

# Early-Onset Response to the Oral Bradykinin B2 Receptor Antagonist Deucricitbant Immediate-Release Capsule in Patients With Hereditary Angioedema Attacks

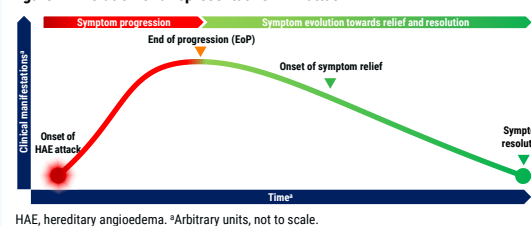
Marc A. Riedl<sup>1</sup>, John Anderson<sup>2</sup>, Emel Ayyören-Pürsün<sup>3</sup>, Danny M. Cohn<sup>4</sup>, Henriette Farkas<sup>5</sup>, H. Henry Li<sup>6</sup>, Markus Magerl<sup>7,8</sup>, Rafael Crabbé<sup>9</sup>, Li Zhu<sup>10</sup>, Peng Lu<sup>10</sup>, Giorgio Giannattasio<sup>11</sup>, Marcus Maurer<sup>7,8</sup>

<sup>1</sup>Division of Allergy and Immunology, University of California, San Diego, La Jolla, CA, USA; <sup>2</sup>Clinical Research Center of Alabama, AllerVie Health Birmingham, AL, USA; <sup>3</sup>Department for Children and Adolescents, University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt, Germany; <sup>4</sup>Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; <sup>5</sup>Department of Internal Medicine and Haematology, Hungarian Angioedema Center of Reference and Excellence, Semmelweis University, Budapest, Hungary; <sup>6</sup>Institute for Asthma and Allergy, Chevy Chase, MD, USA; <sup>7</sup>Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; <sup>8</sup>Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergy, Berlin, Germany; <sup>9</sup>RC Consultancy, Bassins, Switzerland; <sup>10</sup>Pharvaris Inc., Lexington, MA, USA; <sup>11</sup>Pharvaris GmbH, Zug, Switzerland

## Introduction

- The US Hereditary Angioedema Association Medical Advisory Board 2020 Guidelines for the management of hereditary angioedema (HAE) state that "The key to reducing HAE morbidity is to arrest the progression of swelling to prevent disruption to a patient's life."<sup>1</sup>
- The end of progression (EoP) of angioedema manifestations is the first in-time event documenting treatment response and the initial evidence of attacks starting to evolve towards relief and resolution (illustrated in **Figure 1**). A recent consensus study established EoP as a key core outcome score that should be measured and reported in all clinical trials for on-demand treatment of HAE.<sup>2</sup>
- Deucricitbant is an orally administered, highly potent, specific antagonist of the bradykinin B2 receptor under development for on-demand and prophylactic treatment of HAE attacks.<sup>3,7</sup>
- Primary and post-hoc analyses of the RAPiDe-1 (NCT04618211)<sup>5,6</sup> study were conducted to evaluate EoP and symptom relief in response to treatment of HAE attacks with deucricitbant immediate-release (IR) capsule.

**Figure 1. Evolution of a representative HAE attack**



## Methods

- RAPiDe-1 was a Phase 2, double-blind, placebo-controlled, randomized, crossover, dose-ranging trial of deucricitbant IR capsule for the on-demand treatment of angioedema attacks in patients with HAE type 1 or type 2 (HAE-1/2).<sup>5</sup>
- The 3-symptom composite Visual Analogue Scale (VAS-3) is used to evaluate patient-reported severity of skin pain, skin swelling, and abdominal pain, with higher scores indicating higher severity.<sup>5,9</sup>
- Treatment Outcome Score (TOS) is a composite score based on patient-reported response to treatment of attack symptoms: significant improvement = 100, improvement = 50, same = 0, worsening = -50, or significantly worsening = -100. TOS has been validated for HAE in eczallant clinical trials.<sup>10,12</sup> Change in TOS from pre-treatment to 4 h post-treatment was a secondary endpoint of RAPiDe-1.
- Time to EoP was defined as the earliest post-treatment timepoint with the highest VAS-3 score and no use of rescue medication (post-hoc analysis).
  - Post-treatment VAS-3 scores were assessed every 30 ± 10 min from 0–4 h, and at 5 ± 0.5, 6 ± 0.5, 8 ± 1, 24 ± 4, and 48 ± 6 h.
  - Participants using rescue medication were censored at the last assessment before use of rescue medication.
- Two definitions were used to measure onset of symptom relief:
  - VAS-3 score: ≥30% reduction in VAS-3 score vs pre-treatment (secondary endpoint).
  - TOS patient-reported outcome (TOS PRO): achievement of at least "a little better" on the TOS questionnaire 5-point Likert scale ("a lot better/resolved", "a little better", "same", "a little worse", "a lot worse") (post-hoc analysis).

## Results

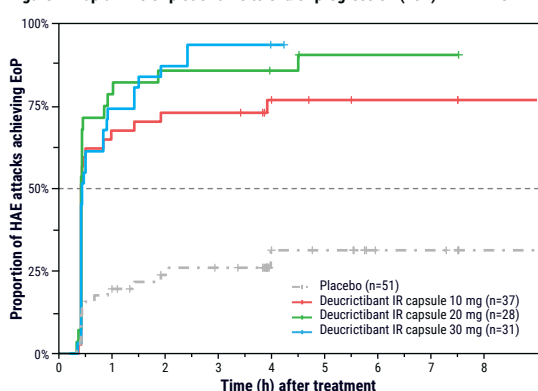
- The analysis included 147 qualifying HAE attacks treated by 62 participants with double-blinded placebo or deucricitbant IR capsule 10, 20, or 30 mg.
- Attacks treated with deucricitbant IR capsule (all dose groups) achieved EoP at a median time of 25–26 min vs 20 h for attacks treated with placebo (**Table 1** and **Figure 2**).

**Table 1. HAE attacks achieving end of progression (EoP) in RAPiDe-1<sup>a</sup>**

	Deucricitbant IR capsule			
	Placebo	10 mg	20 mg	30 mg
<b>Number of participants with treated attacks</b>	51	21	16	20
<b>Number of treated attacks</b>	51	37	28	31
<b>Attacks achieving EoP within 24 h, n (%)</b>	15 (29.4)	29 (78.4)	25 (89.3)	29 (93.5)
<b>Median (95% CI) time to EoP by KM estimate</b>	20.0 h (NE, NE)	25 min (25, 59)	25 min (25, 26)	26 min (25, 50)
<b>Marginal Cox proportional hazard model<sup>b</sup></b>				
Hazard ratio vs placebo (95% CI)		3.87 (2.15, 6.98)	5.09 (2.98, 8.72)	5.23 (2.93, 9.33)
Nominal P value		<0.0001	<0.0001	<0.0001

CI, confidence interval; h, hours; HAE, hereditary angioedema; IR, immediate-release; KM, Kaplan-Meier; min, minutes; NE, not evaluable. <sup>a</sup>EoP was assessed in a post-hoc analysis of RAPiDe-1. <sup>b</sup>Hazard ratio >1 favors active treatment vs placebo.

**Figure 2. Kaplan-Meier plot of time to end of progression (EoP) in RAPiDe-1<sup>a</sup>**



h, hours; HAE, hereditary angioedema; IR, immediate-release. <sup>a</sup>EoP was assessed in a post-hoc analysis of RAPiDe-1.

- Deucricitbant IR capsule significantly reduced time to onset of symptom relief measured by VAS-3, with a median time of 2.1–2.7 h for deucricitbant IR capsule vs 8.0 h for placebo (**Table 2**).
- Median time to onset of symptom relief by TOS PRO was 1.89–2.15 h for deucricitbant IR capsule vs 7.62 h for placebo (**Table 2**).

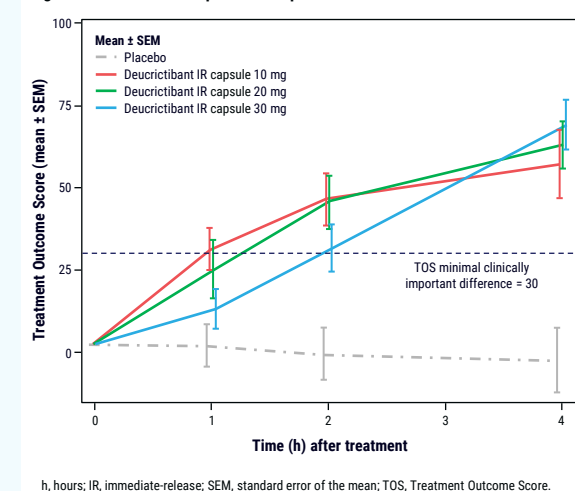
**Table 2. Time to onset of symptom relief by VAS-3 and TOS PRO**

	Deucricitbant IR capsule			
	Placebo	10 mg	20 mg	30 mg
<b>≥30% reduction in VAS-3 score vs pre-treatment</b>				
Number of treated attacks	51	37	28	31
Attacks with ≥30% reduction in VAS-3 within 48 h, n (%)	18 (35.3)	33 (89.2)	25 (89.3)	30 (96.8)
Median (95% CI) time (h) by KM estimate	8.0 (7.6, 46.9)	2.1 (1.5, 2.9)	2.7 (1.9, 3.5)	2.5 (1.9, 3.8)
P value <sup>a</sup>		<0.0001	0.0021	<0.0001
<b>TOS PRO of at least "a little better"<sup>b</sup></b>				
Number of treated attacks	49	36	28	29
Attacks achieving "a little better", n (%) <sup>c</sup>	18 (36.7)	32 (88.9)	25 (89.3)	27 (93.1)
Median (95% CI) time (h) by KM estimate	7.62 (3.95, NE)	1.89 (0.97, 3.97)	2.15 (1.75, 4.00)	1.98 (1.80, 3.87)

CI, confidence interval; h, hours; IR, immediate-release; KM, Kaplan-Meier; NE, not evaluable; TOS PRO, Treatment Outcome Score patient-reported outcome; VAS-3, 3-symptom composite Visual Analogue Scale. <sup>a</sup>The P value for 10 mg is nominal; P values are based on a marginal Cox proportional hazards model. <sup>b</sup>TOS PRO was assessed in a post-hoc analysis of RAPiDe-1. <sup>c</sup>TOS PRO onset of symptom relief is the timepoint when TOS PRO first reaches at least "a little better" for all symptom complexes affected at baseline, and no new symptom in any other symptom complex is reported. Relief is confirmed if the improvement is sustained at 2 consecutive timepoints within 48-hour assessments.

- Mean TOS score achieved clinically meaningful improvement within 2 hours after administration of deucricitbant IR capsule, whereas it did not significantly change in placebo-treated attacks (**Figure 3**).

**Figure 3. TOS measured up to 4 hours post-treatment**



## Conclusions

- Primary and post-hoc analyses of the RAPiDe-1 placebo-controlled trial provide evidence that deucricitbant IR capsule treatment reduced time to end of progression of attack symptoms and time to onset of symptom relief.
- End of progression was achieved at 25–26 minutes after treatment with deucricitbant IR capsule (post-hoc analysis).
- Onset of symptom relief was achieved at approximately 2 hours with deucricitbant IR capsule vs 8 hours with placebo as measured with both VAS-3 (primary analysis) and TOS PRO (post-hoc analysis).
- Clinically meaningful improvement of symptom severity was observed within 2 hours of deucricitbant IR capsule administration as measured with TOS.

## References

- Busse PJ, et al. *J Allergy Clin Immunol Pract.* 2021;19:132-50. 2. Petersen R. Presented at HAE International Regional Conference EMEA. September 1–3, 2023; Munich, Germany. 3. Lesage A, et al. *Front Pharmacol.* 2020;11:916. 4. Lesage A, et al. *Int Immunopharmacol.* 2022;105:108523. 5. Dose-ranging study of oral PHA-022121 for acute treatment of angioedema attacks in patients with hereditary angioedema (RAPiDe-1). *ClinicalTrials.gov* identifier: NCT04618211. Accessed March 13, 2024. <https://clinicaltrials.gov/study/NCT04618211>. 6. Extension study of oral PHA-022121 for acute treatment of angioedema attacks in patients with hereditary angioedema (RAPiDe-2). *ClinicalTrials.gov* identifier: NCT05396105. Accessed March 13, 2024. <https://www.clinicaltrials.gov/study/NCT05396105>. 7. Dose-ranging study of oral PHA-022121 for prophylaxis against angioedema attacks in patients with hereditary angioedema type I or type II (HAE CHAPTER-1). *ClinicalTrials.gov* identifier: NCT05047185. Accessed March 13, 2024. <https://www.clinicaltrials.gov/study/NCT05047185>. 8. Cicardi M, et al. *N Engl J Med.* 2010;363:532-41. 9. Lumry WR, et al. *Ann Allergy Asthma Immunol.* 2011;107:529-37. 10. Vernon MK, et al. *Qual Life Res.* 2009;18:929-39. 11. Cicardi M, et al. *N Engl J Med.* 2010;363:523-31. 12. Levy RJ, et al. *Ann Allergy Asthma Immunol.* 2010;104:523-9.

# Conflicts of interest disclosure

## Grants/research support, honoraria or consultation fees, sponsored speaker bureau

**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; **E.A-P.:** Astria, BioCryst, Biomarin, Centogene, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Shire/Takeda; **D.M.C.:** Astria, BioCryst, CSL Behring, Ionis Pharmaceuticals, KalVista, Pharming, Pharvaris, Takeda; **H.F.:** BioCryst, CSL Behring, Intellia, KalVista, ONO Pharmaceutical, Pharming, Pharvaris, Takeda; **H.H.L.:** BioCryst, BioMarin, CSL Behring, Intellia, KalVista, Pharming, Pharvaris, Takeda; **M.Mag.:** BioCryst, CSL Behring, Intellia, KalVista, Novartis, Octapharma, Pharming, Pharvaris, Shire/Takeda; **R.C.:** Employee of CG Consultancy and consultant to Pharvaris, holds stocks in Pharvaris; **L.Z.:** Employee of Pharvaris, holds stock in Pharvaris; **P.L.:** Employee of Pharvaris, holds stock/stock options in Pharvaris; **G.G.:** Employee of Pharvaris, holds stock in Pharvaris; **M.Mau.:** Adverum, Attune, BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, Shire/Takeda.

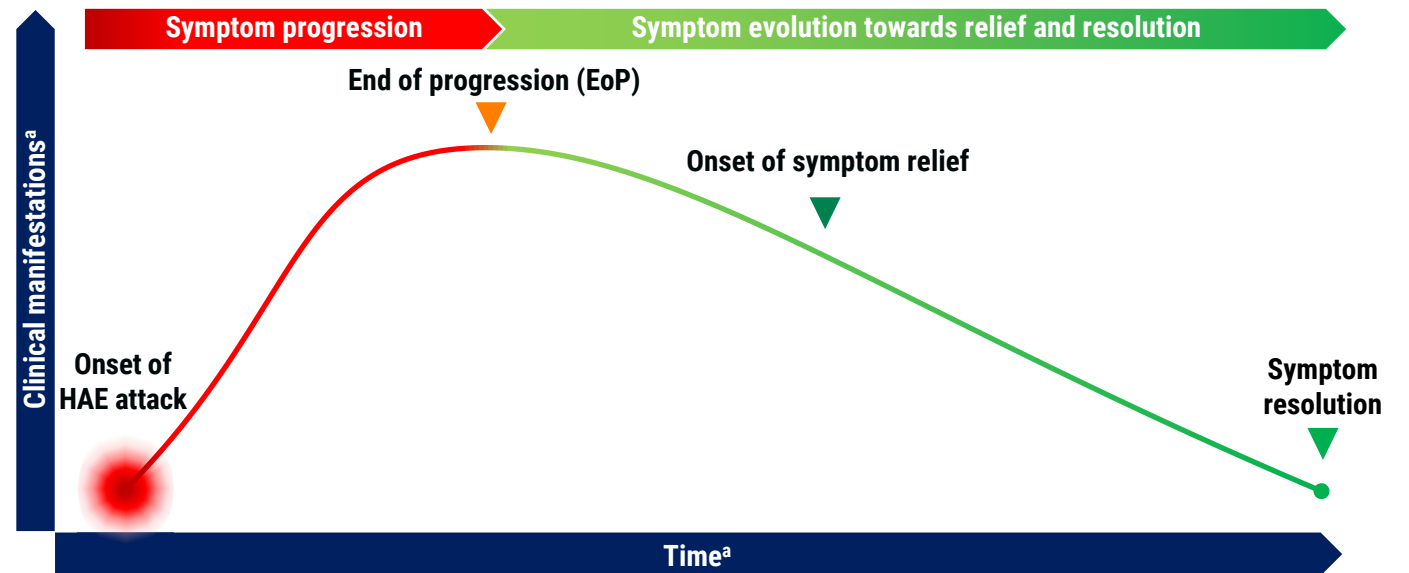
**Acknowledgments:** Medical writing services were provided by Cara Bertozzi, PhD, and Holly Richendrfer, PhD, of Two Labs Pharma Services.

**RAPIDe-1 was a Pharvaris-sponsored clinical trial. ClinicalTrials.gov identifier: NCT04618211.  
EudraCT Number: 2020-003445-11.**

# Introduction

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- End of progression (EoP) of angioedema manifestations is the first in-time event documenting treatment response and initial evidence of attacks starting to evolve towards relief and resolution (**Figure 1**).
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- Deucritibant is an orally administered, highly potent, specific antagonist of the bradykinin B2 receptor under development for on-demand and prophylactic treatment of HAE attacks.<sup>3-7</sup>

**Figure 1. Evolution of a representative HAE attack**



HAE, hereditary angioedema. <sup>a</sup>Arbitrary units, not to scale.

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HAE, hereditary angioedema; EoP, End of Progression.

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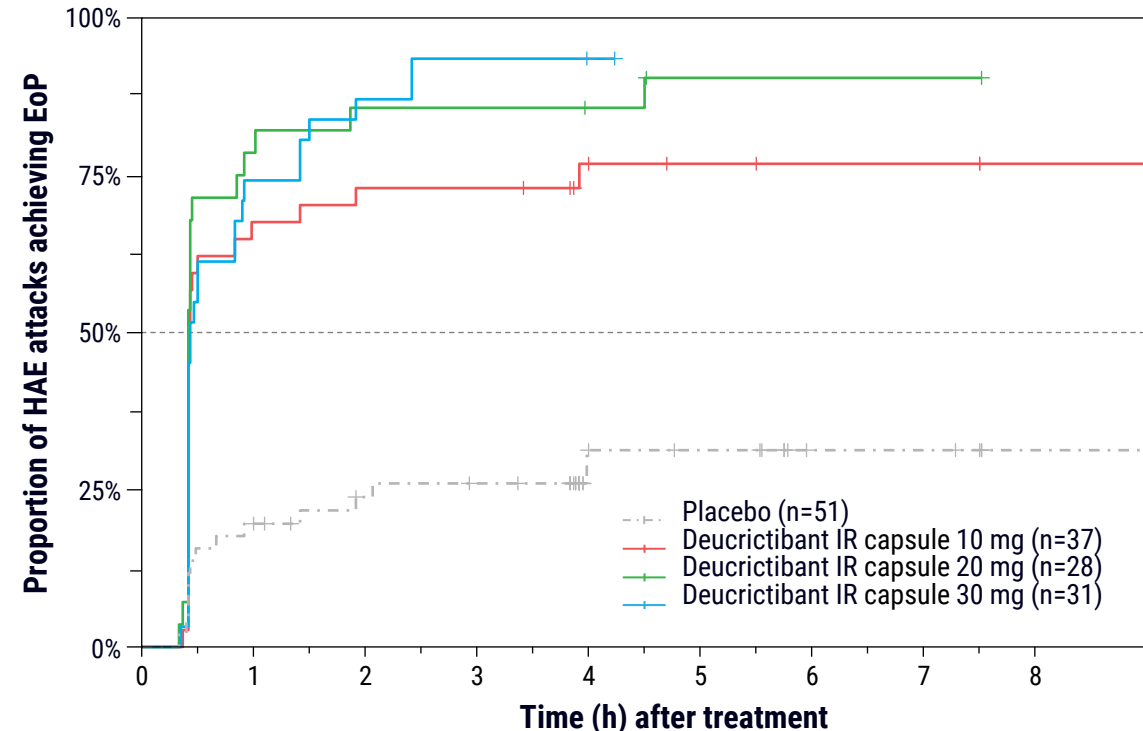
# Results – End of progression

- The analysis included 147 qualifying HAE attacks treated by 62 participants with double-blinded placebo or deucricitbant IR capsule 10, 20, or 30 mg.
- Attacks treated with deucricitbant IR capsule (all dose groups) achieved EoP at a median time of 25–26 min vs 20 h for attacks treated with placebo (**Table 1** and **Figure 2**).

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**Figure 2. KM plot of time to EoP in RAPIDe-1<sup>a</sup>**



CI, confidence interval; h, hours; EoP, End of progression; HAE, hereditary angioedema; IR, immediate-release; KM, Kaplan-Meier; min, minutes; NE, not evaluable. <sup>a</sup>EoP was assessed in a post-hoc analysis of RAPIDe-1.

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# Results – Time to onset of symptom relief

- Deucricitbant IR capsule significantly reduced time to onset of symptom relief measured by VAS-3, with a median time of 2.1–2.7 h for deucricitbant IR capsule vs 8.0 h for placebo (**Table 2**).
- Median time to onset of symptom relief by TOS PRO was 1.89–2.15 h for deucricitbant IR capsule vs 7.62 h for placebo (**Table 2**).

**Table 2. Time to onset of symptom relief by VAS-3 and TOS PRO**

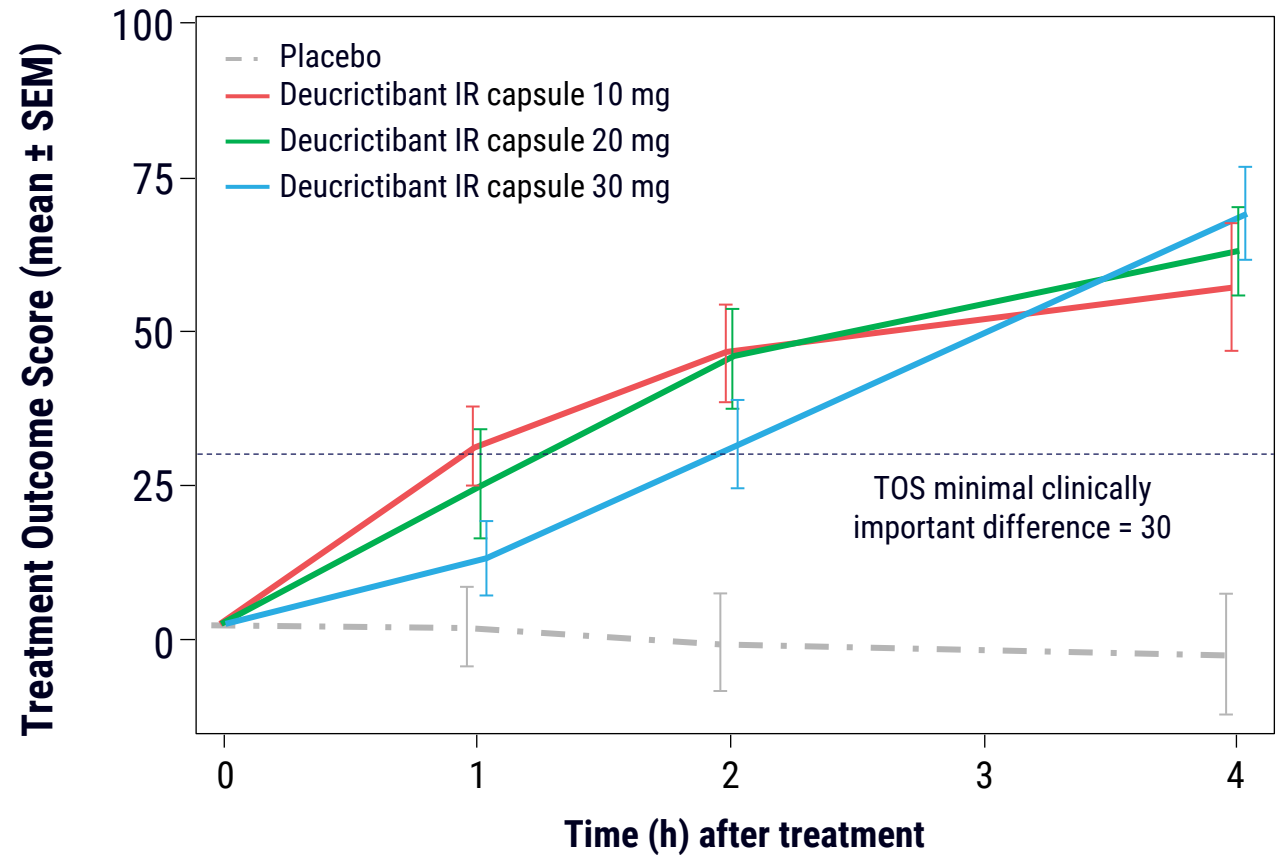
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# Results – Treatment Outcome Score

- Mean TOS score achieved clinically meaningful improvement within 2 hours after administration of deucricitibant IR capsule, whereas it did not significantly change in placebo-treated attacks (**Figure 3**).

Figure 3. TOS measured up to 4 hours post-treatment



h, hours; IR, immediate-release; SEM, standard error of the mean; TOS, Treatment Outcome Score.

# Conclusions

- Primary and post-hoc analyses of the RAPIDe-1 placebo-controlled trial provide evidence that deucricitabant IR capsule treatment reduced time to end of progression of attack symptoms and time to onset of symptom relief.
- End of progression was achieved at 25–26 minutes after treatment with deucricitabant IR capsule (post-hoc analysis).
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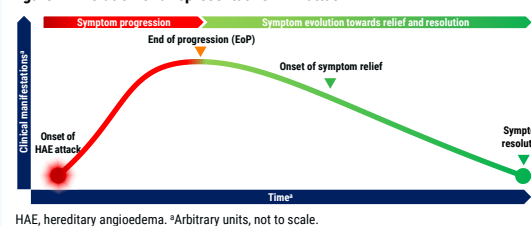
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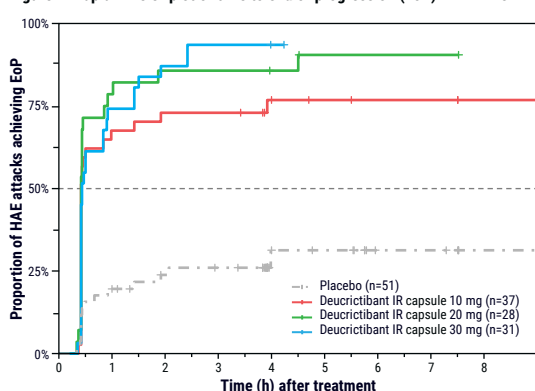
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<b>Number of participants with treated attacks</b>	51	21	16	20
<b>Number of treated attacks</b>	51	37	28	31
<b>Attacks achieving EoP within 24 h, n (%)</b>	15 (29.4)	29 (78.4)	25 (89.3)	29 (93.5)
<b>Median (95% CI) time to EoP by KM estimate</b>	20.0 h (NE, NE)	25 min (25, 59)	25 min (25, 26)	26 min (25, 50)
<b>Marginal Cox proportional hazard model<sup>b</sup></b>				
Hazard ratio vs placebo (95% CI)		3.87 (2.15, 6.98)	5.09 (2.98, 8.72)	5.23 (2.93, 9.33)
Nominal P value		<0.0001	<0.0001	<0.0001

CI, confidence interval; h, hours; HAE, hereditary angioedema; IR, immediate-release; KM, Kaplan-Meier; min, minutes; NE, not evaluable. <sup>a</sup>EoP was assessed in a post-hoc analysis of RAPiDe-1. <sup>b</sup>Hazard ratio >1 favors active treatment vs placebo.

**Figure 2. Kaplan-Meier plot of time to end of progression (EoP) in RAPiDe-1<sup>a</sup>**



h, hours; HAE, hereditary angioedema; IR, immediate-release. <sup>a</sup>EoP was assessed in a post-hoc analysis of RAPiDe-1.

- Deucricitbant IR capsule significantly reduced time to onset of symptom relief measured by VAS-3, with a median time of 2.1–2.7 h for deucricitbant IR capsule vs 8.0 h for placebo (**Table 2**).
- Median time to onset of symptom relief by TOS PRO was 1.89–2.15 h for deucricitbant IR capsule vs 7.62 h for placebo (**Table 2**).

**Table 2. Time to onset of symptom relief by VAS-3 and TOS PRO**

	Deucricitbant IR capsule			
	Placebo	10 mg	20 mg	30 mg
<b>≥30% reduction in VAS-3 score vs pre-treatment</b>				
Number of treated attacks	51	37	28	31
Attacks with ≥30% reduction in VAS-3 within 48 h, n (%)	18 (35.3)	33 (89.2)	25 (89.3)	30 (96.8)
Median (95% CI) time (h) by KM estimate	8.0 (7.6, 46.9)	2.1 (1.5, 2.9)	2.7 (1.9, 3.5)	2.5 (1.9, 3.8)
P value <sup>a</sup>		<0.0001	0.0021	<0.0001
<b>TOS PRO of at least "a little better"<sup>b</sup></b>				
Number of treated attacks	49	36	28	29
Attacks achieving "a little better", n (%) <sup>c</sup>	18 (36.7)	32 (88.9)	25 (89.3)	27 (93.1)
Median (95% CI) time (h) by KM estimate	7.62 (3.95, NE)	1.89 (0.97, 3.97)	2.15 (1.75, 4.00)	1.98 (1.80, 3.87)

CI, confidence interval; h, hours; IR, immediate-release; KM, Kaplan-Meier; NE, not evaluable; TOS PRO, Treatment Outcome Score patient-reported outcome; VAS-3, 3-symptom composite Visual Analogue Scale. <sup>a</sup>The P value for 10 mg is nominal; P values are based on a marginal Cox proportional hazards model. <sup>b</sup>TOS PRO was assessed in a post-hoc analysis of RAPiDe-1. <sup>c</sup>TOS PRO onset of symptom relief is the timepoint when TOS PRO first reaches at least "a little better" for all symptom complexes affected at baseline, and no new symptom in any other symptom complex is reported. Relief is confirmed if the improvement is sustained at 2 consecutive timepoints within 48-hour assessments.

## Conclusions

- Primary and post-hoc analyses of the RAPiDe-1 placebo-controlled trial provide evidence that deucricitbant IR capsule treatment reduced time to end of progression of attack symptoms and time to onset of symptom relief.
- End of progression was achieved at 25–26 minutes after treatment with deucricitbant IR capsule (post-hoc analysis).
- Onset of symptom relief was achieved at approximately 2 hours with deucricitbant IR capsule vs 8 hours with placebo as measured with both VAS-3 (primary analysis) and TOS PRO (post-hoc analysis).
- Clinically meaningful improvement of symptom severity was observed within 2 hours of deucricitbant IR capsule administration as measured with TOS.

## References

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**Figure 3. TOS measured up to 4 hours post-treatment**

