End of Progression Using Patient Global Impression of Change Validation in RAPIDe-3

Danny M. Cohn[1], Philip H. Li[2], John Anderson[3], Aleena Banerji[4], Jonathan A. Bernstein[5], Autumn F. Burnette[6], Paula J. Busse[7], Timothy J. Craig[8,9], Joshua S. Jacobs[10], Donald S. Levy[11], H. Henry Li[12], William R. Lumry[13], Michael E. Manning[14], Cristine Radojicic[15], Cristina J. Ramos[16], Mark D. Scarupa[12], Daniel F. Soteres[17], Marie-Jeanne Holveck[18], Piper Fromy[18], Maggie Chen[19], Joan Mendivil[20], Raffi Tachdjian[21], Marc A. Riedl[22]

[1]Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [2]Queen Mary Hospital, University of Hong Kong, Hong Kong SAR, China; [3]AllerVie Health, Birmingham, AL, USA; [4]Massachusetts General Hospital, Boston, MA, USA; [5]University of Cincinnati College of Medicine, Cincinnati, OH, USA; [6]Howard University Hospital, Washington, DC, USA; [7]Mount Sinai Hospital, New York, NY, USA; [8]Penn State University, Hershey, PA, USA; [9]Vinmec-VinUni Institute of Immunology, Vinmec Hospital, Times City, Vietnam, and Vin University, Hanoi, Vietnam; [10]Allergy and Asthma Clinical Research, Walnut Creek, CA, USA; [11]University of California Irvine School of Medicine, Irvine, CA, USA; [12]Institute for Asthma and Allergy, Chevy Chase, MD, USA; [13]AARA Research Center, Dallas, TX, USA; [14]Allergy, Asthma and Immunology Associates, Ltd., Scottsdale, AZ, USA; [15]Duke University School of Medicine, Durham, NC, USA; [16]FDI Clinical Research, San Juan, Puerto Rico; [17]Asthma & Allergy Associates and Research Center, P.C., Colorado Springs; University CO Health Sciences Center, Aurora, CO, USA; [18]Seeing Theta, Saumur, France; [19]Pharvaris Inc., Lexington, MA, USA; [20]Pharvaris GmbH, Zug, Switzerland; [21]University of California at Los Angeles, Los Angeles, CA, USA; [22]University of California San Diego, La Jolla, CA, USA.

Key takeaways

Psychometric analyses of patient-reported outcomes from the Phase 3 RAPIDe-3 trial collectively support the validity of a Patient Global Impression of Change (PGI-C)–based definition of end of progression (EoP) of hereditary angioedema (HAE) attack symptoms based on the Patient Global Impression of Severity (PGI-S) and three-item Angioedema syMptom Rating scAle (AMRA-3) as anchor measures.

PGI-C ratings

PGI-C ratings aligned closely with the statistically modeled true latent changes in HAE severity ($\beta^a = 0.824$; $R^2 = 0.68^b$). This strong association supports the **PGI-C as a valid and meaningful measure** of how patients perceive changes in their HAE severity over time

PGI-S and AMRA-3

PGI-S and **AMRA-3** responses were **consistent** over time for **stable** participants[c]

Anchor-based and time-to-event analyses converge to support the **PGI-C–based EoP** endpoint **as a clinically meaningful measure of treatment response**

AMRA-3, three-item Angioedema syMptom Rating scAle; EoP, end of progression; HAE, hereditary angioedema; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity. [a]The estimated standardized structural regression coefficient. [b]R^2: the percentage of variance in PGI-C explained by the true latent HAE severity change. [c]PGI-S: stable participants had the same severity rating at 15, 30, 60, 90, and 120 minutes after self-administration of study drug. AMRA-3: stable participants had an AMRA-3 total score within ±20% of their 15-minute score at 30, 60, 90, and 120 minutes after self-administration of study drug.

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

Rationale

- **Hereditary angioedema (HAE):** a bradykinin-mediated condition characterized by unpredictable, painful, potentially life-threatening swelling attacks caused by excess bradykinin activating bradykinin B2 receptors that affects multiple locations in the body, negatively impacting daily activities.[1-5]
- **Unmet need:** convenient on-demand treatment options providing rapid, sustained relief and complete and durable attack resolution remain limited.[6]
- **Deucrictibant:** an oral bradykinin B2 receptor antagonist evaluated in the placebo-controlled Phase 3 RAPIDe-3 trial significantly reduced the time to key HAE attack milestones, including the end of progression (EoP) of symptoms.[7]
- **Clinical implication:** given the clinical importance of halting symptom worsening during acute HAE attacks, this analysis evaluated the psychometric validity of a Patient Global Impression of Change (PGI-C)–based definition of EoP using patient-reported outcomes from RAPIDe-3.

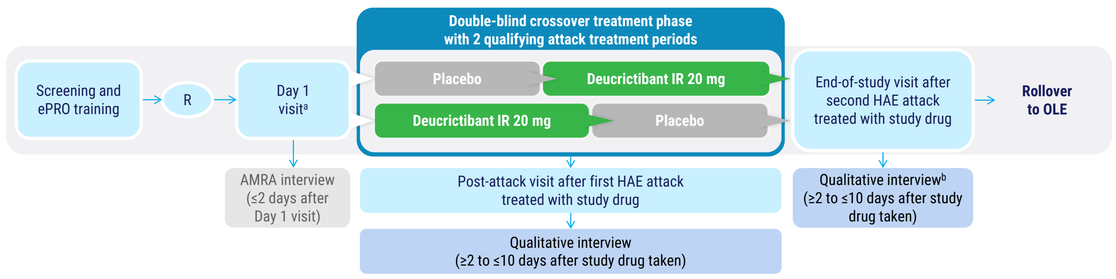
Objective

To evaluate the psychometric validity of PGI-C as a measure of HAE attack symptom change, using Patient Global Impression of Severity (PGI-S) and three-item Angioedema syMptom Rating scAle (AMRA-3) as anchor measures, and to assess whether this evidence supports a PGI-C–based definition of EoP using patient-reported outcomes from RAPIDe-3.

Methods

- **RAPIDe-3 trial (NCT06343779)*:** a completed, global, Phase 3, randomized, double-blind, placebo-controlled, crossover trial that evaluated the efficacy and safety of deucrictibant immediate-release (IR) capsule 20 mg for on-demand treatment of HAE attacks in adolescents and adults (**Figure 1**).[7]
- **Eligible participants:** aged ≥12 to ≤75 years; living with HAE, including HAE with normal C1 inhibitor; having a history of ≥2 HAE attacks in the last 3 months before screening; and having experience using standard-of-care treatment to manage HAE attacks.
- **Time to onset of symptom relief:** the primary endpoint in RAPIDe-3, was defined by a PGI-C rating of "a little better" for two consecutive timepoints within 12 hours following treatment.
- **Time to EoP:** the earliest post-treatment timepoint after which all subsequent PGI-C ratings remained stable or improved within 12 hours of treatment.
- **Psychometric validation:** this analysis is blinded to treatment arm; some results are shown by treatment arm.

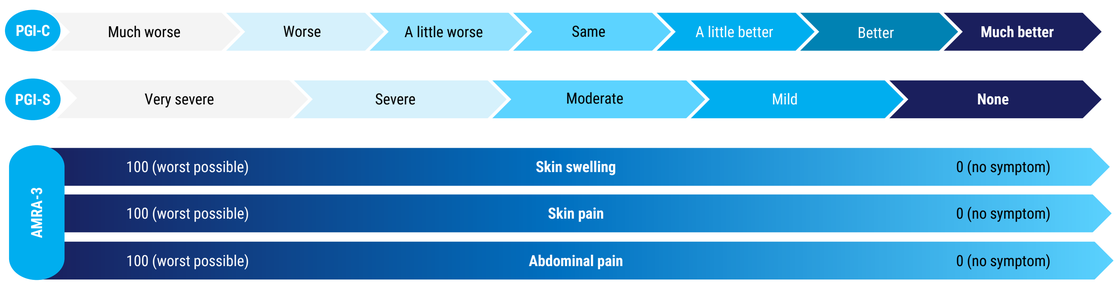
Figure 1. RAPIDe-3 study design



AMRA, Angioedema SyMptom Rating scAle; ePRO, electronic patient-reported outcome; HAE, hereditary angioedema; IR, immediate-release; OLE, open-label extension; R, randomization. [a]Adolescent participants received a non-attack dose for pharmacokinetic sampling at Day 1 visit prior to R. [b]The qualitative interview following the second treated attack must have occurred before completion of the end-of-study visit.

- **Assessment scales:** PGI-C, PGI-S, and AMRA-3 are validated instruments evaluating patient-reported outcomes from clinical trials in HAE to establish a patient's perception of change or severity of their attack symptoms (**Figure 2**).[8-11]

Figure 2. Assessment scales



AMRA-3, three-item Angioedema syMptom Rating scAle; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.

Assessment of PGI-C construct validity

- For the PGI-C to detect EoP, it should be valid as a construct, meaning it should be able to capture meaningful changes in participant status across multiple timepoints.
- To assess whether PGI-C could capture meaningful changes in participant status across multiple assessments, the proportion of participants selecting each PGI-C response category at each timepoint was calculated. This analysis was done on both attacks without accounting for repeated measures but including censoring use of rescue medication.
- To evaluate PGI-C as a valid measure of perceived change in HAE symptom severity, a latent change score model was estimated (using structural equation modeling in the lavaan R package[12]) to separate baseline severity from true change in HAE severity.
- The estimated standardized structural regression coefficient (β) of the association between PGI-C and latent change in HAE severity, as well as the percentage of explained variance in PGI-C (R^2), were determined. This analysis was done on the first attack only.

Assessment of PGI-S and AMRA-3 suitability

- The suitability of PGI-S and AMRA-3 as anchor measures was assessed using test-retest reliability, convergent validity, and longitudinal factor analysis.
- Test-retest reliability was assessed using the Cohen's quadratic weighted kappa[13] for PGI-S score and the Intraclass Correlation Coefficient (ICC)(2,1)[14] for AMRA-3 total score on a selection of stable participants within a short temporal window.
- Convergent validity was assessed using an intra-individual correlation framework[15] to verify that PGI-S and AMRA-3 could measure symptom progression.
- A longitudinal factor analysis was conducted to establish PGI-S and AMRA-3 as valid tools to measure HAE severity across repeated assessments.
- Appropriate fit statistics were computed to assess the goodness of fit between proposed models and observed data.

Meaningfulness assessment of a time-to-EoP endpoint

- Repeated-measures correlation models were used to validate the use of PGI-S change and AMRA-3 change across the attack trajectory before applying them as anchors into subsequent analyses of time to EoP.
  - PGI-C score was correlated with change in PGI-S and percent change in AMRA-3.
  - Anchors with a change correlation above 0.30 were used in the assessment of meaningful change.[16]
- PGI-S– and AMRA-3–based time to EoP were derived using the same sustained-improvement definition as PGI-C–based EoP, applied to PGI-S and AMRA-3 (instruments already shown to reliably and validly capture HAE symptom severity), providing an independent triangulation/convergent validity check rather than comparison against separately validated EoP endpoints.
  - This analysis was conducted on the first attack data only, with moderate relationships expected (r = 0.30 to 0.50).
- Adjusted Kaplan–Meier curves from marginal Cox models accounted for repeated measures and were visually assessed across PGI-S and AMRA-3 change groups.

Results

Participant baseline demographics and disease characteristics

- Analyses to evaluate PGI-C, PGI-S, and AMRA-3 were conducted using blinded data of RAPIDe-3 participants.
  - Analyses were performed for a total of 194 attacks (192 non-laryngeal and 2 laryngeal).
- Participants included in the analyses had a mean (SD) age of 37.7 (14.6) years (**Table 1**), were predominantly female (n=59/110 [53.6%]), White (n=78/110 [70.9%]), and had HAE type 1 (n=99/110 [90.0%]).

Table 1. Participant baseline demographics and disease characteristics

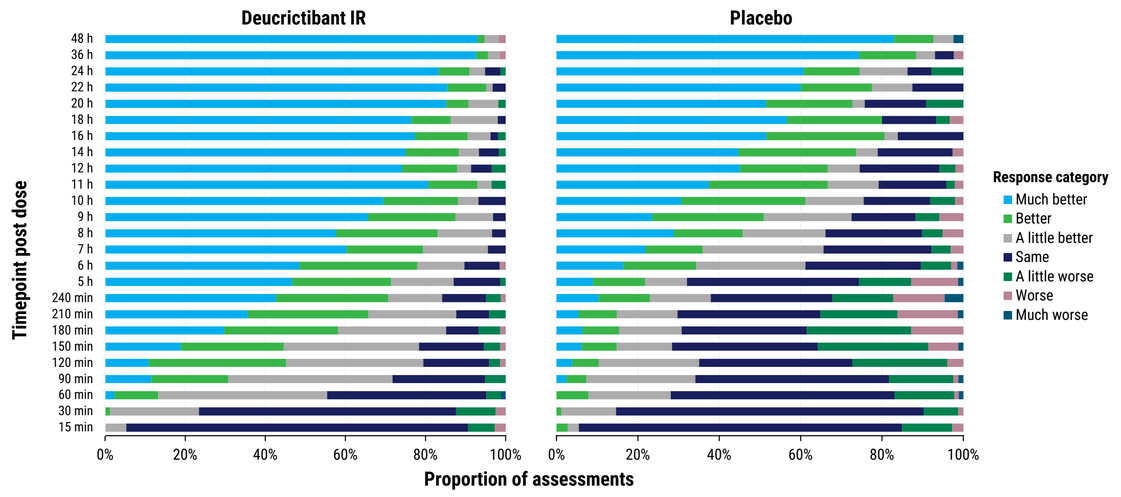
	Analysis population (n=110)[a]	Total RAPIDe-3 population (N=134)
Age, mean (SD), years	37.7 (14.6)	39.0 (14.7)
Range (min–max)	-	12–73
Female, n (%)	59 (53.6)	76 (56.7)
Race, n (%)[b]		
White	78 (70.9)	93 (69.4)
Asian	17 (15.5)	19 (14.2)
Black or African American	5 (4.5)	10 (7.5)
Mean (SD) time since HAE diagnosis, years	17.3 (12.4)	17.7 (13.1)
HAE type, n (%)		
HAE type 1	99 (90.0)	118 (88.1)
HAE type 2	8 (7.3)	10 (7.5)
HAE with normal C1INH	2 (1.8)	4 (3.0)
Unspecified type 1 or 2	1 (0.9)	2 (1.5)

C1INH, C1 inhibitor; HAE, hereditary angioedema; max, maximum; min, minimum; PGI-C, Patient Global Impression of Change; SD, standard deviation.
[a]Number of participants with ≥1 PGI-C measurement. [b]Also included the following categories: American Indian or Alaska Native, 1 (0.9%) vs 1 (0.7%); Other, 5 (4.5%) vs 7 (5.2%); Not reported, 4 (3.6%) vs 4 (3.0%).

Suitability of PGI-C as assessment instrument

- In following the course of an HAE attack, most participants across treatment groups reported the symptoms being the same after 15 minutes of the attack (**Figure 3**).
  - The proportion of participants reporting improvement in health until resolution steadily increased over time, with 55.4% of attacks reported as "a little better," "better," or "much better" with deucrictibant after 60 minutes of the attack versus 28.1% with placebo.
- PGI-C was strongly associated with latent changes in HAE severity (β = 0.824), explaining 68% of variance in PGI-C; these findings support the use of PGI-C as a valid instrument for evaluating EoP.

Figure 3. PGI-C assessment over time by treatment group: item response distributions at all timepoints, censoring assessments after rescue medication



IR, immediate-release; PGI-C, Patient Global Impression of Change.

Assessment of PGI-S and AMRA-3 as suitable anchor measures

- Both PGI-S and AMRA-3 scores varied less over time in participants meeting stability criteria than in those who did not.
- Test-retest results showed that all measures across all assessment windows had a high reliability estimate for both the AMRA-3 and the PGI-S, suggesting high reliability (**Table 2**).
- All within-person empirical correlation estimates were strong (r > 0.5), indicating good convergent validity of PGI-S and AMRA-3 reliability (**Table 3**).
- These findings support the use of PGI-S and AMRA to validate the PGI-C.
- Fit statistics for the longitudinal factor analysis model fell below the reference thresholds for acceptable fit and are therefore not reported here.

Table 2. Test-retest reliability of PGI-S when AMRA-3 defines stability and vice versa – first attack only

Measure (stability criteria)	Assessment window	Number of observations	Kappa/ICC	Interpretation
PGI-S (±20% AMRA-3 total score)	Mean weighted kappa (all timepoints)	266	**0.920**	Excellent
AMRA-3 total score (same PGI-S)	Global ICC (all timepoints)	38	**0.985**	Excellent

AMRA-3, three-item Angioedema syMptom Rating scAle; CI, confidence interval; ICC, intraclass correlation coefficient; PGI-S, Patient Global Impression of Severity; SE, standard error. Kappa was estimated for PGI-C and ICC(2,1) was estimated for the AMRA-3. For the quadratic weighted Cohen's kappa, the approximate 95% CI was computed as CI = K ± 1.96 × SE. For the mean weighted kappa, the mean CI bounds and the sum of the number paired comparisons (n) were calculated. ICC was calculated using the two-way random effects ICC (ICC2,1) for absolute agreement (typical reliability measure). Global ICC is a single measure of reliability across all timepoints, thus a fraction of total variance attributable to true differences between subjects and adjusted for both timepoint variability and residual error.

Table 3. Convergent validity estimates and their hypothesized relationships – first attack only

Measure	Convergent measure	Coefficient type	Hypothesized relationship	Number of participants	Number of observations	Within-person correlation (r_{rm})	95% CI lower limit	95% CI upper limit	Empirical relationship
PGI-S	AMRA-3 total score	Repeated measures correlation	Moderate	108	1523	**0.733**	0.708	0.756	Strong
PGI-S	AMRA-3 skin swelling	Repeated measures correlation	Moderate	108	1523	**0.538**	0.499	0.574	Strong
PGI-S	AMRA-3 skin pain	Repeated measures correlation	Moderate	108	1523	**0.652**	0.621	0.681	Strong
PGI-S	AMRA-3 abdominal pain	Repeated measures correlation	Moderate	108	1523	**0.618**	0.584	0.649	Strong

AMRA-3, three-item Angioedema syMptom Rating scAle; CI, confidence interval; PGI-S, Patient Global Impression of Severity; r_{rm}, repeated measures correlation. Correlation tests are between total scores. Strong correlations (r > 0.50) are indicative of good convergent validity, while moderate correlations (r = 0.30 to 0.50) may still provide some acceptable evidence.

Meaningfulness assessment of a time-to-EoP endpoint

- Within-person correlations between PGI-C and change in PGI-S (correlation for repeated measures, r_{rm} = 0.765) and between PGI-C and percent change in AMRA-3 (r_{rm} = 0.839) exceeded the 0.30 threshold required for use as anchors (**Table 4**).
- Kaplan–Meier curves showed that, at any given timepoint, a greater proportion of participants with improving PGI-S or AMRA-3 scores had already reached EoP than those whose scores remained stable or worsened (median time-to-EoP difference: PGI-S, ~30 min; AMRA-3, ~30-60 min), reinforcing the validity of the PGI-C–based EoP definition through independent, time-to-event evidence.
- Collectively, psychometric, anchor-based, and time-to-event analyses supported the validity of the PGI-C–based EoP definition.

Table 4. Anchor change repeated-measure correlations from 15 minutes to each post-dose timepoint– first attack only

Focus measure	Anchor measure	Method	Number of participants	Number of observations	Within-person correlation (r_{rm})	95% CI lower limit	95% CI upper limit	Degrees of freedom	Empirical relationship
PGI-C score	PGI-S change	Repeated measures correlation	108	1413	**0.765**	0.742	0.787	1304	Suitable anchor
PGI-C score	AMRA-3 percent change	Repeated measures correlation	107	1402	**0.839**	0.822	0.855	1294	Suitable anchor

AMRA-3, three-item Angioedema syMptom Rating scAle; CI, confidence interval; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; r_{rm}, repeated measures correlation. Suitable anchor correlation: r > 0.30.

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D.M.C.: ADARx, Astria Therapeutics, BioCryst, CSL Behring, Gentili Neopharma, Intellia, Ionis, KalVista, Otsuka, Pharvaris, Takeda; Regional Medical Advisory Panel Member for HAEi Central Eastern Europe and the Benelux; **P.H.L.:** Astria, BioCryst, CSL Behring, KalVista, Novartis, Pharvaris, Takeda; **J.A.:** Astria, BioCryst, CSL Behring, Intellia, Ionis, KalVista, Pharming, Pharvaris, Takeda; **A.B.:** Astria, CSL Behring, Intellia, Ionis, KalVista, Pharvaris, Takeda; **J.A.B.:** ADARx, Astria, BioCryst, BioMarin, CSL Behring, Cycle Pharma, Intellia, Ionis, KalVista, ONO Pharmaceutical, Pharming, Pharvaris, Takeda/Shire; **A.F.B.:** Astria, BioCryst, CSL Behring, Intellia, Ionis, KalVista, Pharvaris, Takeda; **P.J.B.:** ADARx, BioCryst, CSL Behring, Intellia, Ionis, KalVista, Pharvaris, Takeda; **T.J.C.:** ADARx, ARGO, Astria, BioCryst, BioMarin, CSL Behring, Grifols, GSK, Intellia, Ionis, KalVista, Pharvaris, Takeda; Director of ACARE International Hereditary Angioedema Center, member of the Medical Advisory Board for the HAE-A; **J.S.J.:** BioCryst, CSL Behring, Cycle Pharma, Intellia, Ionis, KalVista, Pharming, Pharvaris Takeda; **D.S.L.:** BioCryst, CSL Behring, Cycle Pharma, Pharvaris, Takeda; **H.H.L.:** BioCryst, CSL Behring, Intellia, Ionis, Pharming, Pharvaris, Takeda; Medical Advisory Board US HAEA; **W.R.L.:** AstraZeneca, Astria, BioCryst, BioMarin, CSL Behring, Fresenius-Kabi, Grifols, GSK, Intellia, Ionis, KalVista, Magellan, Optinose, Pharming, Pharvaris, Regeneron, Sanofi, Takeda, Teva; **M.E.M.:** AstraZeneca, Astria, BioCryst, Blueprint, Celldex, Cogent, CSL Behring, GSK, Intellia, Ionis, KalVista, Merck, Novartis, Pharming, Pharvaris, Regeneron, Takeda, Teva; **C.R.:** Astria, BioCryst, CSL Behring, Intellia, Ionis, KalVista, Pharvaris; **C.J.R.:** Amgen, GSK, Pfizer, Pharvaris, Sanofi, Takeda; **M.D.S.:** ADRX, Astria, Intellia, Ionis, KalVista, Pharvaris; **D.F.S.:** BioCryst, CSL Behring, Intellia, Ionis, KalVista, Pharvaris, Takeda; **M.-J.H, P.F.:** employee of Seeing Theta; **M.C., J.M.:** employee of Pharvaris, holds stocks in Pharvaris; **R.T.:** ADMA, ARS, AstraZeneca, Astria, BioCryst, CSL Behring, Grifols, GSK, Intellia, Ionis, KalVista, Lilly, Novartis, Pharming, Pharvaris, Sanofi/Regeneron, Takeda; **M.A.R.:** ADARx, Astria, BioCryst, BioMarin, Celldex, CSL Behring, Cycle Pharma, Grifols, Intellia, Ionis, KalVista, Novartis, Pharming, Pharvaris, Sanofi-Regeneron, Takeda.

Acknowledgments: Medical writing services were provided by Sandra Boswell, PhD, and Becky Jarvis, PhD, of Envision Pharma Group, and was funded by Pharvaris.

***RAPIDe-3 trial is a Pharvaris-sponsored clinical trial. ClinicalTrials.gov identifier: NCT06343779.**