Validation of a Scoring Algorithm for the Clinician-Reported Outcome 'Prurigo Activity and Severity (PAS)' Tool: Results Based on Clinical Studies of Dupilumab in Adults with Prurigo Nodularis

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Background

- Prurigo nodularis (PN) is a chronic skin condition, characterised by severe pruritus and multiple localised/generalised pruriginous lesions distributed symmetrically along the extremities and trunk.[1,2]
- Prurigo Activity and Severity (PAS)[a] tool, is a clinician-reported outcome (ClinRO) measure that was used in two parallel, phase 3 double-blind, randomised, placebo-controlled trials (PRIME [NCT04183335] and PRIME2 [NCT04202679]) to evaluate dupilumab in adult patients with PN, uncontrolled on topical therapies.[3,4]

Objectives

- To evaluate the psychometric properties of a PAS score.
- To estimate the within-patient meaningful improvement threshold of this PAS score.

Methods

- A PAS score was derived as the unweighted sum of three items 2, 5a and 5b. **(Table 1)**

Table 1. The PAS scoring system

PAS item	Scoring
Item 2: Estimated number of pruriginous lesions	0 = no lesions to 4 = ≥ 100 lesions
Item 5a: Estimated percentage of pruriginous lesions with excoriations/crusts	0 = 0% to 4 = 76% – 100%
Item 5b: Estimated percentage of healed lesions	0 = 100% to 4 = 0% – 24%

PAS, Prurigo Activity and Severity

- Pooled data from PRIME and PRIME2 trials (N = 311)[4] were used to validate the psychometric properties of the PAS score such as item-to-item correlations, internal consistency, test-retest reliability, construct validity, known-groups validity and sensitivity to change.
- Thresholds for meaningful within-patient improvement were derived from distribution- and anchor-based methods using different PROs and ClinROs as anchors at Week 12 and Week 24.

Results

- A total of 311 patients with PN (mean age: 49.5 years; standard deviation [SD]: 16.1 years; 65.3%, females; mean [SD] PAS score at baseline, 8.5 [1.5]) pooled from the PRIME and PRIME2 clinical trials were included for this analysis.

Item–to–Item correlations

- The item-to-item correlations were sufficient at Week 12 and Week 24 ($r \geq 0.40$), though were lower at baseline.

Internal consistency

- Good internal consistency was found at Week 12 (Cronbach "alpha" = 0.75) and Week 24 (Cronbach "alpha" = 0.77).

Test–retest reliability

- Good test-retest reliability (i.e., Intraclass coefficients [ICC] ≥ 0.70) was observed when stable patients were defined using change in the Patient Global Impression of Severity (PGIS), Investigator's Global Assessment for Prurigo Nodularis Stage (IGA PN-S), and Investigator's Global Assessment for Prurigo Nodularis Activity (IGA PN-A) between Week 8 and Week 12 (ICC range: 0.80–0.89).

Construct validity

- Mostly moderate-to-strong correlations were observed between PAS score and conceptually related-measures (absolute *r*: 0.25–0.87) and weaker-to-moderate correlations with less–related measures (absolute *r:* < 0.5) at baseline and Week 24. (**Table 2**).

Table 2. Construct validity of PAS score at baseline and Week 24

Convergent Validity[a]			Divergent Validity[b]		
Scores	**Baseline *r***	**Week 24 *r***	**Scores**	**Baseline *r***	**Week 24 *r***
IGA PN-Activity	0.62	0.87	WI-NRS	0.15	0.46
IGA PN-Stage	0.59	0.83	Skin Pain-NRS	0.09	0.35
PGIS	0.25	0.61	Sleep-NRS	-0.11	-0.25
PAS Item 4[c]	0.32	0.74	DLQI Total Score	-0.01	0.47
			HADS-A	-0.01	0.29
			HADS-D	0.02	0.30

[a]Calculated using polyserial correlations. [b]Calculated using Spearman's rank correlation. [c]Exact number of pruriginous lesions in a representative area (excluding scars; higher scores = more pruriginous lesions).
DLQI, Dermatology Life Quality Index; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; IGA-PN, Investigator's Global Assessment for Prurigo Nodularis; NRS, Numeric Rating Scale; PAS, Prurigo Activity and Severity; PGIS, Patient Global Impression of Severity; WI-NRS, Worst Itch Numeric Rating Scale.

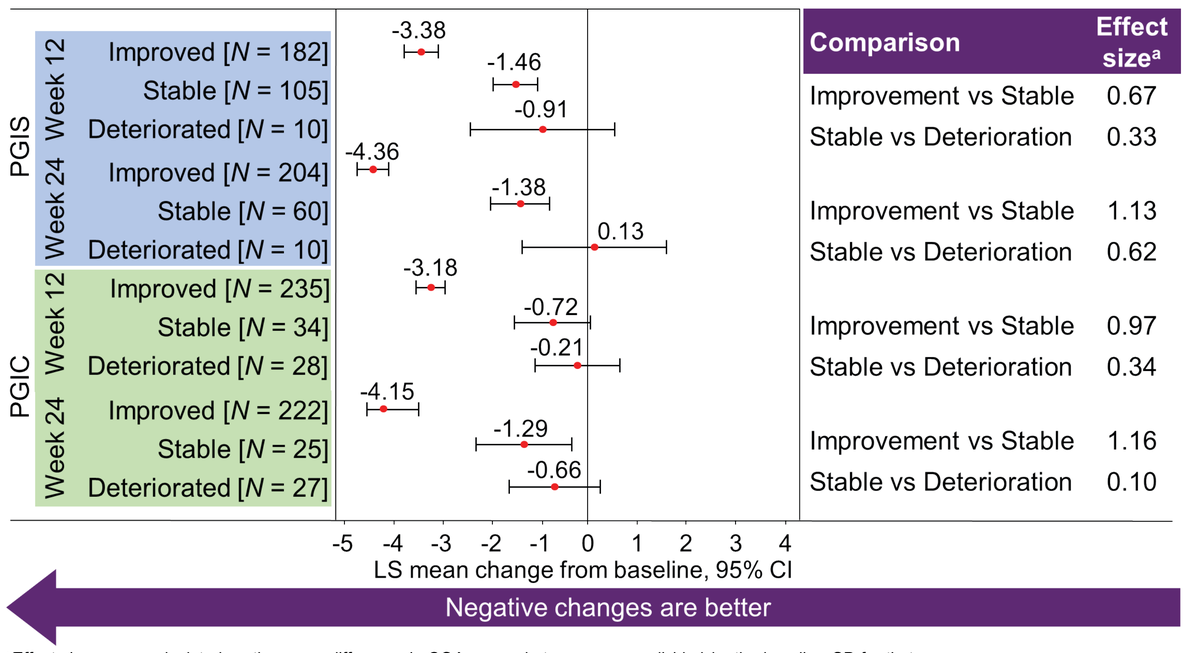
Known-groups validity

- PAS score differentiated well between groups defined by PGIS, IGA PN-S and IGA PN-A (all, $p < 0.0001$) at baseline, Week 12, and Week 24 with moderate-to-large effect sizes (absolute effect size: 0.5–0.8 and ≥ 0.8, respectively) between consecutive group means.

Sensitivity to change

- Statistically significant differences in mean PAS score changes between baseline and Weeks 12 and Week 24 were observed for groups defined using PGIS, PGIC, IGA PN-S and IGA PN-A (all $p < 0.0001$).
- Moderate and large effect sizes were generally observed between stable versus improved groups for PGIS and PGIC (absolute value range: 0.67–1.16) and groups for IGA PN-S and IGA PN-A (absolute value range: 0.43–1.52) (**Figure 1**).

Figure 1. Sensitivity to change of PAS score using absolute change from baseline to Week 12 and Week 24 by PGIC and PGIS groups



Comparison	Effect size[a]
Improvement vs Stable	0.67
Stable vs Deterioration	0.33
Improvement vs Stable	1.13
Stable vs Deterioration	0.62
Improvement vs Stable	0.97
Stable vs Deterioration	0.34
Improvement vs Stable	1.16
Stable vs Deterioration	0.10

[a]Effect sizes were calculated as the mean difference in COA scores between groups divided by the baseline SD for that group.
CI, confidence interval; COA, Clinical Outcome Assessment; LS, least squares; PAS, Prurigo Activity and Severity; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; SD, standard deviation.

Threshold of meaningful improvement

- Correlations ≥ 0.37 (absolute *r*: 0.38–0.79) were reported between change from baseline in PAS scores and in anchor scores at Week 12 and Week 24, suggesting PGIS, PGIC, IGA PN-S and IGA PN-A to be appropriate target anchors. (**Table 3**)

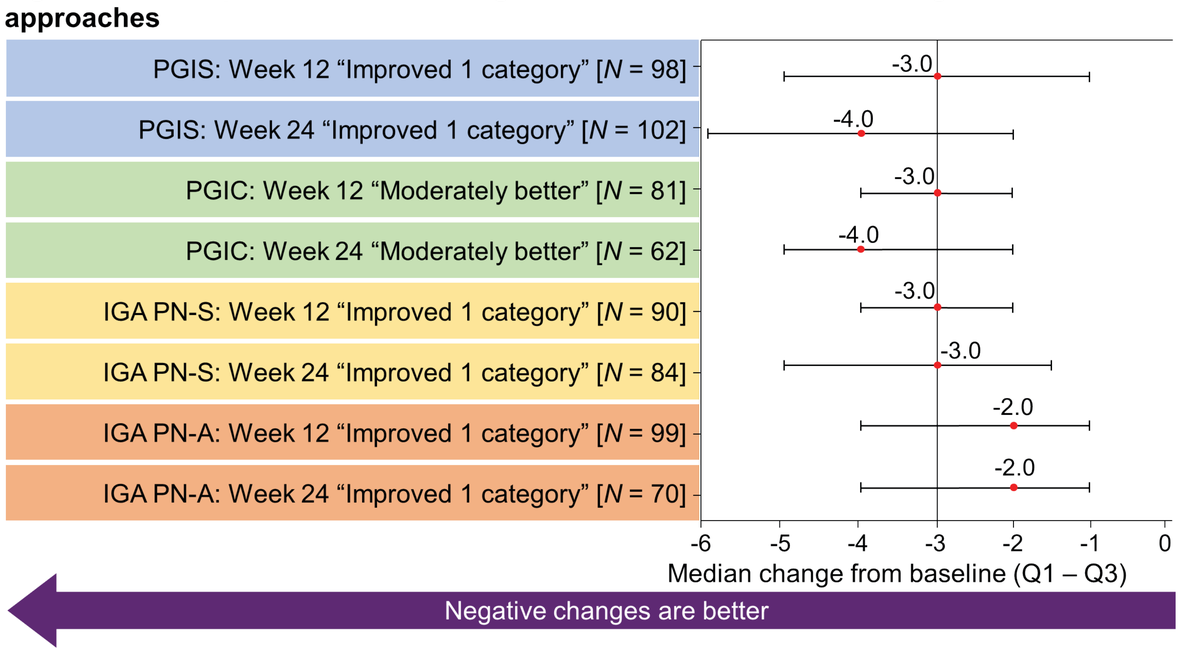
Table 3. Correlation coefficients between change from baseline in PAS score and in anchor scores at Week 12 and Week 24

Polyserial correlations					
Endpoint	**Timepoints**	**Change from baseline in PGIS**	**PGIC score[a]**	**Change from baseline in IGA PN-S**	**Change from baseline in IGA PN-A**
Change from baseline in PAS score	Week 12	0.38	0.50	0.71	0.73
	Week 24	0.53	0.56	0.75	0.79

Appropriate anchors should exhibit a minimum correlation of 0.37.[5]
Polyserial correlations are shown for PAS score with IGA PN-A, IGA PN-S, PGIS.
[a]The actual PGIC response was considered, not the change from baseline.
IGA PN-A, Investigator's Global Assessment for Prurigo Nodularis Activity; IGA PN-S, Investigator's Global Assessment for Prurigo Nodularis Stage; PAS, Prurigo Activity and Severity; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity.

- An absolute change of 3-points (range: 2–4 points; correlation-weighted average = -3.1) represented the within-patient clinically meaningful improvement threshold for PAS score after rounding up to the nearest 1.0 value at Week 24 (**Figure 2**).
- The estimated thresholds exceeded the lowest 95% CI for the "no change" group and the distribution-based results (0.5 x baseline SD = 0.74; Standard error of the measurement with PGIS = 1.14).

Figure 2. Within-patient median change thresholds for PAS score using anchor-based approaches



IGA PN-A, Investigator's Global Assessment for prurigo nodularis Activity; IGA PN-S, Investigator's Global Assessment for Prurigo Nodularis Stage; PAS, Prurigo Activity and Severity; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; Q1, Quartile 1; Q3, Quartile 3

Conclusions

- The PAS score is a fit-for-purpose ClinRO measure for assessing disease activity and severity in adults with PN uncontrolled on topical therapies.
- Based on the anchor-based analysis, a meaningful within-patient improvement threshold of 3-points (range: 2–4) points was estimated for PAS score.

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SR, SW, and DZ: IQVIA — employees
JM, EB, JOM, SW, and DB: Sanofi — employees, may hold stock and/or stock options in the company.
AB, JZ, and RBT: Regeneron Pharmaceuticals — employees, may hold stock and/or stock options in the company.

[a]Previously known as Prurigo Activity Score (PAS) which measures proportion of patients achieving ≥ 75% healed lesions or change in number of lesions from baseline at Week 4, 8, 12 and 24, respectively in PRIME trials.

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