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

H. Henry Li, MD, PhD[1]; John Anderson, MD[2]; Marc A. Riedl, MD, MS[3]; Peng Lu, MD, PhD[4]; Marcus Maurer, MD[5,6]

[1]Institute for Asthma and Allergy, Chevy Chase, MD, United States of America; [2]Clinical Research Center of Alabama, AllerVie Health, Birmingham, AL, United States of America; [3]Division of Allergy and Immunology, University of California, San Diego, La Jolla, CA, United States of America; [4]Pharvaris Inc., Lexington, MA, United States of America; [5]Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [6]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany

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]
- 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.[5-10]
- Primary and post-hoc analyses of the RAPIDe-1 (NCT04618211) study[7,*] were conducted to evaluate the treatment outcomes of substantial symptom relief and symptom resolution following HAE attack treatment with deucrictibant immediate-release (IR) capsule.

Methods

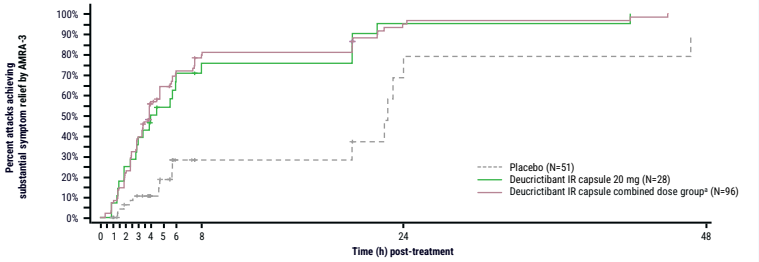
- RAPIDe-1 was a Phase 2, double-blind, placebo-controlled, randomized, crossover, dose-ranging trial of deucrictibant IR capsule for on-demand treatment of angioedema attacks in patients with HAE-1/2.[7] The 20 mg dose was selected for the Phase 3 RAPIDe-3 trial,[10] and those data are reported here.
- 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.[11,12] 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.[13]
- Substantial symptom relief was defined as ≥50% reduction in AMRA-3 score vs pre-treatment (key secondary endpoint).
- Two definitions were used to measure symptom resolution:
  - 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).

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

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 (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 deucrictibant 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 deucrictibant IR capsule combined dose group was 3.9 hours (**Figure 1**).

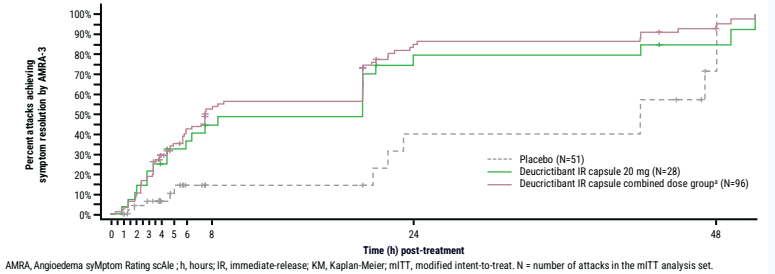
Figure 1. KM plot of time to AMRA-3 substantial symptom relief



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. [a]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 deucrictibant IR capsule 20 mg and 7.5 hours for the combined dose group vs 42.0 hours with placebo (**Figure 2**). The variability is mainly due to the lack of assessments between 8 and 24 hours.

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



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. [a]Includes 10 mg, 20 mg, and 30 mg dose groups.

- Symptom resolution by TOS PRO was achieved at a median time of 5.9 hours for attacks treated with a single dose of deucrictibant IR capsule 20 mg and 5.2 hours for the combined dose group vs 23.3 hours with placebo (**Table 1**).

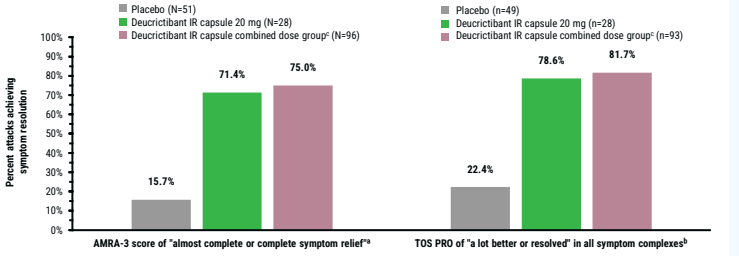
Table 1. TOS PRO symptom resolution by KM estimate[a]

	Placebo	Deucrictibant IR capsule	
		20 mg	Combined[c]
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[b]			
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)

CI, confidence interval; h, hours; IR, immediate-release; KM, Kaplan-Meier; TOS PRO, Treatment Outcome Score patient-reported outcome. [a]Symptom resolution by TOS PRO was assessed in a post-hoc analysis of RAPIDe-1. [b]TOS 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. [c]Includes 10 mg, 20 mg, and 30 mg dose groups.

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

Figure 3. Attacks achieving symptom resolution with a single dose of study drug within 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. [a]All 3 individual AMRA scores ≤10 (key secondary endpoint). [b]TOS PRO was assessed in a post-hoc analysis of RAPIDe-1. [c]Includes 10 mg, 20 mg, and 30 mg dose groups.

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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 within 24 hours after a single dose of oral deucrictibant IR capsule.**

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