure 4. “Moderate and severe” attack rate reduced in the RCT and remained low in the OLE



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.

Results – CHAPTER-1 OLE

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.

Results - PHA022121-C020

- This analysis included 14 participants with evaluable PK data for both deucrictibant XR and IR formulations.

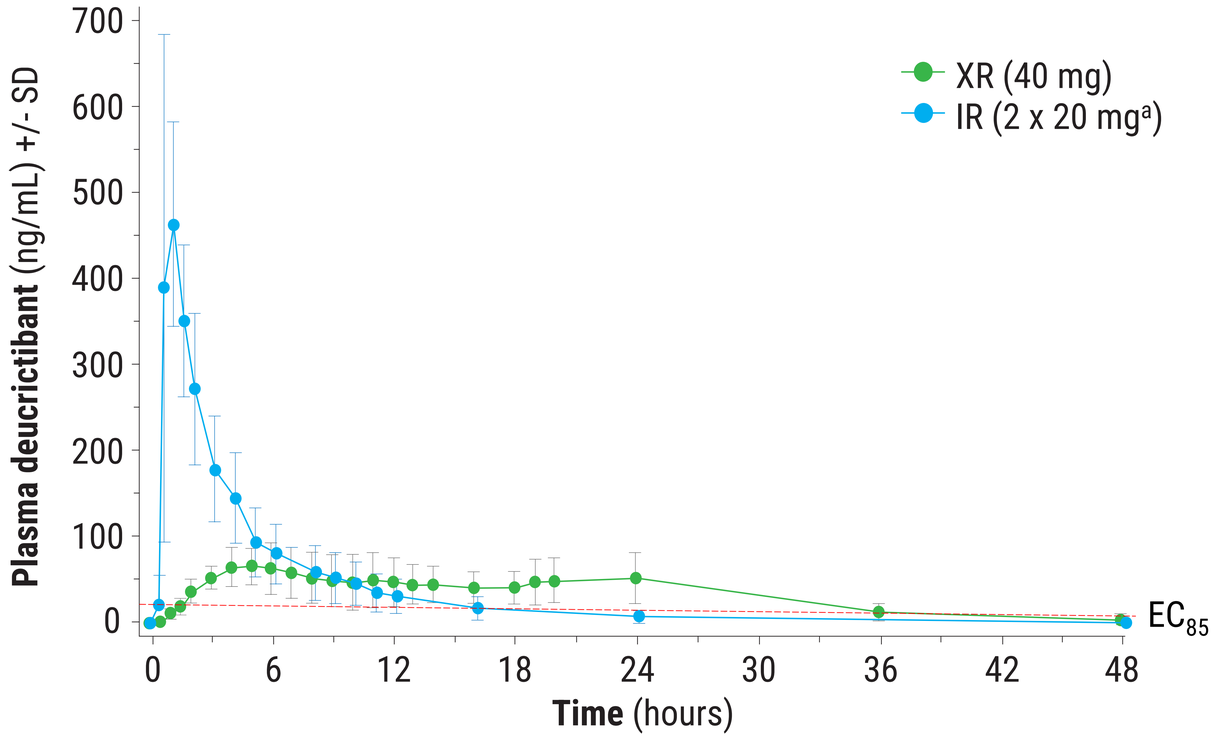
Table 2. Summary of PK characteristics

PK parameter	Deucrictibant XR tablet (N=14[a])	Deucrictibant IR capsule (N=14[b])
C_{max}, ng/mL	87.2 (25.5)	547 (193)
t_{max}, hours, median (range)	5.03 (3.98–24.00)	1.00 (0.50–1.50)
C_{12h}, ng/mL	47.3 (27.7)	31.1 (19.9)
C_{24h}, ng/mL	51.6 (29.7)	7.47 (6.88)
AUC_{12h}, ng·h/mL	571 (188)	1509 (527)
AUC_{24h}, ng·h/mL	1124 (416)	1703 (660)
AUC_{last}, ng·h/mL	1609 (668)	1794 (742)
AUC_{inf}, ng·h/mL	1547 (699)	1799 (745)
t_{last}, hours, median (range)	47.64 (47.25–48.00)	47.55 (23.98–48.00)
$t_{1/2}$, hours	5.72 (1.70)	5.10 (1.28)
CL/F, L/hours	31.5 (14.7)	26.5 (12.7)
V_z/F, L	245 (129)	179 (52.1)

Mean ± standard deviation unless otherwise noted. AUC_{xh}, area under the concentration-time curve from time of drug administration to x hours; AUC_{inf}, area under the plasma concentration-time curve extrapolated to infinity; AUC_{last}, area under the plasma concentration-time curve to the last measurable plasma concentration; CL/F, oral clearance; C_{max}, maximum plasma concentration; C_{12h}, plasma concentration at 12 hours post-dose; C_{24h}, plasma concentration at 24 hours post-dose; IR, immediate-release; L, liter; PK, pharmacokinetic; $t_{1/2}$, terminal elimination half-life; t_{last}, time of last measurable concentration; t_{max}, actual sampling time to reach the maximum observed analyte concentration; V_z/F, volume of distribution during the terminal phase; XR, extended-release. [a]n=12 for AUC_{inf}, $t_{1/2}$, V_z/F, and CL/F. [b]n=15 for C_{max} and t_{max}.

Results - PHA022121-C020

Figure 6. Linear plasma concentration-time profiles



- Mean plasma concentration at 24 hours post-dose (C_{24h}) of deucrictibant XR was approximately 4-fold higher than the effective concentration estimated to provide 85% maximal response (EC_{85}; 13.8 ng/mL).
  - C_{24h} of deucrictibant XR was higher than EC_{85} in 12/14 participants and higher than the effective concentration estimated to provide 50% maximal response (EC_{50}; 2.4 ng/mL) in all participants.
- Compared with IR capsule, XR tablet showed:
  - 84% lower mean values for C_{max} (547 vs. 87.2 ng / mL)
  - A longer median t_{max} (1 vs. 5.03 hours)
  - Mean $t_{1/2}$ of deucrictibant was comparable for the XR tablet and IR soft capsules: 5.72 and 5.10 hours, respectively.
- The efficacy and safety of deucrictibant XR tablet for once-daily prophylaxis of HAE attacks is currently being investigated in a Phase 3 trial.

EC_{85}, effective concentration estimated to provide 85% maximal response; IR, immediate-release; SD, standard deviation; XR, extended-release. Error bars represent standard deviation. n = number of participants in each group. [a]Single oral dose of 2 x 20 mg deucrictibant IR capsule.

Conclusions

- The Phase 2 CHAPTER-1 OLE study provides further evidence on the long-term safety and efficacy of oral deucrictibant for the prevention of HAE attacks.
- Results of a Phase 1 pharmacokinetic study in healthy volunteers supports the once-daily administration in Phase 3 trials investigating the efficacy and safety of deucrictibant XR tablet for prophylaxis of HAE attacks.

Phase 2 long-term extension study

Deucrictibant extended-release (XR) tablet

Deucrictibant was generally well tolerated with one treatment-related TEAE of tooth discoloration

1.5 YEARS

Reduced attack rate in the RCT remained low ≥1.5 years in the OLE

93.1% reduction

in attack rate in the OLE compared with baseline

Sustained exposure through ≥24 hours supports once-daily dosing for HAE attack prevention

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; TEAE, treatment-emergent adverse event.