Long-Term Safety and Efficacy of Oral Deucrictibant for Treatment of Hereditary Angioedema Attacks: Results of the RAPIDe-2 Extension Study

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Conflicts of interest disclosure

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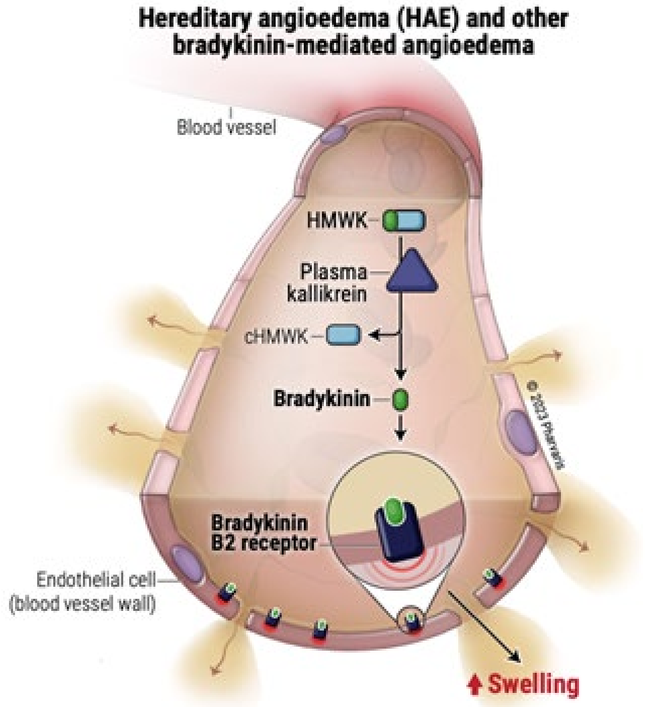
Hereditary angioedema (HAE) is a bradykinin-mediated condition with unmet medical needs



- Bradykinin is the main mediator of the clinical manifestations of HAE attacks.[1]
- Current guidelines recommend HAE attacks are treated as early as possible.[2-4]
- Parenteral administration often leads to on-demand treatment of HAE attacks being delayed or forgone.[5-14]

cHMWK, cleaved HMWK; HAE, Hereditary angioedema; HMWK, high-molecular-weight kininogen. **1.** Busse PJ, et al. *N Engl J Med*. 2020;382:1136-48. **2.** Betschel S, et al. *Allergy Asthma Clin Immunol*. 2019;15:72. **3.** Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-50. **4.** Maurer M, et al. *Allergy*. 2022;77:1961-90. **5.** Berinert® [package insert], https://labeling.cslbehring.com/pi/us/berinert/en/berinert-prescribing-information.pdf. Accessed March 10, 2025. **6.** Cinryze® [summary of product characteristics], https://www.ema. europa.eu/ en/documents/product-information/cinryze-epar-product-information_en.pdf. Accessed March 10, 2025. **7.** Firazyr® [package insert], https://www.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf. Accessed March 10, 2025. **8.** Kalbitor® [package insert], https://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf. Accessed March 10, 2025. **9.** Ruconest® [package insert], https://www.ruconest.com/wp-content/uploads/Ruconest_PI_Apr2020.pdf. Accessed March 10, 2025. **10.** Burnette A, et al. Presented at: AAAAI; February 24–27; San Antonio, TX, USA. **11.** Betschel SD, et al. Allergy Asthma Clin Immunol. 2024;20:43. **12.** 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 March 10, 2025. **13.** Radojicic C, et al. Presented at: AAAAI; February 24–27, 2023; San Antonio, TX, USA. **14.** Mendivil J, et al. Presented at: ACAAI; November 9–13, 2023; Anaheim, CA, USA.

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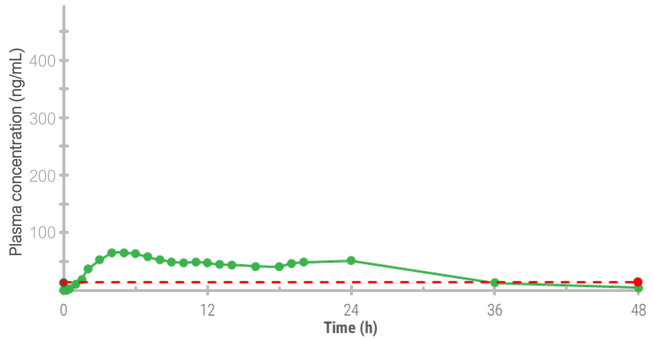
Deucrictibant is a selective, bradykinin B2 receptor antagonist

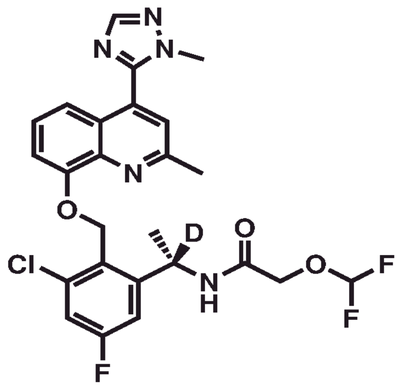
- Currently under development for both prophylactic and on-demand treatment of HAE attacks[1-9]:

DEUCRICTIBANT extended-release (XR) tablet

sustained absorption[9]



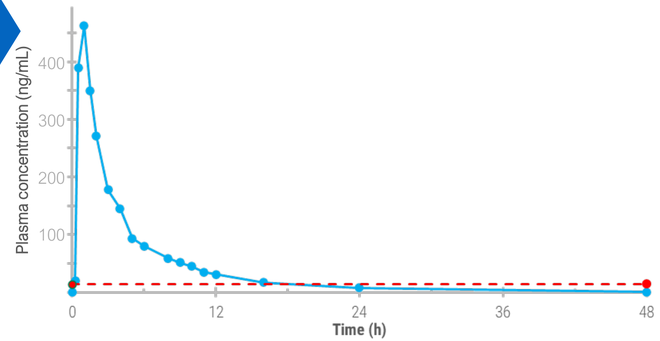
In studies, deucrictibant maintained sustained therapeutic exposure over 24 hours[9] from day one, allowing for once-daily oral prevention of HAE attacks[6]



deucrictibant

DEUCRICTIBANT immediate-release (IR) capsule

rapid absorption[2]



In studies, deucrictibant rapidly reached therapeutic exposure within 15-30 minutes[2], supporting on-demand oral treatment of HAE attacks[4]

HAE, Hereditary angioedema. **1.** RAPIDe-1 https://www.clinicaltrials.gov/study/NCT04618211. Accessed March 10, 2025. **2.** Maurer M, et al. Presented at: AAAAI; February 24–27, 2023; San Antonio, TX, USA. **3.** RAPIDe-2. https://clinicaltrials.gov/study/NCT05396105. Accessed March 10, 2025. **4.** RAPIDe-3. https://www.clinicaltrials.gov/study/NCT06343779. Accessed March 10, 2025. **5.** CHAPTER-1. https://www.clinicaltrials.gov/study/NCT05047185. Accessed March 10, 2025. **6.** CHAPTER-3. https://clinicaltrials.gov/study/NCT06669754. Accessed March 10, 2025. **7.** CHAPTER-4. https://clinicaltrials.gov/study/NCT06679881. Accessed March 10, 2025. **8.** Aygören-Pürsün E, et al. Presented at: EAACI; May 31–June 3, 2024; Valencia, Spain. **9.** Lesage A et al. Presented at IDDST; May 22–24, 2024.

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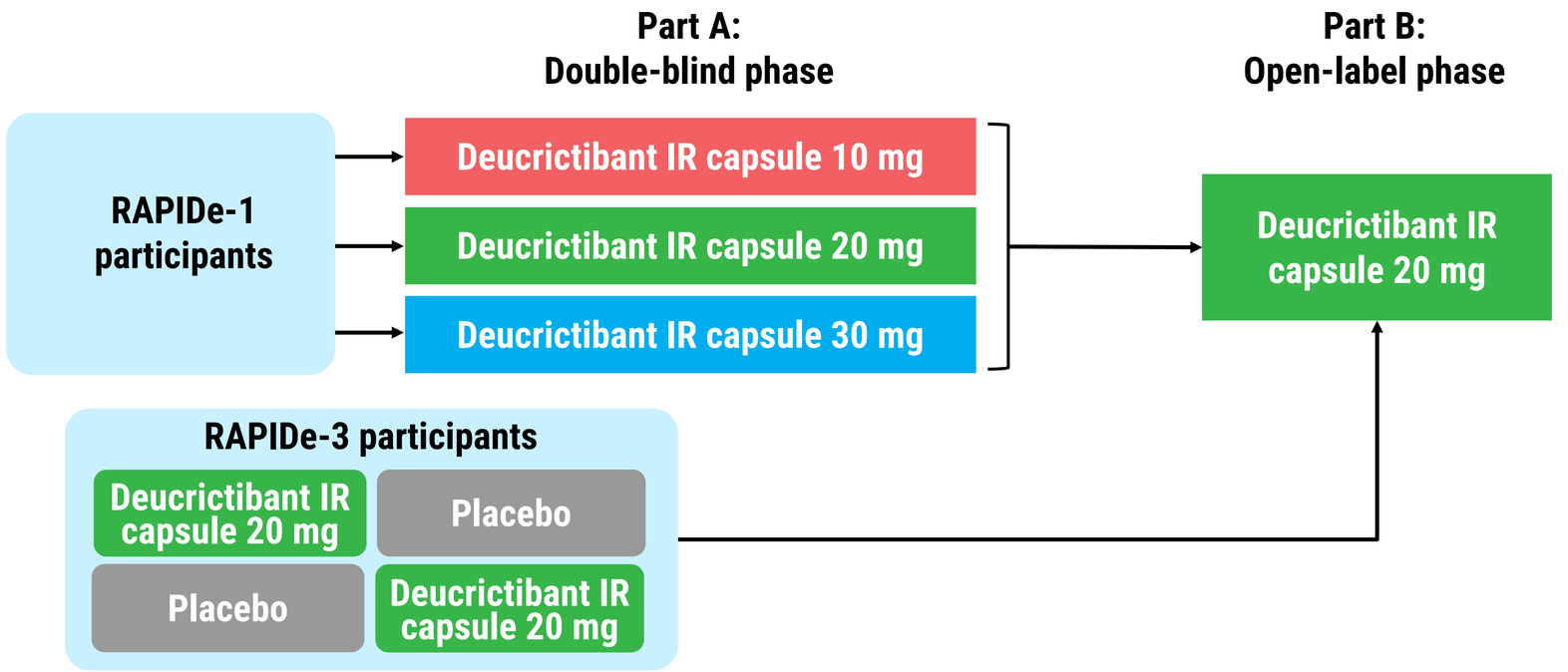
RAPIDe-2: a two-part, double-blind Phase 2/3 extension study of deucrictibant for on-demand treatment of repeat HAE attacks



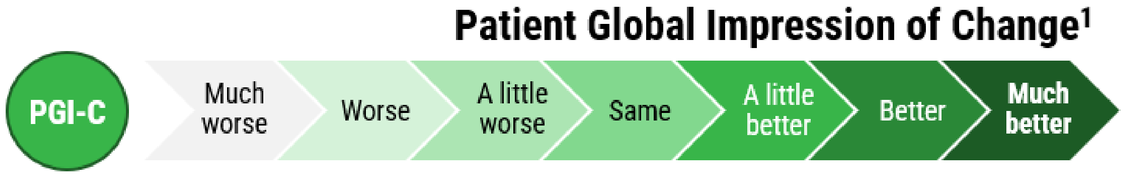
Part A: participants continue self-administering the same double-blinded dose of deucrictibant IR capsule received in RAPIDe-1 to treat qualifying attacks.[a]

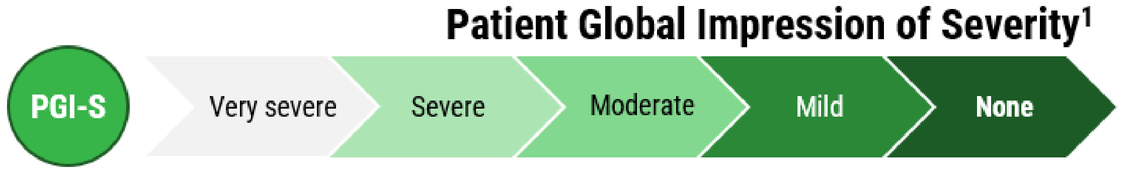
Part A prophylaxis: no long-term HAE prophylaxis treatment is allowed.[b]

HAE, hereditary angioedema; IR, immediate-release. [a]Including non-severe laryngeal attacks presenting without breathing difficulties. [b]Recent use of long-term HAE prophylaxis treatment prior to screening is allowed provided a pre-specified washout period is observed. RAPIDe-1. https://www.clinicaltrials.gov/study/NCT04618211. Accessed March 10, 2025. RAPIDe-2. https://clinicaltrials.gov/study/NCT05396105. Accessed March 10, 2025. RAPIDe-3. https://www.clinicaltrials.gov/study/NCT06343779. Accessed March 10, 2025.

RAPIDe-2 study endpoints and post-hoc analyses

- **Primary endpoint:** safety including TEAEs, clinical laboratory tests, vital signs, and ECG findings.
- **Secondary endpoints**: efficacy endpoints using PRO tools PGI-C and PGI-S.





- **Post-hoc analyses:** Safety and efficacy for on-demand treatment of upper airway attacks, including laryngeal attacks without breathing difficulties.
  - Upper airway attacks confirmed by investigators as per protocol definition: swelling of the lips/tongue or any sensation of lump in the throat, difficulty swallowing, or voice change.
  - Difficulty swallowing and voice change, which were manifestations of the airway attacks prior to treatment, were assessed using the 5-symptom composite Angioedema syMptom Rating scAle (AMRA-5).

ECG, electrocardiogram; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity PRO, patient-reported outcome; TEAE, treatment-emergent adverse events. Data collection pre-specified at pre-treatment, hourly for 6 hours, and at 8, 12, 24, and 48 hours post-treatment. [a]If rescue medication used within 14.5 hours post-treatment, time to event was censored at 14.5 hours regardless of whether event occurred within 12 hours post-treatment. [b]Rescue medication use within 33.5 hours post-treatment was regarded as not achieving complete attack resolution at 24 hours.

1. Cohn DM, et al. *Clin Transl Allergy*. 2023;e12288.

Deucrictibant IR capsule was well tolerated across all doses

- Participants who received ≥1 dose of deucrictibant IR capsule in the study at data cutoff (10 June 2024).
- 337 attacks from 19 participants.

Adverse events	Deucrictibant IR capsule (Combined dose group) (n=19)
Attacks with any TEAE, n (%)	13 (3.9)
Treatment-related TEAEs, n	0
Serious TEAEs, n	1[a]
Treatment-related serious TEAEs, n	0
TEAEs leading to study drug discontinuation, study withdrawal, or death, n	0

IR, immediate-release; TEAE, treatment-emergent adverse event (defined as adverse event occurring during time window from first study drug administration). Data snapshot from RAPIDe-2 Part A. Combined dose-blinded group data shown. [a]Tooth caries unrelated to treatment.

Median time to achieving key efficacy endpoints

- At data cutoff (01 March 2024): 265 attacks from 17 participants.

Median time to (95% CIs)	Onset of symptom relief by PGI-C	Reduction in attack severity by PGI-S	Substantial symptom relief by PGI-C	Complete attack resolution by PGI-S
	1.1 hours (1.0, 1.1)[a]	2.6 hours (2.0, 2.9)[a,b]	2.7 hours (2.1, 2.9)[a]	11.5 hours (11.0, 13.0)[a,b]

CI, confidence interval; PGI-S, Patient Global Impression of Severity. [a]Modified intention-to-treat efficacy analysis set: participants who treated ≥1 attack with deucrictibant IR capsule and non-missing PGI-C results from ≥1 post-treatment timepoint. [b]261 attacks have non-missing pre-treatment PGI-S. Within-participant correlation was not accounted for in all Kaplan-Meier estimates.

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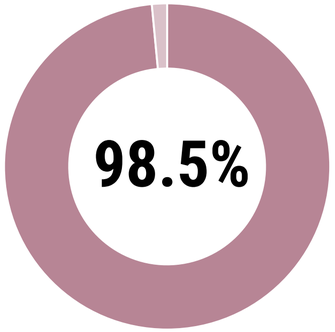
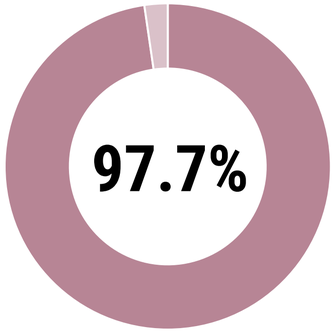
Majority of attacks achieved key efficacy endpoints within timeframe



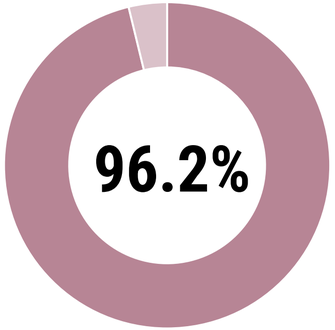
of attacks achieved
onset of symptom relief by 12 hours
(261/265)



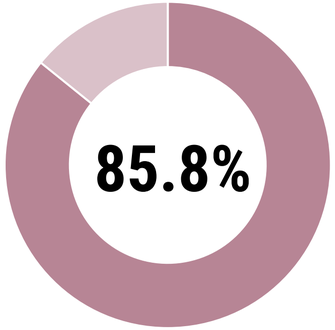
of attacks achieved
reduction in attack severity by 12 hours
(255/261[a])

PGI-C

PGI-S



of attacks achieved
substantial symptom relief by 12 hours
(255/265)



of attacks achieved
complete attack resolution by 24 hours
(224/261[a])

PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity. [a]261 attacks had non-missing pre-treatment PGI-S.

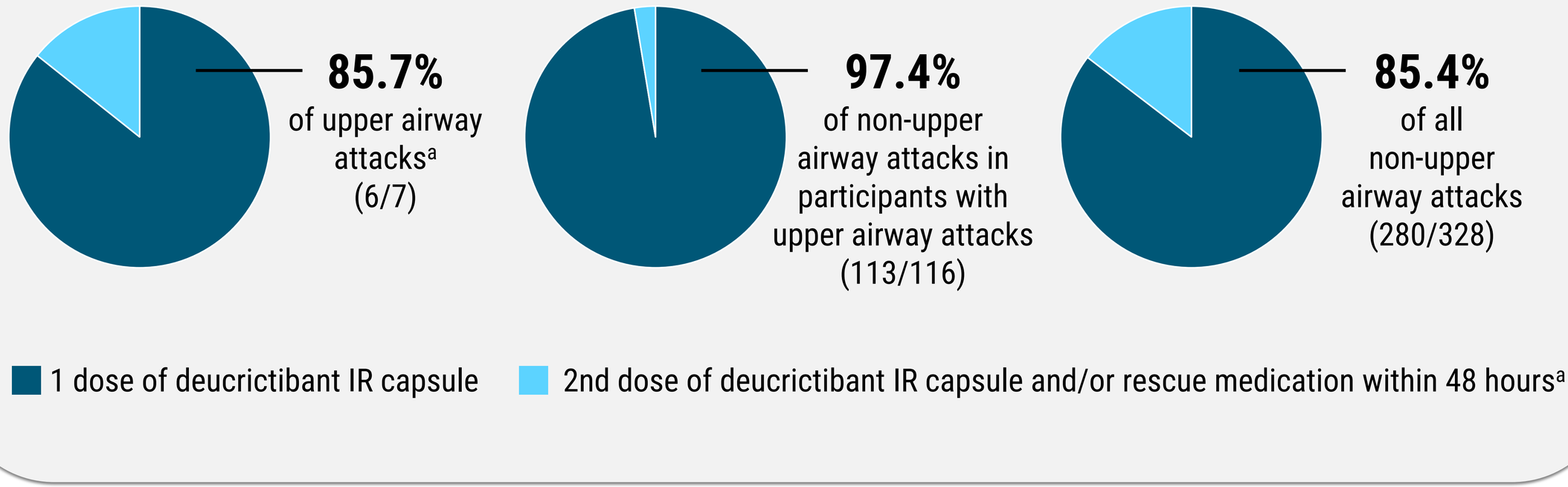
Similar times to symptom relief for upper airway and other attacks

- Difficulty in swallowing and/or voice change were reported as attack manifestations of 3 upper airway attacks before treatment.

	Upper airway attacks	Non-upper airway attacks in participants with upper airway attacks	Total non-upper airway attacks
Number of participants	5	5	19
Total number of attacks treated[a]	7	116	328
Time to onset of symptom relief[b,c]			
Number of attacks[d]	7	112	318
Median hours (95% CI)	**0.9 hours** (0.5, 2.0)	**1.0 hours** (1.0, 1.1)	**1.1 hours** (1.0, 1.1)
Time to reduction in attack severity[c,e]			
Number of attacks[f]	6	111	312
Median hours (95% CI)	**3.0 hours** (0.9, NE)	**2.0 hours** (2.0, 2.7)	**2.7 hours** (2.1, 2.9)

CI, confidence interval; NE, not estimable (insufficient data to calculate reliable estimate); PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity. [a]337 attacks treated by 19 participants at data cutoff (31 May 2024), of which 7 were upper airway, including laryngeal, attacks. [b]PGI-C rating of at least "a little better" for 2 consecutive timepoints by 12 hours post-treatment. [c]Within-participant correlation not accounted for in all Kaplan-Meier estimates. [d]Evaluable attacks include deucrictibant-treated attacks with ≥1 post-treatment PGI-C assessment. [e]≥1-level reduction in PGI-S from pre-treatment for 2 consecutive timepoints by 12 hours. [f]Evaluable attacks included deucrictibant-treated attacks with a pre- and ≥1 post-treatment PGI-S assessment.

Majority of upper airway attacks were treated with a single dose of deucrictibant



HAE, hereditary angioedema; IR, immediate-release. [a]For upper airway attacks with inadequate response or symptom recurrence ≥4 hours after first dose of deucrictibant, only rescue medication was permitted. If needed, patients could use HAE rescue medication for an upper airway attack at any time. For other attacks, a second dose of deucrictibant was permitted ≥4 hours after first dose if symptoms persisted or progressed. If symptoms still persisted or progressed after the second dose of deucrictibant, rescue medication was administered.

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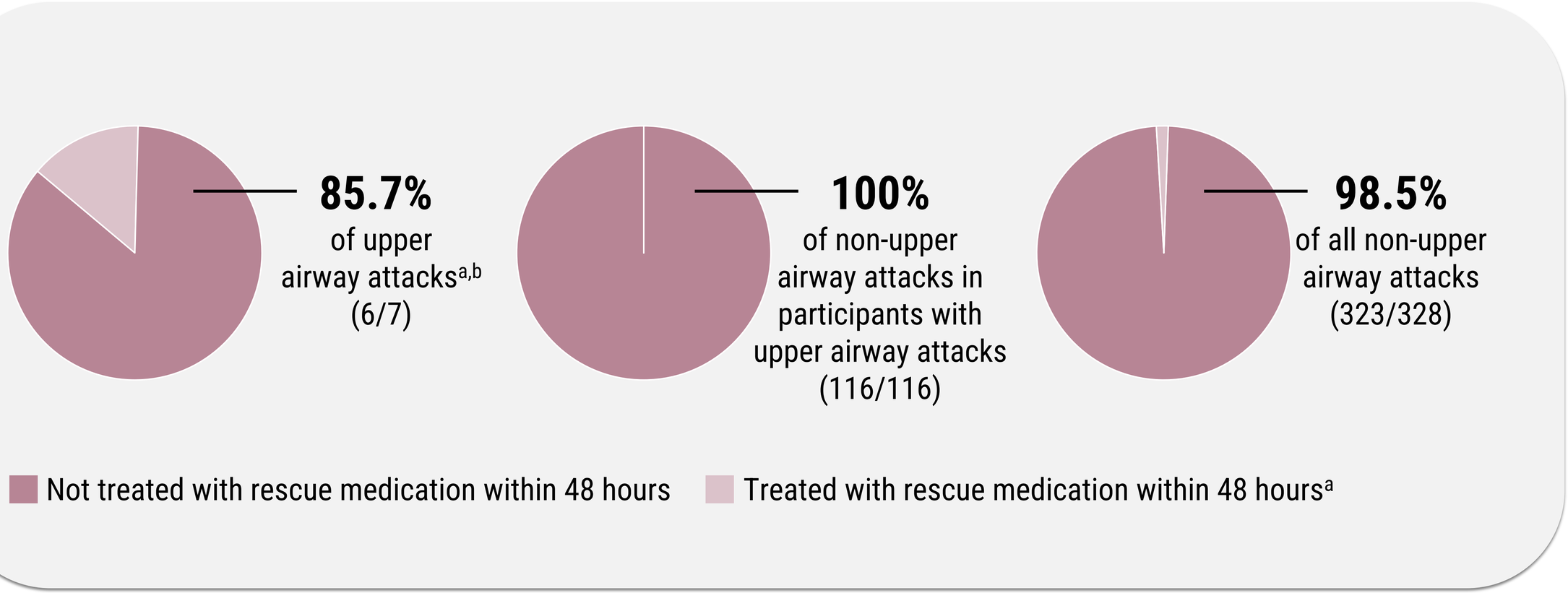
Majority of upper airway and other attacks did not use rescue medication by 48 hours post-treatment



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Conclusions

These data provide additional evidence on the long-term safety and efficacy of deucrictibant IR capsule for on-demand treatment of repeat HAE attacks.

- **Safety:** Deucrictibant was well tolerated with no safety signals.
- **Efficacy – All attacks:**
  - Median time to onset of symptom relief was 1.1 hours.
  - 85.8% of attacks achieved complete attack resolution by 24 hours.
- **Efficacy – Upper airway attacks:**
  - Similar times to symptom relief for upper airway attacks and other attacks.
  - Majority of upper airway attacks were treated with a single dose of deucrictibant and did not use rescue medication by 48 hours.

The Authors and the Sponsor would like to thank all the people with HAE as well as all study Sites' staff who participated in the RAPIDe-2 trial

HAE, hereditary angioedema; IR, immediate-release.