Content Validity of the Angioedema syMptom Rating scAle (AMRA) to Assess Symptoms of Hereditary Angioedema Attacks

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Key takeaways

These collated analyses from a mixed-methods study and the RAPIDe-3 study provide evidence to support the content validity of AMRA-3/5 scales across age groups, including adolescents and adults, and support the use of these scales in assessing severity of key symptoms associated with hereditary angioedema (HAE) attacks.

Participants reported a variety of symptoms, with those most frequently observed captured by the AMRA-3/5 scales

AMRA-3

≥50% of participants across all age groups reported:
- Swelling (cutaneous attacks)
- Abdominal pain (abdominal attacks)

AMRA-5

≥50% of participants who experienced upper airway attacks, including laryngeal attacks, reported:
- Voice change
- Difficulty swallowing
- Throat swelling

AMRA, Angioedema syMptom Rating scAle.

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

Background

- **Hereditary angioedema (HAE):** a bradykinin-mediated condition with painful swelling attacks caused by excess bradykinin activating bradykinin B2 receptors that affects multiple locations in the body and negatively impacts health-related quality of life (HRQoL).[1-7]
- The Angioedema syMptom Rating scAle (AMRA), a numerical rating scale derived from the visual analog scale (VAS), is being used to assess the severity of key symptoms associated with HAE attacks.[8-10]
  - AMRA-3 allows composite scoring of skin swelling, skin pain, and abdominal pain.
  - For upper airway attacks, including laryngeal attacks, AMRA-5 includes additional scoring items for voice changes and difficulty swallowing.
- An observational mixed-methods study supported the content validity of AMRA-3/5,[11] and additional confirmatory evidence is warranted to support the content validity of AMRA-3/5 in the RAPIDe-3 population (adults and adolescents aged ≥12 years).

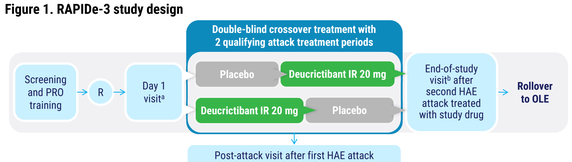
Objective

This study was conducted to generate additional confirmatory evidence to support the validity of AMRA-3/5 in assessing the severity of key symptoms associated with HAE attacks.

Methods

- **RAPIDe-3 (NCT06343779)*:** a completed, global, phase 3, randomized, double-blind, crossover trial evaluated the efficacy and safety of deucrictibant immediate-release (IR) capsule for on-demand treatment of HAE attacks in adolescents and adults (**Figure 1**).[12]
- **Eligible participants:** aged ≥12 to ≤75 years, diagnosed with HAE type 1/2 or HAE with normal C1 inhibitor, a history of ≥2 HAE attacks in the last 3 months before screening, and experience with using standard-of-care treatment to manage HAE attacks.

Figure 1. RAPIDe-3 study design



HAE, hereditary angioedema; IR, immediate-release; OLE, open-label extension; PRO, patient-reported outcome; R, randomization. [a]Adolescent participants receive a non-attack dose for pharmacokinetic sampling at Day 1 visit prior to R. [b]Data from the end-of-study visit may be used to qualify the participant for an OLE study with deucrictibant.

Methods

Participants

- **Mixed-methods study population:** a subset of participants completed a 60-minute interview to generate evidence of content validity for AMRA-3/5 ahead of their inclusion in RAPIDe-3.[10]
- **RAPIDe-3 study population:** participants who enrolled in RAPIDe-3 and consented to the entry interview, completed a 30-minute interview.
  - Participants were interviewed remotely within 48 hours of the Day 1 visit (randomization to study treatment sequence).

Interviews

- Open-ended questions were used to elicit insights into the symptoms, HAE attack characteristics, and impacts on daily life experienced by participants.
  - Spontaneous responses refer to instances when concepts were spontaneously reported by participants.
  - Probed responses refer to instances when concepts were reported only after being specifically asked about it by the interviewer.

Analysis

- Qualitative evidence was collated from the mixed-methods study and the RAPIDe-3 population relating to the suitability of the AMRA-3/5 scales.

Participant-reported outcome scales evaluated

- **AMRA-3:** a 3-item composite scale that measures skin pain, skin swelling, and abdominal pain as values 0 to 100 (representing no symptoms to worst possible symptoms).
- **AMRA-5:** an extension of the AMRA-3 scale that incorporates AMRA-3 symptoms plus voice change and difficulty swallowing.

Results

Study population

- The mixed-methods study population included an interview subsample of participants (n=20) aged 23–70 years; the RAPIDe-3 entry population included participants (n=20) aged 12–55 years (**Table 1**).

Table 1. Baseline characteristics

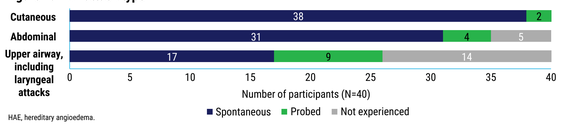
	Mixed-methods study population (n=20)	RAPIDe-3 population (n=20)	Combined population (N=40)
Age group, n (%)			
Older adults, ≥30 y	15 (75)	10 (50)	25 (63)
Young adults, 18–29 y	5 (25)	6 (30)	11 (28)
Adolescents, 12–17 y	-	4 (20)	4 (10)
Sex: Male / female, n (%)	4 (20) / 16 (80)	9 (45) / 11 (55)	13 (33) / 27 (68)
Race: White / other, n	19 / 1	12 / 8	31 / 9

HAE attack experience

- Monthly attacks (54%) was the most commonly reported frequency among the 37 participants who discussed their HAE attack frequency.
  - A higher percentage of adolescents described the frequency of their HAE attacks as variable (50%) compared with young adults (18%) and older adults (4%).
  - No adolescents experienced weekly HAE attacks (0%) compared with young adults (36%) and older adults (16%).
  - All participants reported experiencing cutaneous attacks (100%) and most reported experiencing abdominal (88%) and upper airway HAE attacks, including laryngeal attacks (65%) (**Figure 2**).
- All participants across all age groups reported cutaneous attacks (100%).
- However, abdominal attacks in adolescents (n=2/4 [50%]) and upper airway attacks, including laryngeal attacks, in young adults (n=3/11 [27%]) were reported less frequently (**Figure 3**).

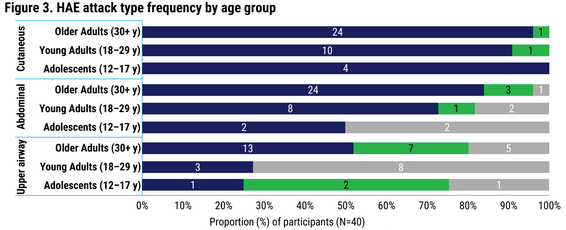
Results

Figure 2. HAE attack type



HAE, hereditary angioedema.

Figure 3. HAE attack type frequency by age group

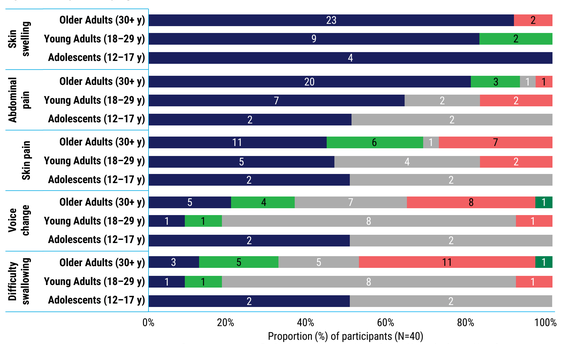


HAE, hereditary angioedema.

Key HAE symptoms included in AMRA

- Most commonly reported AMRA symptoms were skin swelling (95%), abdominal pain (80%), and skin pain (60%). Voice change (33%) and difficulty swallowing (30%) were also reported (**Figure 4;** additional symptoms shown in **Table 2**).
  - Abdominal pain was more common in older adults and young adults, and skin pain was more common in older adults.

Figure 4. Key HAE symptoms included in AMRA



AMRA, Angioedema symptom Rating scAle; HAE, hereditary angioedema.

Results

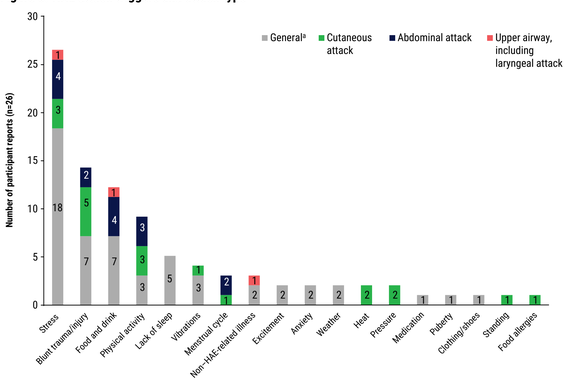
Table 2. Additional symptoms frequently reported by participants from all age groups

Additional symptoms, n (%) (N=40)		Areas of swelling, n (%) (n=38/40)		Location of pain, n (%) (n=36/40)	
		Feet	27 (71)	Abdomen	32 (89)
Throat swelling	19 (48)	Hands	23 (61)	Hands[a]	9 (25)
Vomiting	17 (43)	Abdomen	22 (58)	Feet[a]	7 (19)
Abdominal swelling	15 (38)	Genitals	15 (39)	Extremities[a]	4 (11)
		Eyes	5 (13)		

[a]Only reported by young adults and older adults.

- Participants reported 18 types of HAE attack triggers, most frequently stress (n=26), blunt trauma or injury (n=14), and food and drink (n=12) (**Figure 5**).
  - Stress (n=21/26 [81%]), blunt trauma/injury (n=11/26 [42%]), food/drink (n=9/26 [35%]), and physical activity and lack of sleep (both n=5/26 [19%]) were reported as HAE attack triggers by participants from all age groups.
  - Puberty and clothes/shoes were only reported by adolescents (both n=1/4 [25%]), standing and food allergies were only reported by young adults (n=1/11 [9%]), and non–HAE-related illnesses (n=2/25 [8%]), and medication (n=1/25 [4%]) were only reported by older adults.

Figure 5. HAE attack triggers and attack type



HAE, hereditary angioedema. [a]General attack properties refer to where participants discussed their HAE attack experience more generally without associating it with any of the three attack types (cutaneous, abdominal, and laryngeal).

References

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