

Relief and Resolution of Hereditary Angioedema Attack Symptoms Following On-Demand Treatment With a Single Dose of Oral Bradykinin B2 Receptor Antagonist Deucricitbant Immediate-Release Capsule

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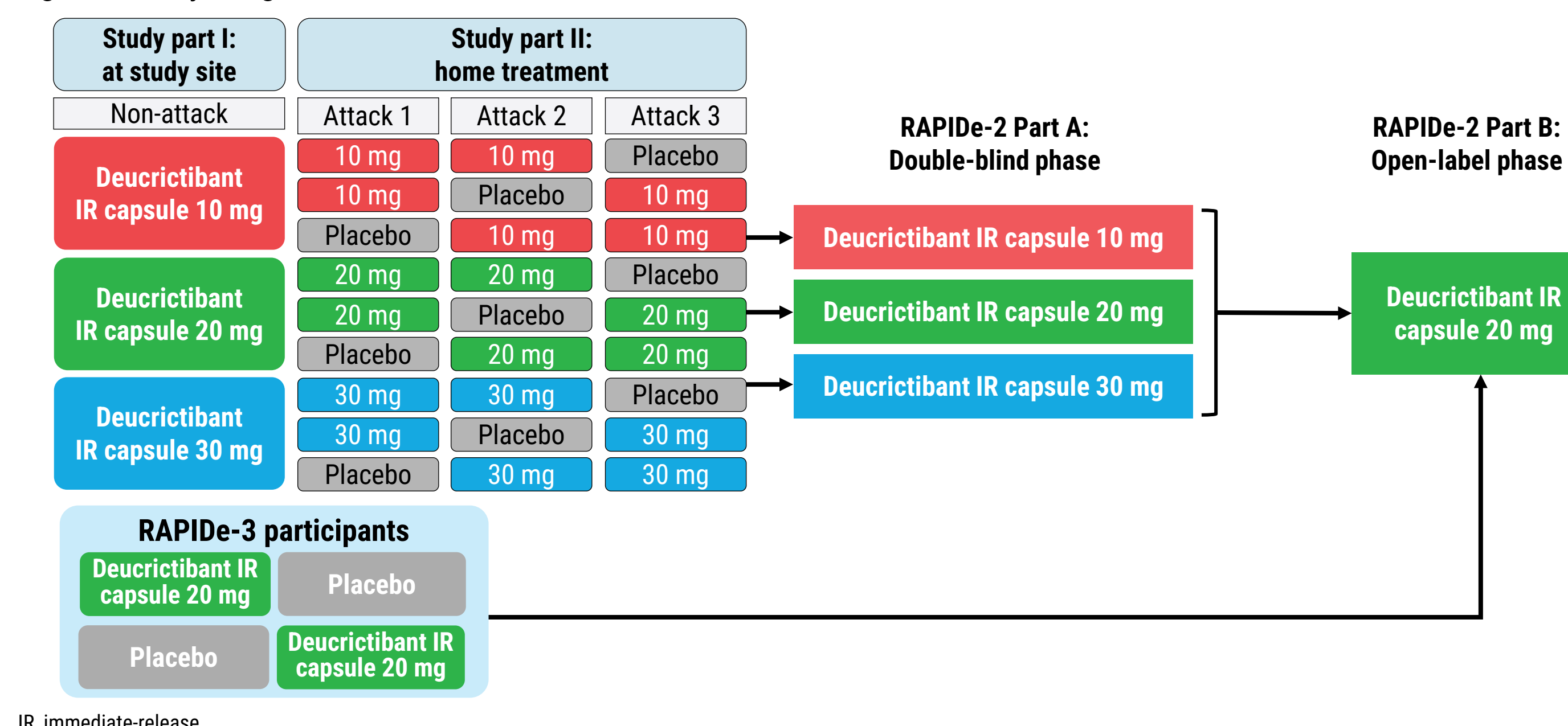
Introduction

- Excess bradykinin is the cause of signs and symptoms of hereditary angioedema (HAE) attacks.¹
- International guidelines recommend early treatment to improve symptom control and minimize impact of attacks.²⁻⁴
- Deucricitbant is an orally administered bradykinin B2 receptor antagonist under development for prophylactic and on-demand treatment of HAE attacks.⁵⁻¹¹

Methods

- RAPIDE-1 (NCT04618211)^{7*} was a Phase 2, double-blind, placebo-controlled, dose-ranging, crossover trial of deucricitbant IR capsule for on-demand treatment of angioedema attacks in patients with HAE-1/2 (Figure 1).
- RAPIDE-2 (NCT05396105)^{11†} is an ongoing two-part Phase 2/3 extension study evaluating long-term safety and efficacy of orally administered deucricitbant IR capsule for the treatment of HAE attacks (Figure 1).

Figure 1. Study design



IR, immediate-release.

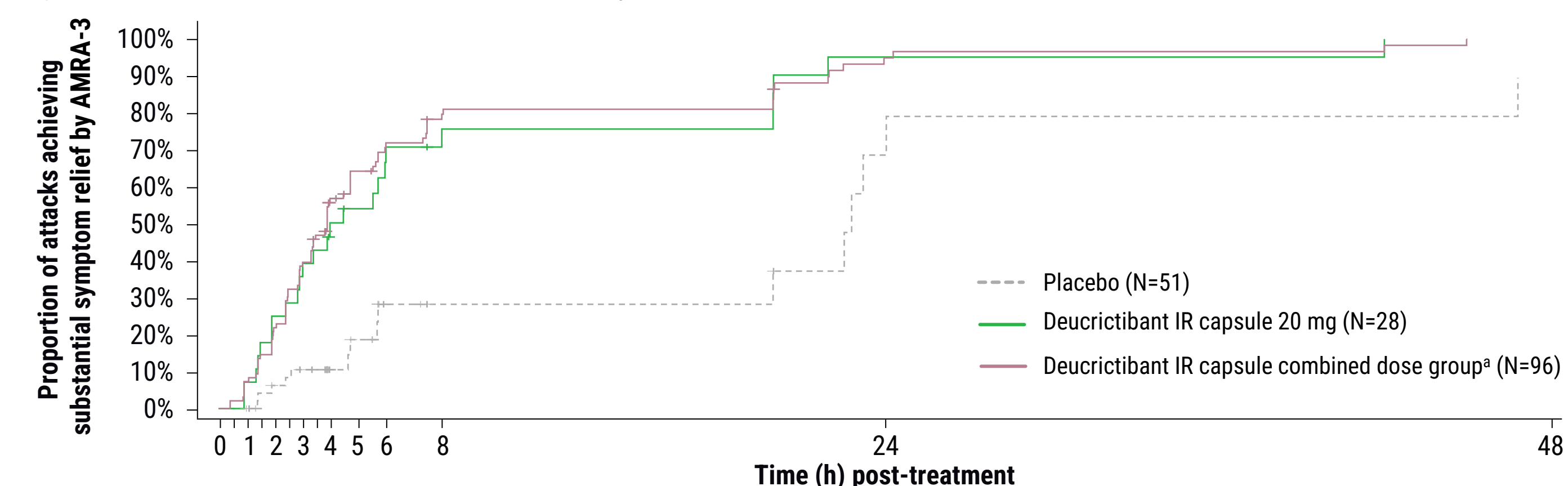
- The Angioedema Symptom Rating scale (AMRA-3, a digital version of the 3-symptom composite Visual Analogue Scale [VAS-3]) is used to evaluate patient-reported severity of skin pain, skin swelling, and abdominal pain, with higher scores indicating greater severity.^{12,13} AMRA-3 was called the 3-symptom composite Visual Analogue Scale (VAS-3) in the RAPIDE-1 trial but was administered digitally and later renamed for clarity.
- The Treatment Outcome Score (TOS) questionnaire for patient-reported outcomes (TOS PRO) is a composite score that evaluates changes in symptoms in response to treatment in 5 body areas, taking into account symptom severity.¹⁴
- In RAPIDE-1, substantial symptom relief was defined as $\geq 50\%$ reduction in AMRA-3 score vs pre-treatment (key secondary endpoint).
- Two definitions were used to measure symptom resolution in RAPIDE-1:
 - AMRA-3 score: "almost complete or complete symptom relief" (all 3 individual AMRA scores ≤ 10) (key secondary endpoint).
 - TOS PRO: achievement of "a lot better or resolved" in all symptom complexes (post hoc analysis).
- Key efficacy endpoints in RAPIDE-2 include:
 - Onset of symptom relief, defined as Patient Global Impression of Change (PGI-C) rating of at least "a little better" for 2 consecutive timepoints by 12 hours post-treatment.
 - Time to reduction in attack severity, defined as achieving ≥ 1 -level reduction in the Patient Global Impression of Severity (PGI-S) from pre-treatment for 2 consecutive timepoints by 12 hours post-treatment.
 - Proportion of attacks achieving complete attack resolution, defined as achieving PGI-S rating of "none" at 24 hours post-treatment.

Results

RAPIDE-1

- The analysis included 147 qualifying HAE attacks treated by 62 participants with double-blinded placebo or deucricitbant IR capsule 10, 20, or 30 mg (modified intent-to-treat analysis set included treated attacks with AMRA-3 results at both pre-treatment and ≥ 1 post-treatment timepoints).
- Attacks treated with a single dose of deucricitbant IR capsule 20 mg achieved earlier substantial symptom relief by AMRA-3 (median time, hours: 4.0) compared with attacks treated with placebo (22.8). Median time for the deucricitbant IR capsule combined dose group was 3.9 hours (Figure 2).

Figure 2. KM plot of time to AMRA-3 substantial symptom relief



AMRA, Angioedema Symptom Rating scale; h, hours; IR, immediate-release; KM, Kaplan-Meier; mITT, modified intent-to-treat. N = number of attacks in the mITT analysis set. *Includes 10 mg, 20 mg, and 30 mg dose groups.

- The median time to symptom resolution by AMRA-3 was 20.0 hours with a single dose of deucricitbant IR capsule 20 mg and 7.5 hours for the combined dose group vs 42.0 hours with placebo. The variability was mainly due to the lack of assessments between 8 and 24 hours.
- Symptom resolution by TOS PRO was achieved at a median time of 5.9 hours for attacks treated with a single dose of deucricitbant IR capsule 20 mg and 5.2 hours for the combined dose group vs 23.3 hours with placebo (Table 1).

Table 1. TOS PRO symptom resolution by KM estimate^a

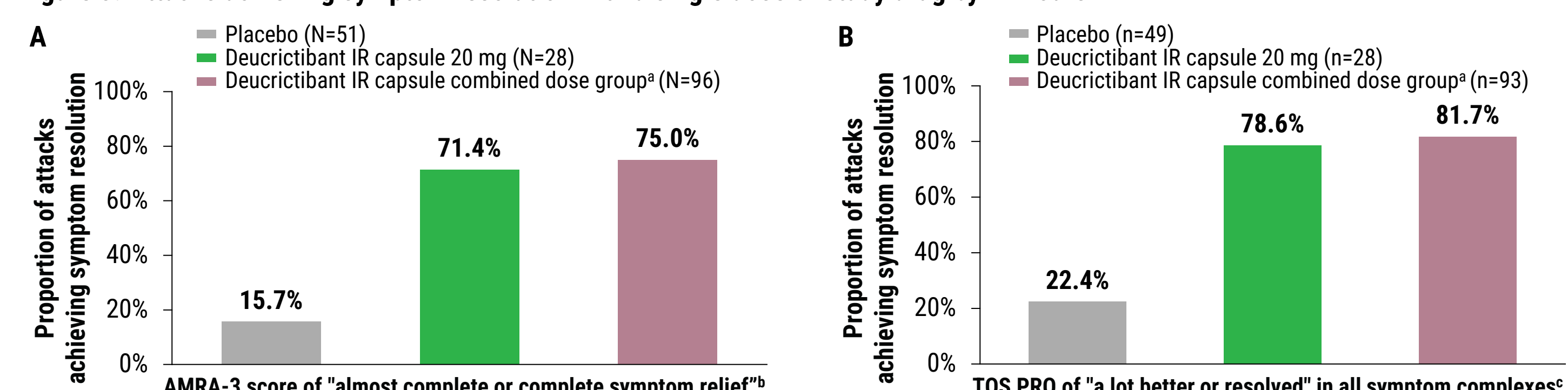
	Deucricitbant IR capsule		
	Placebo	20 mg	Combined ^b
Number of participants with post-treatment TOS	49	16	56
Number of treated attacks with post-treatment TOS	49	28	93
Symptom resolution by TOS PRO^c			
Median time (h) to event by KM estimate (95% CI)	23.28 (5.78, 47.17)	5.93 (3.90, 8.58)	5.23 (3.98, 5.78)

h, hours; IR, immediate-release; KM, Kaplan-Meier; TOS PRO, Treatment Outcome Score patient-reported outcome. ^aSymptom resolution by TOS PRO was assessed in a post hoc analysis of RAPIDE-1. ^bIncludes 10 mg, 20 mg, and 30 mg dose groups. ^cTOS PRO symptom resolution is the timepoint when TOS PRO first reaches "a lot better or resolved" in all symptom complexes affected at baseline, and no new symptom in any other symptom complex is reported.

Results

- The percentage of attacks achieving symptom resolution by AMRA-3 with a single dose of study drug by 24 hours was approximately 5-fold greater with deucricitbant IR capsule 20 mg (71.4%) and the combined dose group (75.0%) than with placebo (15.7%) (Figure 3A).
- In total, 78.6% of attacks treated with deucricitbant IR capsule 20 mg and 81.7% of combined dose group attacks achieved symptom resolution by TOS PRO with a single dose of study drug by 24 hours compared with 22.4% of placebo-treated attacks (Figure 3B).

Figure 3. Attacks achieving symptom resolution with a single dose of study drug by 24 hours



AMRA, Angioedema Symptom Rating scale; IR, immediate-release; mITT, modified intent-to-treat; TOS PRO, Treatment Outcome Score patient-reported outcome. N = number of attacks in the mITT analysis set. n = number of attacks with post-treatment TOS. ^aIncludes 10 mg, 20 mg, and 30 mg dose groups. ^bAll 3 individual AMRA scores ≤ 10 (key secondary endpoint). ^cTOS PRO was assessed in a post hoc analysis of RAPIDE-1.

RAPIDE-2 Part A

- Deucricitbant was well-tolerated across all doses, with no treatment-emergent adverse events (TEAE).
- No treatment-related serious or severe TEAEs, no treatment-related TEAEs in laboratory parameters, vital signs, or ECG findings, and no TEAEs leading to treatment discontinuation, study withdrawal, or death were reported.
- The median time to onset of symptom relief was 1.1 hours (95% CI, 1.0, 1.2) (Table 2).
- 98.5% (261/265) of attacks achieved onset of symptom relief by 12 hours (Figure 4).

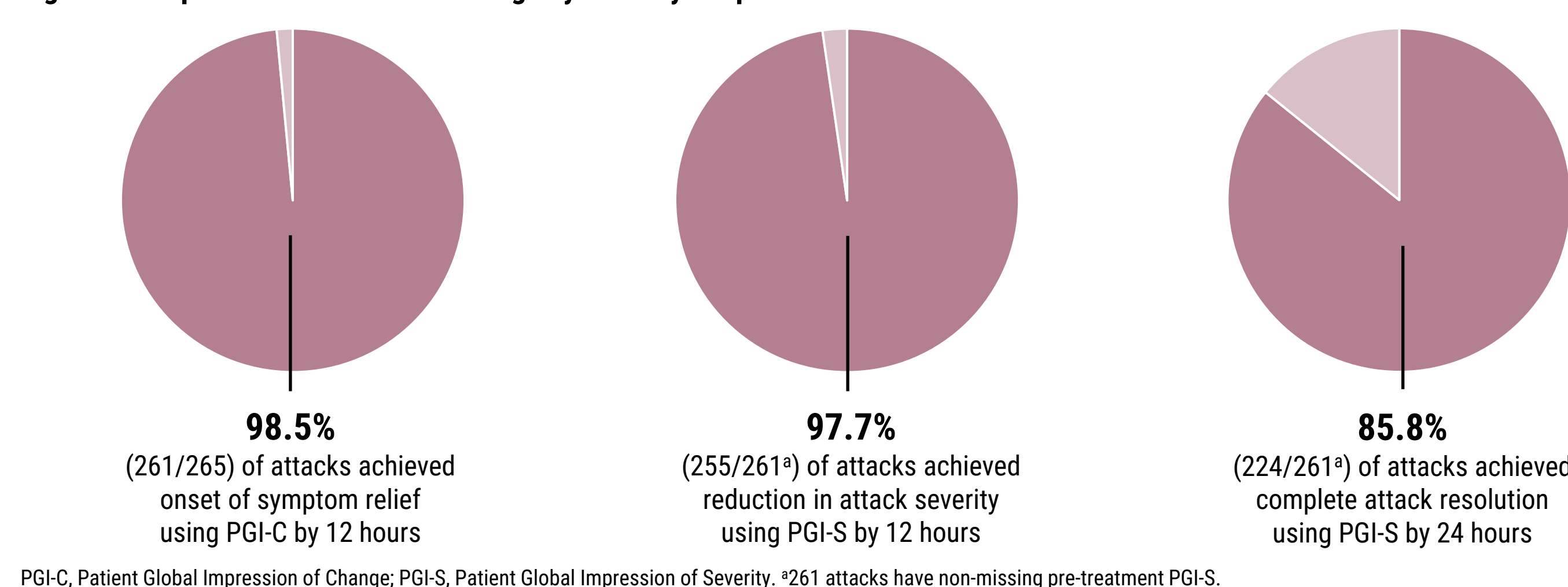
Table 2. Median time to achieving key efficacy endpoints

	Deucricitbant IR capsule (combined dose group)
Number of attacks treated ^a	265
Number of participants with treated attacks ^a	17
Median time to onset of symptom relief by PGI-C, hours (95% CI)	1.1 (1.0, 1.2)
Median time to reduction in attack severity by PGI-S, ^b hours (95% CI)	2.6 (2.0, 2.9)
Median time to complete attack resolution by PGI-S, ^b hours (95% CI)	11.5 (11.0, 13.0)

IR, immediate-release; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity. ^aNumber in the modified intention-to-treat efficacy analysis set (data cutoff: 01 March 2024). ^b261 attacks have non-missing pre-treatment PGI-S.

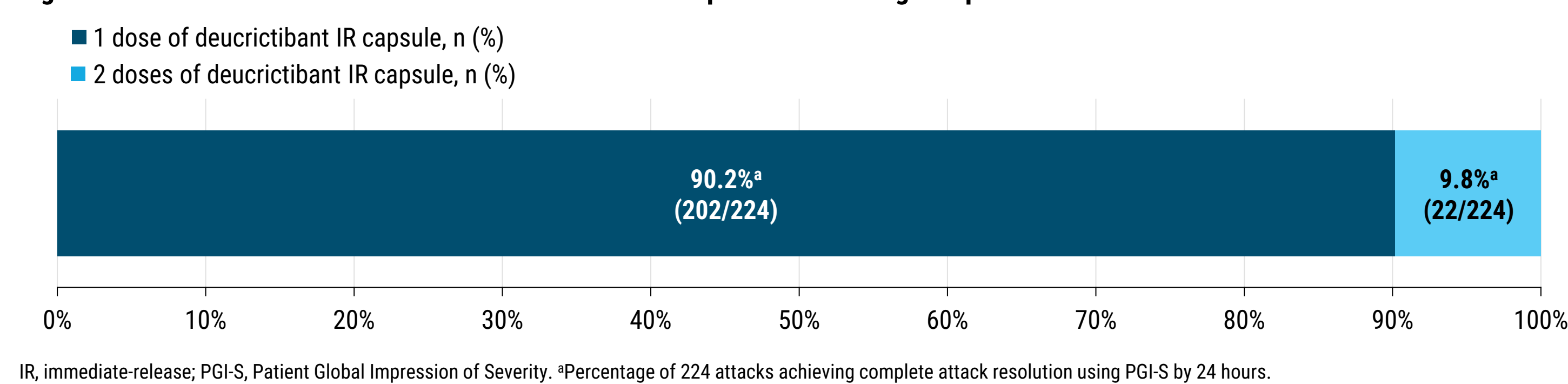
- 85.8% (224/261) of attacks achieved complete attack resolution by 24 hours (Figure 4). 90.2% (202/224) of attacks achieved this milestone with a single dose of deucricitbant IR capsule (Figure 5).

Figure 4. Proportion of attacks achieving key efficacy endpoints



PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity. ^a261 attacks have non-missing pre-treatment PGI-S.

Figure 5. Attacks treated with 1 or 2 doses of deucricitbant prior to achieving complete attack resolution



IR, immediate-release; PGI-S, Patient Global Impression of Severity. ^aPercentage of 224 attacks achieving complete attack resolution using PGI-S by 24 hours.

Conclusions

- Primary and post hoc analyses of the RAPIDE-1 Phase 2 trial provide consistent evidence that the majority of HAE attacks achieved the treatment outcomes of substantial symptom relief and symptom resolution by 24 hours after a single dose of oral deucricitbant IR capsule.
- Results from the ongoing RAPIDE-2 extension are consistent with the Phase 2 RAPIDE-1 study and provide evidence on the long-term safety and efficacy of deucricitbant IR capsule for repeat treatment of HAE attacks.

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