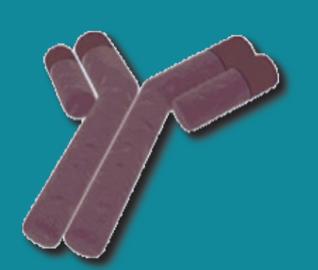


Psychometric properties of patient reported outcome instruments in patients with chronic inducible cold urticaria

ColdU



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Background

- Chronic inducible cold urticaria (ColdU) is characterized by the development of itchy wheals, angioedema, or both in response to cold exposure, potentially impacting the health-related quality of life of patients^{1,2,3}.
- A 24-week, randomized, double-blind, placebo-controlled study (LIBERTY-CINDU CUrIADS: NCT04681729) evaluated the use of dupilumab in patients with ColdU who remained symptomatic despite the use of H1-antihistamine treatment.
- Several patient-reported outcome measures (PROMs) were included in the trial.

Objective

- To assess the psychometric properties of selected PROMs from the trial: Peak Pruritus-Numeric Rating Scale (PP-NRS), Peak Pain-NRS, and Peak Burning Sensation-NRS (PBS-NRS) in patients with ColdU.
- To estimate the within-patient and between-group meaningful change thresholds (MCTs) of these PROMs.

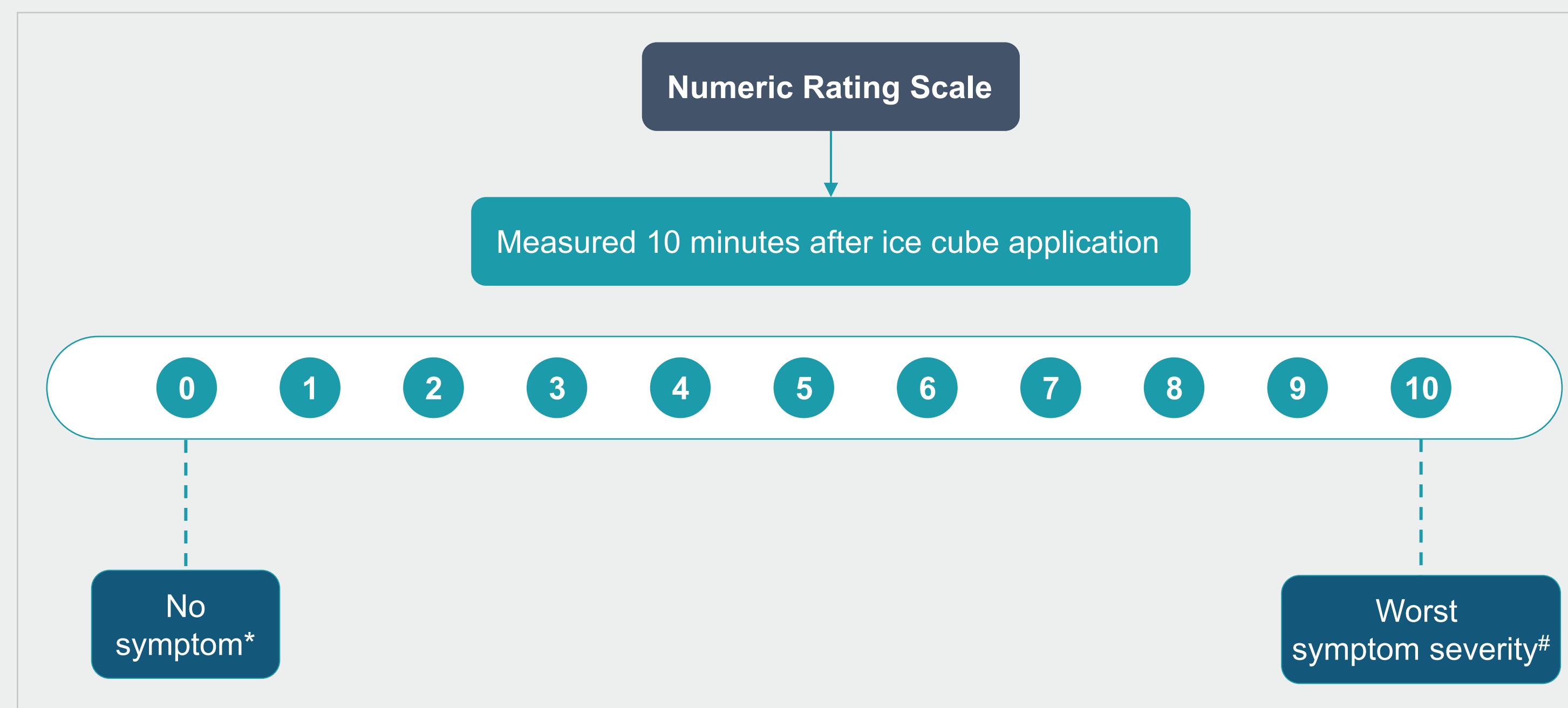
Conclusions

- This study demonstrated the acceptable psychometric properties of PP-NRS, Peak Pain NRS, and PBS-NRS, and provided thresholds to aid interpretation of data.
- The three NRS scores under investigation support their use in clinical trial to capture changes in symptoms experienced by patients with ColdU.

Methods

- The single item PP-NRS, Peak Pain-NRS, and PBS-NRS assessed patient reported symptom severity (Figure 1).

Figure 1. The peak pruritus, peak pain, and peak burning sensation numeric rating scales



*Peak pruritus (PP)-numeric rating scale (NRS): no itch; peak pain-NRS: no pain; peak burning sensation (PBS)-NRS: no burning sensation

#PP-NRS: worst imaginable itch; Peak pain-NRS: worst imaginable pain; PBS-NRS: worst imaginable burning sensation

- Data from the LIBERTY-CINDU CUrIADS trial were used to assess the following properties:
 - Test-retest reliability
 - Convergent validity
 - Known-groups validity
 - Sensitivity to change
 - Within-patient and between-group MCTs

Results

Baseline characteristics

- Psychometric analyses were conducted on 82 patients with ColdU.
- Baseline mean (SD) age: 35.4 (14.9) years; Female: 76.8%.
- High completion rates for the three questionnaires (baseline: 96.3% to Week 24: 77.8%).

Evolution of the scores over time

- At baseline, the mean (SD) PP-NRS score was 6.47 (2.76), which decreased to 3.91 (3.32) by Week 24.
- Similarly, patients reported a lower Peak Pain-NRS score at Week 24 (3.66 [2.96]) compared to baseline (5.62 [3.18]).
- The PBS-NRS score also decreased from 5.85 (3.05) at baseline to 4.14 (3.35) by Week 24.

Test-retest reliability

- All three NRS scores demonstrated close to moderate or low test-retest reliability (Table 1).

Table 1. Test-retest reliability for NRS scores

Scores	Test-retest reliability, ICC (95% CI)			
	N	Using PGIS	N	Using PGIC
PP-NRS	32	0.66 (0.41, 0.82)	21	0.56 (0.18, 0.79)
Peak Pain-NRS	32	0.68 (0.44, 0.83)	21	0.67 (0.34, 0.85)
PBS-NRS	32	0.61 (0.35, 0.79)	21	0.68 (0.36, 0.86)

Note: Stable patients were defined as those patients with no change on PGIS between Weeks 12 and 24 and reporting no change on the PGIC at Week 12 in separate analyses. CI, confidence interval; ICC, Intraclass correlation coefficient; N, number of patients; NRS, Numerical rating scale; PBS-NRS, peak burning sensation NRS; PGIC: Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PP-NRS, peak pruritus NRS.

Construct Validity

- Moderate-to-strong correlations were observed between most scores of similar constructs.
 - Lower-than-predicted correlations were noted between EuroQol 5 dimensions (EQ-5D) Pain/Discomfort item and Cold Urticaria Activity Score (ColdUAS) item 1 which could support the discriminant nature of these measures (Table 2).

Table 2. Convergent and divergent validity at Week 24

Score	PP-NRS, r	Peak Pain-NRS, r	PBS-NRS, r
PP-NRS (N = 56)	-	0.69	0.68
Peak Pain-NRS (N = 56)	0.69	-	0.69
PBS-NRS (N = 56)	0.68	0.69	-
PGIS (N = 56)	0.49	0.43	0.70
WILS (N = 56)	0.50	0.41	0.52
DLQI/CDLQI item 1 [a] (N = 54)	0.50	0.42	0.52
EQ-5D Pain/Discomfort item (N = 54)	-	0.17	-
ColdUAS item 1 (1-week) (N = 40)	0.13	-0.00	0.14
ColdUAS item 2 (1-week) (N = 40)	0.31	0.34	0.42

Spearman correlation coefficients are presented, except for PGIS and DLQI item 1 vs ColdUAS where polychoric correlation coefficients are shown. DLQI item 1[a]: "Over the last week, how itchy, sore, painful, or stinging has your skin been?"; CDLQI item 1: "Over the last week, how itchy, 'scratchy', score or painful has your skin been?"; ColdUAS item 1: "Have you had wheals, or a swelling episode cause by cold?"; ColdUAS item 2: "Did you experience itching, burning, pain, or feeling hot because of cold exposure?". CDLQI, Children's Dermatology Life Quality Index; ColdUAS, Cold Urticaria Activity Score; DLQI, Dermatology Life Quality Index; EQ-5D, EuroQol 5 dimensions; N, Number of observations; NRS, Numerical rating scale; PBS-NRS, peak burning sensation NRS; PGIS, Patient Global Impression of Severity; PP-NRS, peak pruritus NRS; WILS, Wheal intensity Likert scale.

Known-groups validity

- At Week 24, adequate known-groups validity was demonstrated for PP-NRS, Peak Pain-NRS, and PBS-NRS, defined based on PGIS, Dermatology Life Quality Index (DLQI), and urticaria control test (UCT) (all $p < 0.05$).
- Peak Pain-NRS and PBS-NRS demonstrated known-groups validity defined based on ColdUAS Item 2 ($p = 0.05$ for Peak Pain-NRS, $p < 0.01$ for PBS-NRS) at Week 24.

Sensitivity to Change

- Moderate-to-strong correlations were observed for the change in all three NRS scores with most measures.
 - Slightly lower correlations were noted for ColdUAS items (Table 3).
- Significant differences in mean score changes over time were observed for groups defined based on change in PGIS and PGIC for all three NRS scores (all $p < 0.05$).

Table 3. Sensitivity to change: NRS scores correlations between change from baseline to Week 24

Score	PP-NRS, r	Peak Pain-NRS, r	PBS-NRS, r
PP-NRS (N = 55)	-	0.81	0.81
Peak Pain NRS (N = 55)	0.81	-	0.80
PBS-NRS (N = 55)	0.81	0.80	-
PGIS (N = 55)	0.65	0.61	0.60
PGIC (N = 55)	0.55	0.66	0.54
WILS (N = 55)	0.46	0.44	0.45
DLQI/CDLQI item 1 [a] (N = 53)	0.57	0.45	0.43
ColdUAS item 1 (1-week) (N = 35)	0.22	0.22	0.16
ColdUAS item 2 (1-week) (N = 35)	0.32	0.30	0.27

Spearman correlation coefficients are presented. DLQI item 1[a]: "Over the last week, how itchy, sore, painful, or stinging has your skin been?"; CDLQI item 1: "Over the last week, how itchy, 'scratchy', score or painful has your skin been?"; ColdUAS item 1: "Have you had wheals, or a swelling episode cause by cold?"; ColdUAS item 2: "Did you experience itching, burning, pain, or feeling hot because of cold exposure?". CDLQI, Children's Dermatology Life Quality Index; ColdUAS, Cold Urticaria Activity Score; DLQI, Dermatology Life Quality Index; N, Number of observations; NRS, Numerical rating scale; PBS-NRS, peak burning sensation NRS; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PP-NRS, peak pruritus NRS; r, correlation coefficient; WILS, Wheal intensity Likert scale.

Meaningful Change Thresholds

- Correlations ≥ 0.37 were reported between change from baseline to Week 24 in NRS scores and in PGIS and PGIC.
- MCTs for within-patient improvement using PGIS and PGIC as anchors at Weeks 12 and 24 were:
 - PP-NRS: 4 (range: 3–6)
 - Peak Pain-NRS: 3 (range: 2–3)
 - PBS-NRS: 3 (range: 2–5)
- MCTs for between-group improvement were:
 - PP-NRS: 2.7 (range: 2.5–3.3)
 - Peak Pain-NRS: 2.2 (range: 1.6–3.2)
 - PBS-NRS: 2.7 (range: 1.6–3.4)

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CONFLICTS OF INTEREST

SR, CI, IG, RO, and MK are employees of IQVIA who were contracted to conduct psychometric analysis. JM, RM, EZ, LBC, CCC, and EB are employees of Sanofi and may hold stock or stock options in the company. JC is an employee of Regeneron and may hold stock or stock options in the company.



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