Meaningful Change Thresholds for the Psoriasis Symptoms and Signs Diary
A Secondary Analysis of a Randomized Clinical Trial

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Importance Change from baseline score on the validated Psoriasis Symptoms and Signs Diary (PSSD) is a widely used, patient-reported end point in clinical trials for psoriasis. Meaningful score change thresholds anchored to patient-reported assessments have not been established in a clinical trial setting.

Objective To evaluate meaningful within-patient score change thresholds for the PSSD using data from the phase 3 Program to Evaluate the Efficacy and Safety of Deucravacitinib, a Selective TYK2 Inhibitor (POETYK), PSO-1 clinical trial, which compared the efficacy and safety of deucravacitinib vs placebo and apremilast among adults with moderate to severe plaque psoriasis.

Design, Setting, and Participants In this predefined analysis using data from the POETYK PSO-1 multicenter, randomized, double-blind, placebo-controlled phase 3 clinical trial, conducted from August 7, 2018, to September 2, 2020, 666 adults with moderate to severe plaque psoriasis completed the PSSD daily throughout the trial. Meaningful change thresholds were derived by anchoring mean PSSD score change from baseline to week 16 to category improvements on the Patient Global Impression of Change (PGI-C) and the Patient Global Impression of Severity (PGI-S).

Interventions Deucravacitinib, 6 mg, once daily; placebo; or apremilast, 30 mg, twice daily.

Main Outcome and Measures The main outcome was score change from baseline to week 16 on the PSSD, anchored to the PGI-C and PGI-S.

Results The trial included 666 patients (mean [SD] age, 46.1 [13.4] years; 453 men [68.0%]). Three thresholds were identified using an analysis set of 609 patients. Score improvement of at least 15 points from baseline reflected meaningful within-patient change anchored to the PGI-C. Score improvements of 25 points were supported by both the PGI-C and the PGI-S, while a 30-point score change identified patients with greater improvements in their psoriasis symptoms and signs.

Conclusions and Relevance This analysis suggests that PSSD score improvements of 15, 25, or 30 points represent increasing improvements in disease burden that are meaningful to patients with psoriasis.

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The Psoriasis Symptoms and Signs Diary (PSSD) is a validated patient-reported outcome instrument that assesses patient-perceived psoriasis sign and symptom severity. A PSSD score change of ~40 points from baseline, derived with reference to clinician-assessed anchors, has been proposed as a threshold reflecting clinically meaningful improvement. However, regulatory guidelines, including recent draft guidance issued by the US Food and Drug Administration, recommend that thresholds defining responders on patient-reported outcome instruments be derived using patient-reported, rather than clinician-rated, anchor-based methods and suggest the Patient Global Impression of Change (PGI-C) and the Patient Global Impression of Severity (PGI-S) as suitable anchors. A meaningful within-patient change threshold (MWPTC) for the PSSD using patient-reported anchors has not been identified in clinical trials, to our knowledge. We describe the determination of MWPTCs for the PSSD incorporating patient perspectives using pooled, treatment-blinded PSSD, PGI-S, and PGI-C data from baseline to week 16 in the Program to Evaluate the Efficacy and Safety of Deucravacitinib, a Selective TYK2 Inhibitor (POETYK), PSO-1, a recent phase 3 clinical trial in plaque psoriasis.

Methods

POETYK PSO-1 was conducted from August 7, 2018, to September 2, 2020, in accordance with the Declaration of Helsinki. Independent institutional review board approval was obtained from all 154 sites, and all participants provided written informed consent (NCT03624127) (trial protocols and statistical analysis plans in Supplement 1), which applies to this analysis. The clinical trial collected patients, baseline demographics, including race and ethnicity (patients were categorized as Asian, Black, White, or other). The secondary analysis presented here did not stratify patients by race or ethnicity. Patients (N = 666; eFigure 1 in Supplement 2) completed the PSSD daily throughout the trial, rating 5 skin symptoms (itch, pain, stinging, burning, and tightness) and 6 skin signs (dryness, cracking, scaling, shedding or flaking, redness, and bleeding) associated with psoriasis on an 11-point scale from 0 (absent) to 10 (worst imaginable). If more than 3 items were missing, the domain score was considered missing. To obtain symptom and sign scores, responses within each domain were averaged and multiplied by 10. Domain summary scores were averaged to derive total scores ranging from 0 to 100; higher scores indicated greater disease burden. Weekly scores were calculated by averaging daily scores for each 7-day period; baseline PSSD scores were calculated from daily diary data collected during screening. If more than 3 days of the weekly period were missing, that week’s score was set to missing.

Any patient who completed at least 1 PSSD item at baseline and a postbaseline visit was included in the derivation analysis (n = 609; deucravacitinib, n = 303; placebo, n = 150; apremilast, n = 156). At week 16, patients responded to the PGI-C question, “Since you started taking the study medication, how would you rate the overall impact of psoriasis on your life currently?” on a 7-point scale ranging from very much better to very much worse. At baseline and week 16, patients responded to the PGI-S question, “How severe are your psoriasis symptoms currently?” using a scale from 0 (absent) to 3 (severe).

With all treatment groups combined, patients were grouped according to their responses on the anchors. Polysomial correlations were calculated between category changes on the anchors and change from baseline in the PSSD domain and total scores at week 16; a coefficient of at least 0.4 was considered suitable for use. With each anchor group, the mean (SD) PSSD score change from baseline, the 95% CI, and the standardized effect size (SES) were calculated. The smallest improvement category on each anchor with an SES of at least 0.5 and a significant P value was identified (P ≤ .05 [2-sided]) from a paired (within-samples) t test. The lowest point outside the overlap in the 95% CI between the anchor group with no change and the improved group constituted the preliminary estimate. All analyses were performed using SAS, version 9.4 or higher (SAS Institute Inc).

Anchor-based and distribution-based estimates (0.5 SDs and standard error of measurement [SEM]) were triangulated. Distribution-based approaches yield the lowest score change exceeding that expected to occur by chance; they cannot determine patient-perceived meaningfulness. Thus, anchor-based analysis formed the primary approach, while distribution-based methods were supportive. This process was repeated for the change from baseline in each individual PSSD item.

Cumulative distribution functions were generated for each anchor category. Any given point on the continuous line indicated the cumulative proportion of patients who reported that degree of score change from baseline or lower. Derived MWPTCs were applied to unblinded data from POETYK PSO-1 after database lock to compare the cumulative distribution of patients achieving meaningful PSSD responses at week 16 by treatment group. These cumulative distribution functions permit visualization of between-group differences in within-patient PSSD score changes from baseline.
Results

The trial included 666 patients (mean [SD] age, 46.1 [13.4] years; 453 men [68.0%]). Of the 601 patients who completed the PGI-S and PSSD at baseline, 481 patients completed the PGI-S and PSSD at week 16, and 486 patients completed the PGI-C and PSSD at week 16. Of the 666 included patients, 121 (18.2%) were Asian, 6 (0.9%) were Black, 534 (80.2%) were White, and 5 (0.8%) identified their race as “other.” The secondary analysis did not collect data on race or ethnicity. Correlation coefficients between week 16 change from baseline in each PSSD domain, and each anchor (0.541-0.606) indicated suitability for MWPCT derivation (eTable I in Supplement 2).

Table. Anchored Mean PSSD Domain and Total Score Change From Baseline at Week 16 in the POETYK PSO-1 Trial

<table>
<thead>
<tr>
<th>Change category</th>
<th>PSSD symptom score</th>
<th>PSSD sign score</th>
<th>PSSD total score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) CFB [95% CI]</td>
<td>SES</td>
<td>Mean (SD) CFB [95% CI]</td>
</tr>
<tr>
<td>Patient Global Impression of Change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very much better (n = 187)</td>
<td>−36.3 (24.4) [−39.9 to −32.8]</td>
<td>−1.42</td>
<td>−39.9 (23.2) [−43.3 to −36.6]</td>
</tr>
<tr>
<td>Moderately better (n = 87)</td>
<td>−27.9 (21.4) [−32.5 to −23.7]</td>
<td>−1.09</td>
<td>−29.7 (19.4) [−33.8 to −25.6]</td>
</tr>
<tr>
<td>A little better (n = 96)</td>
<td>−18.7 (19.9) [−22.8 to −14.7]</td>
<td>0.73</td>
<td>−19.1 (18.2) [−22.8 to −15.5]</td>
</tr>
<tr>
<td>No change (n = 69)</td>
<td>−5.7 (21.5) [−10.9 to −0.6]</td>
<td>0.22</td>
<td>−6.1 (22.2) [−11.5 to −0.8]</td>
</tr>
<tr>
<td>A little worse (n = 15)</td>
<td>−8.5 (21.0) [−20.1 to 3.1]</td>
<td>0.33</td>
<td>−8.3 (18.9) [−18.7 to 2.2]</td>
</tr>
<tr>
<td>Moderately worse (n = 13)</td>
<td>1.8 (23.6) [−12.5 to 16.0]</td>
<td>0.19</td>
<td>0.07 (19.4) [−11.8 to 11.6]</td>
</tr>
<tr>
<td>Very much worse (n = 19)</td>
<td>2.1 (14.3) [−4.8 to 9.0]</td>
<td>0.08</td>
<td>2.9 (14.4) [−4.0 to 9.9]</td>
</tr>
</tbody>
</table>

Patient Global Impression of Severity

<table>
<thead>
<tr>
<th>Change category</th>
<th>Mean (SD) CFB [95% CI]</th>
<th>SES</th>
<th>Mean (SD) CFB [95% CI]</th>
<th>SES</th>
<th>Mean (SD) CFB [95% CI]</th>
<th>SES</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Point improvement (n = 21)</td>
<td>−48.2 (26.9) [−60.4 to −35.9]</td>
<td>−1.88</td>
<td>−51.1 (25.3) [−62.6 to −39.6]</td>
<td>−2.00</td>
<td>−49.6 (25.6) [−61.3 to −38.0]</td>
<td>−1.94</td>
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<tr>
<td>2-Point improvement (n = 124)</td>
<td>−38.2 (26.3) [−42.8 to −31.5]</td>
<td>−1.49</td>
<td>−41.6 (24.4) [−45.9 to −37.2]</td>
<td>−1.62</td>
<td>−39.9 (24.6) [−44.2 to −35.5]</td>
<td>−1.56</td>
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<tr>
<td>1-Point improvement (n = 186)</td>
<td>−26.5 (19.6) [−29.3 to −23.6]</td>
<td>−1.03</td>
<td>−27.7 (18.5) [−30.4 to −25.0]</td>
<td>−1.08</td>
<td>−27.1 (18.6) [−29.8 to −24.4]</td>
<td>−1.06</td>
</tr>
<tr>
<td>No change (n = 132)</td>
<td>−5.2 (17.7) [−8.2 to −2.2]</td>
<td>0.20</td>
<td>−6.3 (17.7) [−9.3 to −3.2]</td>
<td>−0.24</td>
<td>−5.7 (17.1) [−8.7 to −2.8]</td>
<td>−0.22</td>
</tr>
<tr>
<td>1-Point worsening (n = 17)</td>
<td>−1.1 (21.4) [−12.1 to 9.9]</td>
<td>0.04</td>
<td>−1.5 (21.7) [−12.6 to 9.7]</td>
<td>−0.06</td>
<td>−1.3 (21.5) [−12.3 to 9.8]</td>
<td>−0.05</td>
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<tr>
<td>2-Point worsening (n = 0)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>3-Point worsening (n = 1)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
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</table>

Abbreviations: CFB, change from baseline; NA, not applicable; PSSD, Psoriasis Symptoms and Signs Diary; SES, standardized effect size.

Figure 1. Cumulative Distribution Function for Psoriasis Symptoms and Signs Diary (PSSD) Total Score Change From Baseline to Week 16 With All Treatment Groups Combined

A, Anchored to the Patient Global Impression of Change (PGI-C). B, Anchored to the Patient Global Impression of Severity (PGI-S). The horizontal dashed line indicates the median. The vertical line at zero indicates no change.
better PGI-C category (mean [SD] change from baseline: PSSD symptom score, –18.7 [19.9] [95% CI, –32.5 to 23.7]; P < .001; PSSD sign score, –19.1 [18.2] [95% CI, –22.8 to –15.5]; P < .001; PSSD total score, –18.9 [18.6] [95% CI, –22.7 to –15.2]; P < .001) and the 1-point improvement PGI-S category (mean [SD] change from baseline: PSSD symptom score, –26.5 [19.6] [95% CI, –29.3 to –23.6]; P < .001; PSSD sign score, –27.7 [18.5] [95% CI, –30.4 to –25.0]; P < .001; PSSD total score, –27.1 [18.6] [95% CI, –29.8 to –24.4]; P < .001) each showed significant within-group improvements in week 16 PSSD score, with medium to large SES (Table). Changes from baseline from –14.7 to –15.5 points were the lowest levels of change falling outside the 95% CI for the no-change group and within that of the improved group on the PGI-C; changes from baseline from –23.6 to –25.0 points were the lowest levels of change falling outside the 95% CI for the no-change group and within that of the improved group on the PGI-S (Table). Cumulative distribution function curves for change from baseline in PSSD total score, using each anchor, showed clear separation between the no-change groups and each improvement category, indicating that the response categories on the anchor scale adequately discerned the difference in scores (Figure 1). eFigures 2 and 3 in Supplement 2 show similar cumulative distribution function curves for PSSD domain scores.

Figure 2. Cumulative Proportion of Patients Reporting Any Change From Baseline in Psoriasis Symptoms and Signs Diary (PSSD) Total Score at Week 16 of POETYK PSO-1, by Treatment Group

The horizontal dashed line indicates the median. The vertical line at zero indicates no change. The vertical lines at –15, –25, and –30 indicate meaningful change.

The interpretability of patient-reported outcome end points is best established with reference to MWPC Ts derived from patient-reported anchors rather than clinician assessments.10 Armstrong et al12 recommended a −40-point change from baseline threshold on the PSSD to indicate a minimum clinically meaningful improvement, derived from clinician-rated anchors; however, smaller changes in score may be meaningful to patients themselves. The use of the PGI-C and PGI-S as anchors for determining patient-relevant change measured by the PSSD therefore constitutes an important advance in interpreting changes in PSSD scores. Moreover, this anchored analysis conforms to published credibility criteria13 and regulatory guidelines for determining MWPC Ts.

Limitations
This study has some limitations. The lowest MWPC T identified, −15 points, corresponds to a rating of change rather than the rating of concept recommended by some researchers to overcome present-state bias.12-15 In addition, the applicability of MWPC Ts for improvement to worsening psoriasis symptoms or signs has not been examined.16

Conclusions
In this analysis, data from the POETYK PSO-1 trial anchored to responses on the PGI-C established PSSD domain and total score decreases of 15 points as meaningful to patients with psoriasis. The patient-perceived meaningfulness of a −25-point change from baseline is supported by both the PGI-C and the PGI-S, while a −30-point MWPC T identified patients who reported higher improvement on the PGI-C. The determination of MWPC Ts allows for responder analyses of the PSSD score change from baseline, enhancing the patient-relevant interpretation of this widely used instrument in clinical trials of psoriasis.
Meaningful Change Thresholds for the Psoriasis Symptoms and Signs Diary

Brief Report Research

the accuracy of the data analysis.

Concept and design: Strober, Zhuo, Becker, Zhong, Kisa.

Acquisition, analysis, or interpretation of data: Papp, Gordon, Zhuo, Becker, Zhong, Beaumont, Pham, Kisa, Napoli, Banerjee, Armstrong.

Drafting of the manuscript: Zhong, Pham.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Beaumont, Pham.

Obtained funding: Zhuo.

Administrative, technical, or material support: Papp, Zhong, Pham, Armstrong.

Supervision: Strober, Zhuo, Zhong, Pham, Kisa, Napoli.

Conflict of Interest Disclosures: Dr Papp reported receiving grants and personal fees from Bristol Myers Squibb Co during the conduct of the study; and serving as a speaker and investigator for AbbVie, Amgen, Eli Lilly, Galderma, Janssen, Leo Pharma, Novartis, Bausch Health, and UCB outside the submitted work. Dr Gordon reported receiving grants from Bristol Myers Squibb Co during the conduct of the study; grants and personal fees from AbbVie, Boehringer Ingelheim, Eli Lilly, Novartis, UCB, Janssen; and personal fees from Celgene, Amgen, Almirall, Dermira, Dermavant, Leo Pharma, and Pfizer, Sun, Union, and Moonlake outside the submitted work. Dr Strober reported receiving personal fees from Bristol Myers Squibb, AbbVie, Janssen, Eli Lilly, Amgen, Novartis, Talecris, and UCB outside the submitted work. Dr Zhuo reported being employed by and holding stock in Bristol Myers Squibb during the conduct of the study. Dr Zhong reported being employed by and holding stock in Bristol Myers Squibb during the conduct of the study. Ms Beaumont reported her employer receiving funding from Bristol Myers Squibb to conduct the analytic planning and execution activities associated with this research during the conduct of the study. Dr Kisa reported being employed by and holding stock in Bristol Myers Squibb during the conduct of the study. Dr Napoli reported being employed by and holding stock in Bristol Myers Squibb during the conduct of the study. Dr Banerjee reported being employed by and holding stock in Bristol Myers Squibb during the conduct of the study. Dr Armstrong reported receiving research funding from and serving as a scientific advisor and speaker for AbbVie and Bristol Myers Squibb; receiving personal fees from Almirall, Arcutis, Beiersdorf, Modernizing Medicine, Regeneron, and Sun Pharma; receiving research funding from and serving as a scientific advisor for ASLAN, Dermavant, Eli Lilly, Galderma, Incyte Research, Janssen, Leo Pharma, Nimbus, Novartis, Ortho Derm, Pfizer, Sanofi Genzyme, and UCB; and serving on the data safety monitoring board for Boehringer Ingelheim and Parexel outside the submitted work. No other disclosures were reported.

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REFERENCES


