Clinically meaningful change of pruritus numeric rating scale in adults with primary biliary cholangitis with moderate to severe pruritus

Abstract number 857; **Poster THU-291**
(Immune-mediated and cholestatic disease: Clinical aspects)

Cynthia Levy[1], Andreas E. Kremer[2], Anne M. Skalicky[3], Milena Anatchkova[3], Adam Smith[4], Caroline Burk[5], Marvin Rock[5], Chong Kim[5], Susheela Carroll[6], Daria B. Crittenden[6], Ariane Kawata[3], David Jones[7]

[1]Schiff Center for Liver Diseases, Division of Digestive Health and Liver Diseases, University of Miami Miller School of Medicine, Miami, FL, United States; [2]Department of Gastroenterology and Hepatology, University of Zürich, University Hospital Zürich, Zurich, Switzerland; [3]Patient-Centered Research, Evidera, Inc., Wilmington, NC, United States; [4]Patient-Centered Research, Evidera, Inc., Hammersmith, London, United Kingdom; [5]Global Value and Access-Global Health Economics and Outcomes Research (GHEOR), Gilead Sciences Inc., Foster City, CA, United States; [6]Clinical Development, Gilead Sciences Inc., Foster City, CA, United States [7]Faculty of Medical Science, Newcastle University, Newcastle, United Kingdom

Copies of this poster obtained through QR (Quick Response) and/or text key codes are for personal use only and may not be reproduced without written permission of the authors.

Conclusions

- A decrease of ≥3 points in the pruritus NRS represents a clinically meaningful change for PBC patients with moderate to severe pruritus based on data from the RESPONSE study.
- This validates the clinical relevance of the pruritus reduction seen with seladelpar in RESPONSE.

Plain language summary

- The Pruritus Numeric Rating Scale (PNRS) is a single question that measures itch severity from 0 (no itch) to 10 (worst imaginable itch).
- Researchers asked patients with Primary Biliary Cholangitis (PBC) to answer this question before and after treatment to see if their itch changed.
- A decrease of 3 points or more in PNRS represents a meaningful change in itch for patients with PBC in the RESPONSE trial.

Abbreviations: eCDF, empirical cumulative distribution function; PBC, primary biliary cholangitis; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PNRS, Pruritus Numeric Rating Scale; PROM, patient-reported outcome measure; SD, standard deviation; SEM, standard error of measurement.

References:
1. Bowlus CL, et al. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. *Hepatology.* 2022;00:1–44. **2.** Phan NQ, et al. Assessment of pruritus intensity: Prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. *Acta Derm Venereol.* 2012; 92(5):502-7. **3.** Vernon M, et al. Clinically meaningful change in itch intensity scores: An evaluation in patients with chronic kidney disease-associated pruritus. *J Am Acad Dermatol.* 2021 84(4):1132-1134. **4.** Skalicky A, et al. Capturing the experience and impact of itch in patients with primary biliary cholangitis (PBC). Poster Mo1486. Digestive Disease Week®(DDW), San Diego, CA, May 18–21, 2019. **5.** National Institute of Mental Health (NIMH). Patient Global Impressions scale - Change, Improvement, Severity (PGI-C, PGI-I, PGI-S). 2025. URL: https://eprovide.mapi-trust.org/instruments/patient-global-impressions-scale-change-improvement-severity. **6.** Revicki D, et al. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J Clin Epidemiol.* 2008;61(2):102-109. **7.** Food and Drug Administration. Guidance for industry. Patient-reported outcome measures: Use in medical product development to support labeling claims. *U.S. Department of Health and Human Services;* 2009. **8.** Food and Drug Administration. Patient-focused drug development: Incorporating clinical outcome assessments into endpoints for regulatory decision-making. Guidance for industry, Food and Drug Administration staff, and other stakeholders. *U.S. Department of Health and Human Services;* 2023. **9.** Guyatt GH, et al. Methods to explain the clinical significance of health status measures. Mayo Clin Proc. 2002 Apr;77(4):371-83. **10.** FDA Livdelzi Integratted Reviewiw, Sectioin 16.5 Interpretatioin of Clinical Meaningfulness of the Pruritus Numerical Rating Scale. Page 423.

Acknowledgments: Medical writing was provided by Maddy L. Dyer, PhD, (PPD clinical research business of Thermo Fisher Scientific) in accordance with Good Publication Practice guidelines and was funded by Gilead Sciences, Inc.

Disclosures: This study was funded by Gilead Sciences, Inc. CB, CK, DBC, MR, and SC are employed by Gilead Sciences. AEK is an advisor / consultant for Abbvie, Advanz, Alentis, AlphaSigma, Astellas, AstraZeneca, Attovia Therapeutics, Avior, Bayer, BMS, Böhringer-Ingelheim, CymaBay, Dr. Falk, Gilead, GSK, Guidepoint, Intercept, Ipsen, Mirum, MSD, Novo Nordisk, Rectify Pharma, Roche, and Takeda. AK, AS, AMS and MA work for Evidera who received funding for conducting/presenting this data. CL holds research grants from Calliditas, Cymabay, Escient, Gilead, GSK, Ipsen, Kowa, intercept, Mirum, Target RWE, and Zydus.

Correspondence: Cynthia Levy (clevy@med.miami.edu).

INTRODUCTION

- **Cholestatic pruritus** affects up to 70%–80% of patients with **primary biliary cholangitis (PBC)**, a progressive autoimmune liver disease.[1]
- The **Pruritus Numeric Rating Scale (PNRS)**, a single concept item patient-reported outcome measure (PROM) assessing the severity of worst itch over the past 24 hours, has been used to evaluate antipruritic treatment effects in clinical trials.[2,3]
- A significant reduction in pruritus was seen with seladelpar in the RESPONSE study.
- **Clinically meaningful change** of the PNRS has not previously been assessed quantitatively in patients with PBC who experience cholestatic pruritus.
- This is important because the magnitude of change in PNRS scores must represent a **meaningful improvement for patients** for antipruritic treatment effects to be clinically relevant.[3]
- Examining the **psychometric properties** of the PNRS in patients with PBC is also important to ensure that the PROM is valid, reliable, and responsive in this target population (poster #TH-291).

OBJECTIVE

- To quantitatively estimate the **clinically meaningful within-person change** in pruritus on the **PNRS** for patients with PBC and moderate to severe pruritus.

METHODS

Design and patients

- This study used data from the randomized, placebo-controlled, phase 3 **RESPONSE (NCT04620733) trial of seladelpar.** Data from the active and placebo arms up to month 6 were pooled and blinded for anchor-based analyses.
- The analysis included patients with **moderate to severe pruritus**, defined as scoring ≥4 on the PNRS at baseline.
- Prior to RESPONSE, a separate **cognitive interview study** was conducted with adults with PBC and **moderate to severe pruritus** to evaluate meaningful change.[4]

Measures

- The 11-point **PNRS** (range: 0=no itch to 10=worst imaginable itch) with 24-hour recall was collected daily for 6 months from run-in (up to 2 weeks before day 1 [treatment initiation]) then for seven consecutive days each month until month 12.
- The **Patient Global Impression of Severity of pruritus (PGI-S)**[5] measured experiences in the past 7 days, and it was collected at run-in, day 1, month 1, and every 3 months until month 12.
- The **Patient Global Impression of Change of pruritus (PGI-C)**[5] measured experiences since the start of the study, and it was collected at month 1 and every 3 months until month 12.

Analyses

- Anchor-based analyses were used to evaluate potential thresholds of clinically meaningful change in PNRS using the PGI-S and PGI-C.
- The **suitability of the PGI-S, and PGI-C anchors** were tested by correlating their change scores with PNRS change scores at month 6 to confirm adequate associations. Moderate to strong correlations (|r| ≥0.30) were hypothesized.[6]
- Meaningful change estimates were derived using **anchor-based methods and empirical cumulative distribution function (eCDF) curves.**
- **Distribution-based methods** provided the observed degree of variation in the sample (SD and SEM). These methods compare the difference in a scale-based outcome measure to the pre-specified threshold value of its uncertainty (e.g. SD and SEM) which facilitates understanding minimum clinically important difference.[7,8,9]
- Estimates were triangulated to determine the **clinically meaningful within-person change** including examining feedback from patient interviews evaluating PNRS meaningful change.

RESULTS

Patients

- Of the 193 patients enrolled in the RESPONSE trial, **72** (seladelpar, n=49; placebo, n=23) patients who had moderate to severe pruritus (mean [range], 53.8 [32–75] years of age; 97.2% female) were included in the current analysis.
- Prior to RESPONSE, **12** patients were included in qualitative interviews. Most of the study participants were female (n=11; 91.7%). Patients were Asian (n=1; 8%), Black or African American (n=1; 8%), American Indian (n=1, 8%), and White (n=12; 100%; races not mutually exclusive).[4]

PNRS anchor correlations

- At month 6, change in the PNRS was strongly correlated with the PGI-C (r=-0.52) and change in the PGI-S (r=0.50; **Table 1**). Therefore, the **PGI-S and PGI-C were suitable anchor measures** to evaluate clinically meaningful change of the PNRS.

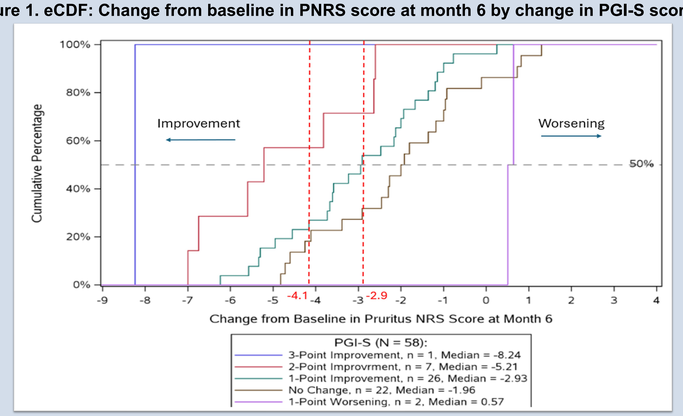
eCDF curves

- eCDF curves had clear separation between PNRS change scores and anchor categories reflecting treatment improvement between baseline and month 6 for PGI-S **(Figure 1)** and PGI-C **(Figure 2).**

Table 1. Correlations between change scores of PNRS with PGI anchors, baseline to month 6.

	Moderate to Severe Pruritus Sample N, Spearman correlation (*p*-value) with PNRS				
PNRS score change by PGI categories	**Overall score change**	**≥1-point score change**	**≥2-point score change**	**≥3-point score change**	**≥4-point score change**
PGI-S [N, r, (p-value)]	58, 0.50 (<0.0001)	49, 0.39 (0.005)	36, 0.38 (0.024)	24, 0.46 (0.022)	17, 0.77 (<0.001)
PGI-C [N, r, (p-value)]	56, -0.52 (<0.0001)	47, -0.42 (0.003)	34, -0.40 (0.019)	22, -0.24 (0.289)	15, -0.33 (0.229)

Figure 1. eCDF: Change from baseline in PNRS score at month 6 by change in PGI-S score.



The vertical, dashed, red lines indicate the meaningful change threshold (upper and lower bounds) for the PGI-S.

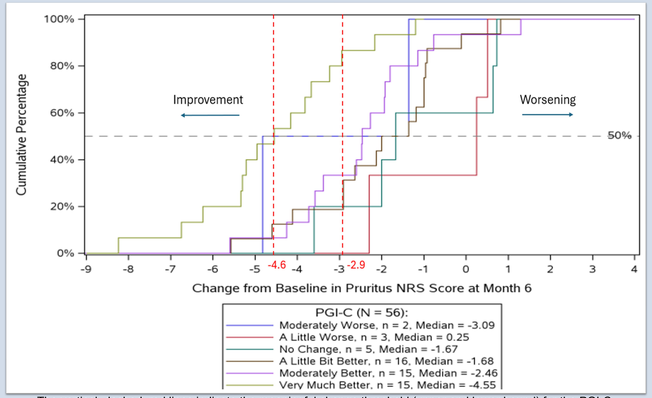
Anchor-based estimates

- Anchor-based estimates of mean (median) change on the PNRS corresponded to a **-2.98 (-2.93) point decrease for a 1-point improvement** in PGI-S, and a **-4.80 (-5.21) point decrease for a 2-point improvement** in PGI-S**.**
- Using PGI-C, mean (median) changes on the PNRS among patients who were **"a little bit better" were -2.04 (-1.68)** and those among patients who were **"moderately better" were -2.44 (-2.46).**
- The mean (median) change on the PNRS was -2.01 (-1.96) in patients with no change on the PGI-S and -1.18 (-1.67) in patients with no change on the PGI-C.
- A one-category improvement on the four-category PGI-S scale and a response of "moderately better" in the PGI-C were considered acceptable to support further anchor-based meaningful change analyses.[10]
- On the anchor-based analysis, >20% of patients who reported "no change" on the PGI-S or "no change" on the PGI-C were misclassified as experiencing meaningful change.
- To reduce the misclassification rate for participants reporting 1-point improvement on the PGI-S to 20%, the meaningful change threshold range was determined as ≥4.1-point improvement in pruritus PNRS score as the higher bound and a 2.9-point improvement as the lower bound **(Figure 1)**.

Anchor-based estimates, continued

- For the PGI-C, ≥4.6 was the higher bound and 2.9 was also the lower bound **(Figure 2)**.
- Therefore, the anchor-based analysis using both the PGI-S and PGI-C as the anchor scales suggests a possible threshold range of -2.9- to -4.6-point improvement on the PNRS in patients with moderate-to-severe pruritus.

Figure 2. eCDF: Change from baseline in PNRS at month 6 by PGI-C.



The vertical, dashed, red lines indicate the meaningful change threshold (upper and lower bound) for the PGI-C.

Figure 3. Supportive interview quotes of PNRS 3-point meaningful score change.

INTERVIEWER: How much would your itch improve if it moved from a six on the scale to a three on the scale?

001-010: *I think it would be great not to be sitting there scratching during church and not to be itching when you get, the minute you get hot. I think it'd be great if I wasn't scratching in front of people as much. I think a three and I'd expect once in a while to have some itch, but I'm so afraid it's going to get worse. The disease is going to progress.*

INTERVIEWER: If you are in a clinical trial and you're seeking treatment for your itch, you're at the six up here on the top of the scale, for you to feel like the treatment is working, where would you want to move to on the scale?

001-006: *I think anything three or less would be success. Three I can deal with as a symptom of PBC that is just there but isn't bad, isn't something I can't manage or deal with.*

Distribution-based estimates

- Distribution-based estimates of the PRNS change from baseline were 0.36 (0.25 standard deviation [SD]) – 0.72 (0.50 SD) and 0.54 (SEM). Previous research suggests that a SEM of 1 or 0.5 SD may constitute a group-level threshold for meaningful change while 0.2 SD may represent a lower boundary for a small effect.[7,8,9]

Qualitative interviews

- Of the 12 qualitative interviews participants, 50% agreed that a ≤3-point improvement on the PNRS indicated a clinically meaningful change **(Figure 3).**[4]
- Cumulatively, results from anchor-based analyses, distribution-based analyses, and qualitative interviews suggest that at least a 3-point decrease represents the starting point for clinically meaningful change in PNRS from the patient perspective.

LIMITATIONS

- One limitation was some small sample sizes in the anchor categories.
- Furthermore, missing data may have biased the meaningful within-patient change analysis.