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

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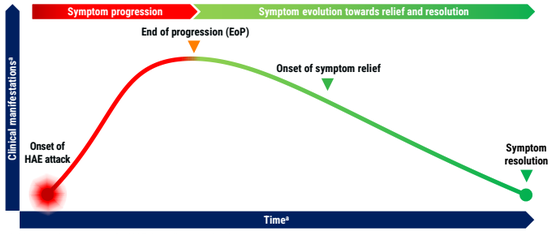
Introduction

- 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."[1]
- 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.[2]
- Deucrictibant is an orally administered, highly potent, specific antagonist of the bradykinin B2 receptor under development for on-demand and prophylactic treatment of HAE attacks.[3-7]
- Primary and post-hoc analyses of the RAPIDe-1 (NCT04618211)[5,*] study were conducted to evaluate EoP and symptom relief in response to treatment of HAE attacks with deucrictibant immediate-release (IR) capsule.

Figure 1. Evolution of a representative HAE attack



[a]Arbitrary units, not to scale. HAE, hereditary angioedema.

Methods

- RAPIDe-1 was a Phase 2, double-blind, placebo-controlled, randomized, crossover, dose-ranging trial of deucrictibant IR capsule for the on-demand treatment of angioedema attacks in patients with HAE type 1 or type 2 (HAE-1/2).[5]
- The 3-symptom composite Visual Analogue Scale (VAS-3) is used to evaluate patient-reported severity of skin pain, skin swelling, and abdominal pain.[8,9]
- Treatment Outcome Score (TOS) is a validated composite score based on patient-reported symptoms of attacks at the affected body sites, included in ecallantide clinical trials.[10-12] 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 with 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" (post-hoc analysis).

Results

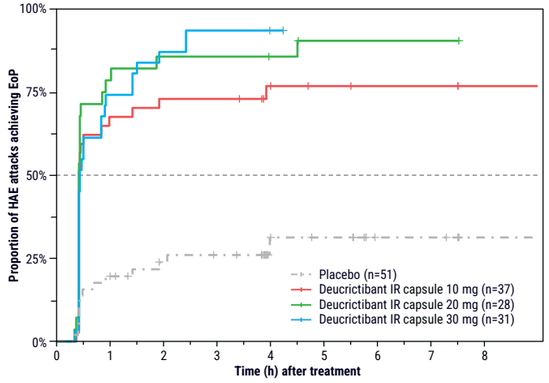
- The analysis included 147 qualifying HAE attacks treated by 62 participants with double-blinded placebo or deucrictibant IR capsule 10, 20, or 30 mg.
- Attacks treated with deucrictibant IR capsule (all dose groups) achieved EoP at a median time of 25–26 min vs 20 h for attacks treated with placebo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

Table 1. HAE attacks achieving end of progression (EoP) in RAPIDe-1[a]

	Placebo	Deucrictibant IR capsule 10 mg	Deucrictibant IR capsule 20 mg	Deucrictibant IR capsule 30 mg
Number of participants with treated attacks	51	21	16	20
Number of treated attacks	51	37	28	31
Attacks achieving EoP within 24 h, n (%)	15 (29.4)	29 (78.4)	25 (89.3)	29 (93.5)
Median (95% CI) time to EoP by KM estimate	20.0 h (NE, NE)	25 min (25, 59)	25 min (25, 26)	26 min (25, 50)
Marginal Cox proportional hazard model[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.
[a]EoP was assessed in a post-hoc analysis of RAPIDe-1. [b]Hazard ratio >1 favors active treatment vs placebo.

Figure 2. Kaplan-Meier plot of time to end of progression (EoP) in RAPIDe-1[a]



[a]EoP was assessed in a post-hoc analysis of RAPIDe-1. HAE, hereditary angioedema; IR, immediate-release.

- Deucrictibant IR capsule significantly reduced time to onset of symptom relief measured on VAS-3, with a median time of 2.1–2.7 h for deucrictibant IR capsule vs 8.0 h for placebo (**Table 2**).
- Time to onset of symptom relief on TOS PRO was 1.89–2.15 h vs 7.62 h for deucrictibant IR capsule-treated vs placebo-treated attacks, respectively (**Table 2**).

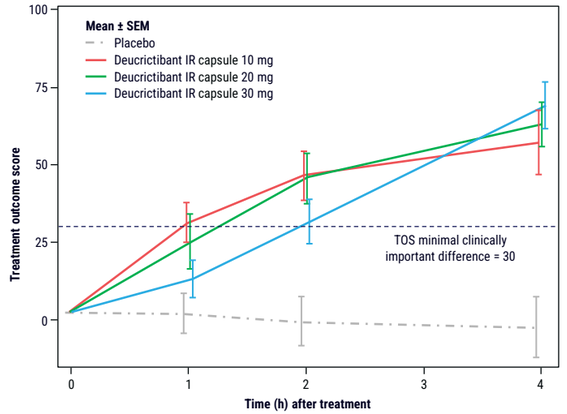
Table 2. Time to onset of symptom relief by VAS-3 and TOS PRO

	Placebo	Deucrictibant IR capsule 10 mg	Deucrictibant IR capsule 20 mg	Deucrictibant IR capsule 30 mg
≥30% reduction in VAS-3 score vs pre-treatment				
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 by KM estimate (h)	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[a]		<0.0001	0.0021	<0.0001
TOS PRO of at least "a little better"[b]				
Number of treated attacks	49	36	28	29
Attacks achieving "a little better", n (%)[c]	18 (36.7)	32 (88.9)	25 (89.3)	27 (93.1)
Median (95% CI) time by KM estimate (h)	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.
[a]The *P* value for 10 mg is nominal; *P* values are based on a marginal Cox proportional hazards model. [b]TOS PRO was assessed in a post-hoc analysis of RAPIDe-1. [c]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 deucrictibant 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 first evidence that deucrictibant 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 deucrictibant IR capsule vs 20 hours for placebo (post-hoc analysis).**
- **Onset of symptom relief was achieved at approximately 2 hours with deucrictibant 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, as measured with TOS, was observed within 2 hours of deucrictibant IR capsule administration.**

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