Psoriasis: Targets and Therapy

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ORIGINAL RESEARCH

# The Physician Global Assessment and Body Surface Area composite tool is a simple alternative to the Psoriasis Area and Severity Index for assessment of psoriasis: post hoc analysis from PRISTINE and PRESTA

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Jessica A Walsh[1]
Heather Jones[2]
Lotus Mallbris[2]
Kristina Callis Duffin[3]
Gerald G Krueger[3]
Daniel O Clegg[1]
Annette Szumski[4]

[1]Division of Rheumatology, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA; [2]Inflammation and Immunology, Global Medical Affairs, Pfizer, Collegeville, PA, USA; [3]Department of Dermatology, University of Utah School of Medicine, Salt Lake City, UT, USA; [4]Pfizer Business Unit (PBU) Syneos Health, Princeton, NJ, United States

**Background:** The product of Physician Global Assessment and Body Surface Area (PGA × BSA) is a new outcome measure for psoriasis severity and response to therapy. The objective of this study was to evaluate PGA × BSA as an alternative to Psoriasis Area and Severity Index (PASI) for psoriasis assessments.

**Methods:** The relationship between PASI and PGA × BSA was assessed in a post hoc analysis of pooled data from the PRISTINE (NCT00663052) and PRESTA (NCT00245960) trials in patients with moderate-to-severe psoriasis who received etanercept 50 mg/week. Data were analyzed using Spearman and intra-class correlation coefficients, effect sizes, scatterplots, Bland–Altman plots, and Kappa statistics.

**Results:** Spearman correlations at baseline, week 12, and week 24 were strong for PGA × BSA versus PASI ($r$=0.78, 0.87, and 0.90, respectively; all $P$<0.0001) as were intra-class correlations (0.76 [95% confidence interval 0.73–0.80], 0.80 [0.76–0.83], and 0.85 [0.82–0.87], respectively). The effect size was −1.53 for PASI and −0.94 for PGA × BSA (baseline to week 24). Scatterplots and Bland–Altman plots detected a trend across the range of measurement. Kappa statistics (at 12 and 24 weeks) between PASI50/75/90 and 50/75/90% improvement in PGA × BSA showed good agreement (0.58–0.69 at week 12 and 0.63–0.67, respectively; all $P$<0.0001). At baseline, the Spearman correlation coefficients were 0.96, 0.51, 0.19, and 0.17 for PGA × BSA versus BSA, PGA, Patient Global Assessment, and Dermatology Life Quality Index, respectively (all $P$<0.001).

**Conclusion:** PGA × BSA has advantages over PASI for measuring moderate-to-severe psoriasis; it is intuitive, sensitive, and easy to use.

**Keywords:** etanercept, PASI, PGA × BSA, psoriasis, correlation, agreement, responsiveness

## Background

The most commonly used psoriasis outcome measures do not individually capture all aspects of psoriatic disease and are of limited use in clinical practice.[1] Specifically, Psoriasis Area and Severity Index (PASI) is considered impractical for everyday clinical practice because it is complicated to calculate, difficult to interpret, time consuming, and insensitive in mild psoriasis.[2] Physician Global Assessment (PGA) is more practical; however, its value as a stand-alone instrument is limited because

Correspondence: Jessica A Walsh
Division of Rheumatology, Department of Internal Medicine, School of Medicine, University of Utah, George E Wahlen Veterans Affairs Medical Center, Room 4B200, 30 N 1900 E, Salt Lake City, UT 84132, USA
Tel +1 801 581 7724
Email jessica.walsh@hsc.utah.edu

it does not assess the extent of body surface involvement. Likewise, Body Surface Area (BSA) is not suitable as a sole outcome measure because it does not measure the quality or morphology of lesions. In an evolving climate of outcome-based clinical practice,[3] there remains an unmet need for a practical, uniform, validated, and standardized outcome measure of psoriasis for use in both clinical practice and clinical trials.[1,4–6]

The product of PGA and BSA (PGA × BSA) has previously been reported by our group as a simple and sensitive instrument for measuring psoriasis severity.[2] However, response to therapy could not be assessed in that observational registry study because the participants were on many different therapies and were not evaluated at predefined time intervals, which would be necessary for evaluating response to therapy over time. Additionally, the previous study was limited because of low numbers of participants with severe psoriasis. PGA × BSA, also known as Simple-Measure for Assessing Psoriasis Activity, is increasingly being used as a simple measure for psoriasis severity.[7–11]

The objective of this post hoc analysis was to evaluate PGA × BSA as a simpler alternative to PASI for measuring psoriasis severity and response to therapy.

# Methods

## Study design

Data were pooled from two randomized, controlled trials, PRISTINE (NCT00663052)[12] and PRESTA (NCT00245960),[13] in patients with moderate-to-severe psoriasis. These two studies were selected for the current analysis because participants were on a predefined treatment regimen and PASI, PGA, and BSA measurements were recorded at weeks 0, 12, and 24 in both studies, thus allowing analysis of PGA × BSA as a static measure of disease activity at baseline and as a measure of response to therapy over time. The study design and primary outcomes of both trials have been described in detail previously.[12,13] Patients received double-blind etanercept 50 mg twice weekly or once weekly for 12 weeks, then open-label etanercept 50 mg/week for 12 weeks. This retrospective analysis was conducted on the pooled etanercept 50 mg/week group in the modified intention-to-treat population at baseline, and weeks 12 and 24.

Both trials were conducted in accordance with the ethical principles of the Declaration of Helsinki and all patients signed and dated an approved informed consent form prior to participation in the trial. Regional Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) reviewed and approved the study protocols (Table S1).

## Assessments

PGA was a global assessment of all lesions scored on a scale of 0–5 in both trials, with 0 representing clear skin, 1 almost clear skin, and 5 representing severe psoriasis.[12,13] BSA was defined as the percent of BSA involvement, where 1% is approximately the area of the patient's handprint. The PASI score consisted of the sum of the erythema, induration, and desquamation for each body region, multiplied by weighted area scores.[14] Patient Global Assessment (PtGA) was scored on a scale of 1–100 in the PRESTA study and 0–5 in the PRISTINE study. The scale for PtGA in the PRESTA study was converted from 0–100 to 0–5 by dividing by 20. The Dermatology Life Quality Index (DLQI) is a validated patient-reported instrument that contains 10 questions used to assess the impact of skin disease on health-related quality of life and daily activities, with total scores ranging from 0 to 30 and higher scores indicating greater impairment of quality of life.[15]

## Statistical analysis

PASI was used as the reference standard since it is frequently used as an efficacy endpoint in clinical trials and has been widely considered as the standard for measuring psoriasis severity. Means and standard deviation (SD), medians, frequencies, and percentages were used to describe samples. Chi-square or Fisher's exact tests were performed to compare categorical variables, and one-way analysis of variance with treatment as a factor was used to compare continuous variables.

Correlations between PASI and PGA × BSA were evaluated using Spearman correlation coefficients. Agreement was evaluated with intra-class correlation coefficients (ICCs), scatterplots, Bland–Altman plots, and Cohen's Kappa coefficients. For the Spearman correlation coefficients and ICCs, values of 0.30–0.50, 0.50–0.70, 0.70–0.90, and ≥0.90 roughly correspond to low, moderate, high, and very high correlation or agreement, respectively. ICCs differ from Spearman correlations in that ICCs take into account both correlation and the difference in values, whereas Spearman correlations take into account only the correlation. For example, parameter 1 might have values of 1, 2, 3, and parameter 2 might have values of 3, 4, 5. Spearman coefficients would give a correlation of 1.0 (perfectly correlated with identically sloping lines). However, the ICC would be lower because it also takes into account the differences in the values (the lines are not superimposed).

For each assessment, responsiveness to change was assessed using effect size estimates, with larger effect size indicating greater responsiveness to change. Effect size was

calculated as the difference between the post-baseline mean and the baseline mean scores divided by the baseline SD.

Scatterplots and Bland–Altman plots were used to visually detect systemic differences and trends between PASI and PGA × BSA. In order to make the instruments comparable, PGA × BSA (scale 0–500) needed to be placed on the same scale as PASI (0–72) by dividing all PGA × BSA values by a constant factor (6.94) for some of the analyses. For scatterplots, the diagonal line represents the line of agreement, and data points that are dispersed above or below this line would indicate that PGA × BSA underestimates or overestimates psoriasis severity, respectively, when PASI is used as the reference standard. For Bland–Altman plots, the differences between PASI and PGA × BSA were plotted against the averages of these two assessments, along with vertical lines to denote the mean difference and its 95% limit of agreement (defined as the mean difference ±1.96*SD). Good agreement is indicated in a Bland–Altman plot by a small mean difference and low dispersion around the mean difference line and no apparent correlation between the average and the difference. Increasing or decreasing trends in the Bland–Altman plots would indicate that the level of agreement differs across the range of instrument scores.

Concordance between PASI50/75/90 and PGA × BSA50/75/90 was defined as the percentage of patients achieving specific outcomes as measured by each instrument; that is, the percentage of patients who achieved > PASI50/75/90 and >50/75/90% improvement for PGA × BSA (PGA × BSA50/75/90) plus the percentage of patients who were below the threshold for both measures (< PASI50/75/90 and < PGA × BSA50/75/90).

Correlations between PGA × BSA and BSA, PGA, PtGA, and DLQI were evaluated using Spearman correlation coefficients at baseline, week 12, and week 24.

The data analysis software UNIX SAS® version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses.

## Results

The mean age in the pooled patient group (N=510) was 46.1 years and 64.9% of patients were male. The mean duration of psoriasis was 18 years and the median BSA involvement was 22.0% (Table 1). Spearman correlation coefficients (Table 2) for PASI versus PGA × BSA were statistically significant ($P<0.0001$) and ranged from 0.78 (baseline) to 0.90 (week 24). ICC coefficients ranged from 0.76 to 0.85 (Table 2).

Scatterplots between PASI and PGA × BSA at baseline and week 24 are shown in Figure 1A and B, respectively. Most of the data points fell above the line of agreement at

**Table 1** Baseline demographic and disease characteristics

| Characteristics | Etanercept 50 mg/week (N=510) |
|---|---|
| Age, years | 46.1 (11.8) |
| Male, n (%) | 331 (64.9) |
| Body mass index, kg/m$^2$ | 28.6 (5.7) |
| Race, n (%) | |
| Asian | 53 (10.4) |
| White | 421 (82.5) |
| Other | 36 (7.1) |
| Duration of psoriasis, years | 18.0 (11.2) |
| Diagnosis of psoriatic arthritis, n (%) | 412 (80.8) |
| Duration of psoriatic arthritis, years | 7.3 (7.3) |
| PGA of psoriasis | 3.6 (0.7) |
| Affected BSA, % median (min, max) | 22.0 (9.0, 92.5) |
| PASI | 19.5 (9.7) |
| PGA × BSA | 115.0 (95.4) |

**Note:** Values are mean (standard deviation) unless otherwise stated.
**Abbreviations:** BSA, Body Surface Area; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment.

**Table 2** Correlations, agreement, and responsiveness to change between PASI and PGA × BSA

| Time | PASI | | PGA × BSA | | PASI versus PGA × BSA | PASI versus rescaled PGA × BSA |
|---|---|---|---|---|---|---|
| | Mean (SD) | Effect size | Mean (SD) | Effect size | *r* | ICC (95% CI) |
| Baseline (N=493) | 19.6 (9.7) | – | 115.6 (96.2) | – | 0.78* | 0.76 (0.73–0.80) |
| Week 12 (N=493) | 7.2 (6.4) | – | 41.9 (56.6) | – | 0.87* | 0.80 (0.76–0.83) |
| Week 12 CFB (N=493) | –12.3 (8.5) | –1.27 | –73.7 (73.3) | –0.77 | 0.78* | – |
| Baseline (N=470) | 19.6 (9.8) | – | 115.6 (96.2) | – | – | – |
| Week 24 (N=470) | 4.6 (5.6) | – | 25.2 (44.3) | – | 0.90* | 0.85 (0.82–0.87) |
| Week 24 CFB (N=470) | –15.0 (9.5) | –1.53 | –90.4 (85.2) | –0.94 | 0.77* | – |

**Notes:** *$P<0.0001$. Modified intention-to-treat population, observed cases by treatment. N = patients with baseline, week 12, or week 24 values. Effect size was calculated as the ratio of the difference between post-baseline and baseline mean scores, divided by baseline SD. Higher effect sizes suggest more responsiveness to change.
**Abbreviations:** BSA, Body Surface Area; CFB, change from baseline; CI, confidence interval; ICC, intra-class correlation coefficient; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; *r*, Spearman correlation coefficient; SD, standard deviation.

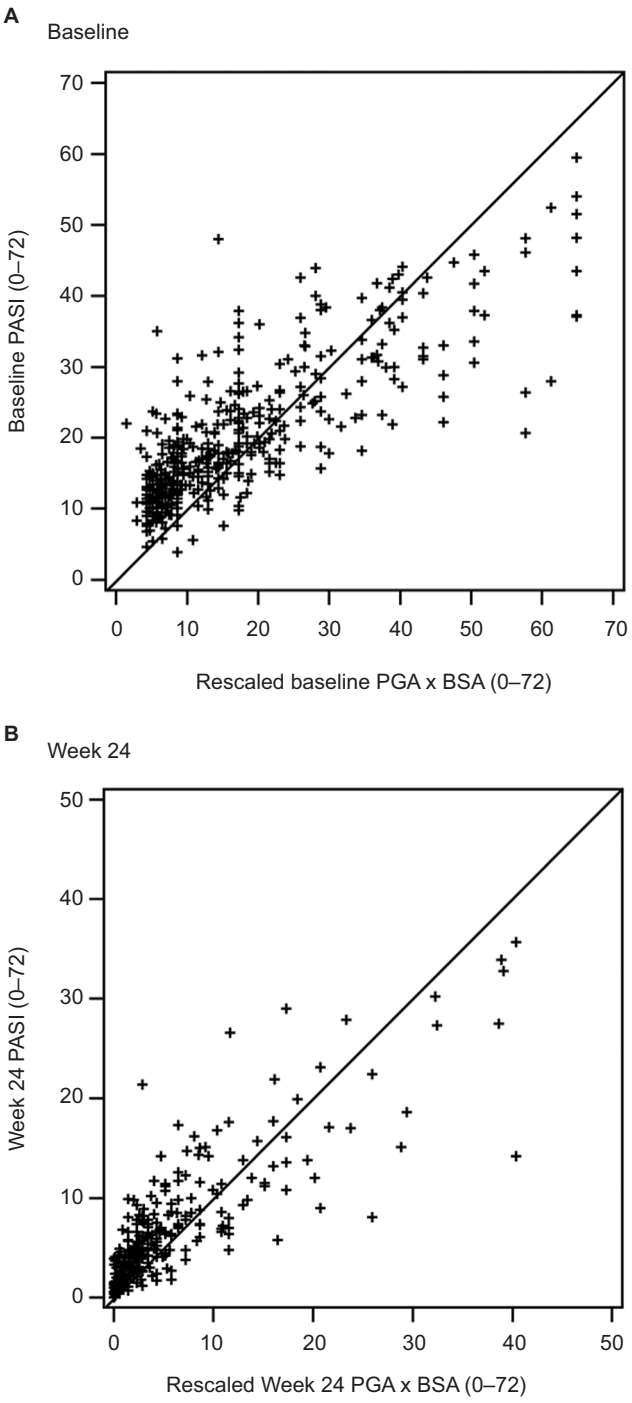


**Figure 1** PASI versus PGA × BSA scatterplots at baseline **(A)** and week 24 **(B)**.
**Abbreviations:** BSA, Body Surface Area; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment.

the low end of the scale and below the line of agreement at the high end of the scale, demonstrating that psoriasis was rated more severely with PASI than scaled PGA × BSA at the low end of the scale and less severely at the high end. The magnitude of agreement between the instruments was further quantified with Bland–Altman plots at baseline (Figure 2A) and week 24 (Figure 2B). At both time points, as the average increased, a decreasing trend from positive to negative differences and more observations falling below the expected 95% lower bound of agreement can be seen.

Concordance between PASI50/75/90 and PGA × BSA50/75/90 at week 12 and week 24 is shown in Figure 3. An overall concordance >80% (that is, agreement, which included both PASI50/75/90 and PGA × BSA50/75/90 response and nonresponse) was achieved at both week 12 and 24. Among the patients who were discordant (that is, disagreement, which included both underrated and overrated responses), a greater percentage of patients achieved improvement with PGA × BSA50/75/90 than with PASI50/75/90 (overrated), at all time points except at week 12 for PGA × BSA50. Cohen's Kappa coefficients ranged from 0.58 to 0.69 at week 12 and from 0.63 to 0.67 at week 24 (all $P<0.0001$).

Spearman correlation coefficients between PGA × BSA and other measures of psoriasis (Table 3) indicated very high correlations for PGA × BSA versus BSA, moderate to high correlations for PGA × BSA versus PGA, and low to moderate correlations for PGA × BSA versus PtGA and DLQI.

## Discussion

The aim of this study was to evaluate the use of PGA × BSA as an alternative to PASI for measuring psoriasis severity and response to therapy. The results demonstrated strong correlation (from Spearman correlation coefficients) and strong agreement (from ICC statistics) between PASI and PGA × BSA in measuring psoriasis severity.[16–18] Additionally, the correlations found between PASI and PGA × BSA in this study ($r$=0.78–0.90) are consistent with those in our earlier study ($r$=0.87 in all patients)[2] as well as those reported in a recent post hoc analysis of data from the ESTEEM 1 and 2 studies ($r$=0.74–0.84).[10] The ICCs in the current study (ICC =0.76–0.85) were also similar to those reported in the ESTEEM studies (ICC =0.80–0.92).[10]

This study is unique in evaluating PGA × BSA and PASI scores across the range of psoriasis severity. The scatterplots show that PGA × BSA underestimates psoriasis severity relative to PASI for the low end of the scale and it overestimates psoriasis severity relative to PASI for the high end of the scale. This is supported by the Bland–Altman plots, which show that the differences between PGA × BSA and PASI are not constant across the range of measurement. While the magnitude of these differences was not large, PGA × BSA should not be considered an exact surrogate for PASI. The high rate of concordance (81.5%–91.7%) and corresponding Kappa statistics showed that there was good agreement between PGA × BSA50/75/90 and PASI50/75/90.[18,19] PASI50/75/90 and PGA × BSA50/75/90 concordance and discordance data

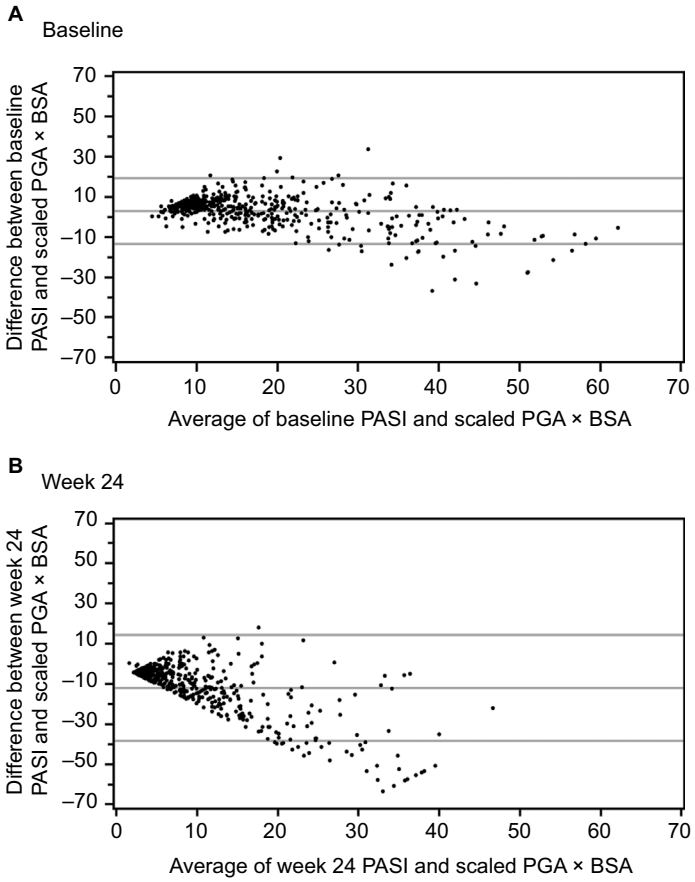


**Figure 2** Bland–Altman plots at baseline **(A)** and week 24 **(B)**.
**Abbreviations:** BSA, Body Surface Area; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment.

from this study were in a similar range to those reported at week 16 in the ESTEEM studies.[10]

In this study, PGA × BSA had strong correlations with the component measure BSA, moderate/strong correlations with the component measure PGA, and low/moderate correlations with patient-reported measures (PtGA and DLQI), which has also been reported in other studies.[9,10] The strong correlations between PGA × BSA and BSA demonstrated that PGA × BSA and BSA measure psoriasis severity similarly at the population level. However, on an individual level, PGA × BSA would be better at differentiating disease severity with regard to different plaque morphologies. For example, patient A with severe plaque morphology (PGA of 4) over a surface area of 10% will have a PGA × BSA score of 40 and a BSA of 10%, whereas patient B with mild plaque morphology (PGA 1) and identical surface area will have a lower PGA × BSA score of 10, but an identical (non-differentiating) BSA of 10%. The ability of PGA × BSA to capture changes in both plaque morphology and surface area is particularly important when measuring response to treatment, since plaque morphology and area may improve at different rates after treatment initiation.

This study was limited because inter-rater reliability, used to assess the degree to which different raters give consistent estimates of the same phenomenon, and test–retest reliability, used to assess the consistency of a measure from one time to another, were not assessed. These reliability analyses were not feasible because the same ratings were not given by different observers and the same test was not given twice in a short period of time. However, some information on this is already available; a systematic review of outcome measures for psoriasis reported moderate inter-rater reliability for PASI and PGA, high inter-rater reliability for BSA, and limited test–retest reliability for PASI, BSA, and PGA.[4]

Future studies should include evaluation of PGA × BSA (including response to change) in patients with mild-to-moderate psoriasis. Our expectation is that PGA × BSA will be more sensitive than PASI to differences in BSA in these patients. In our previous publication, we gave an example of two patients with identical PGA scores of 3; patient 1 had

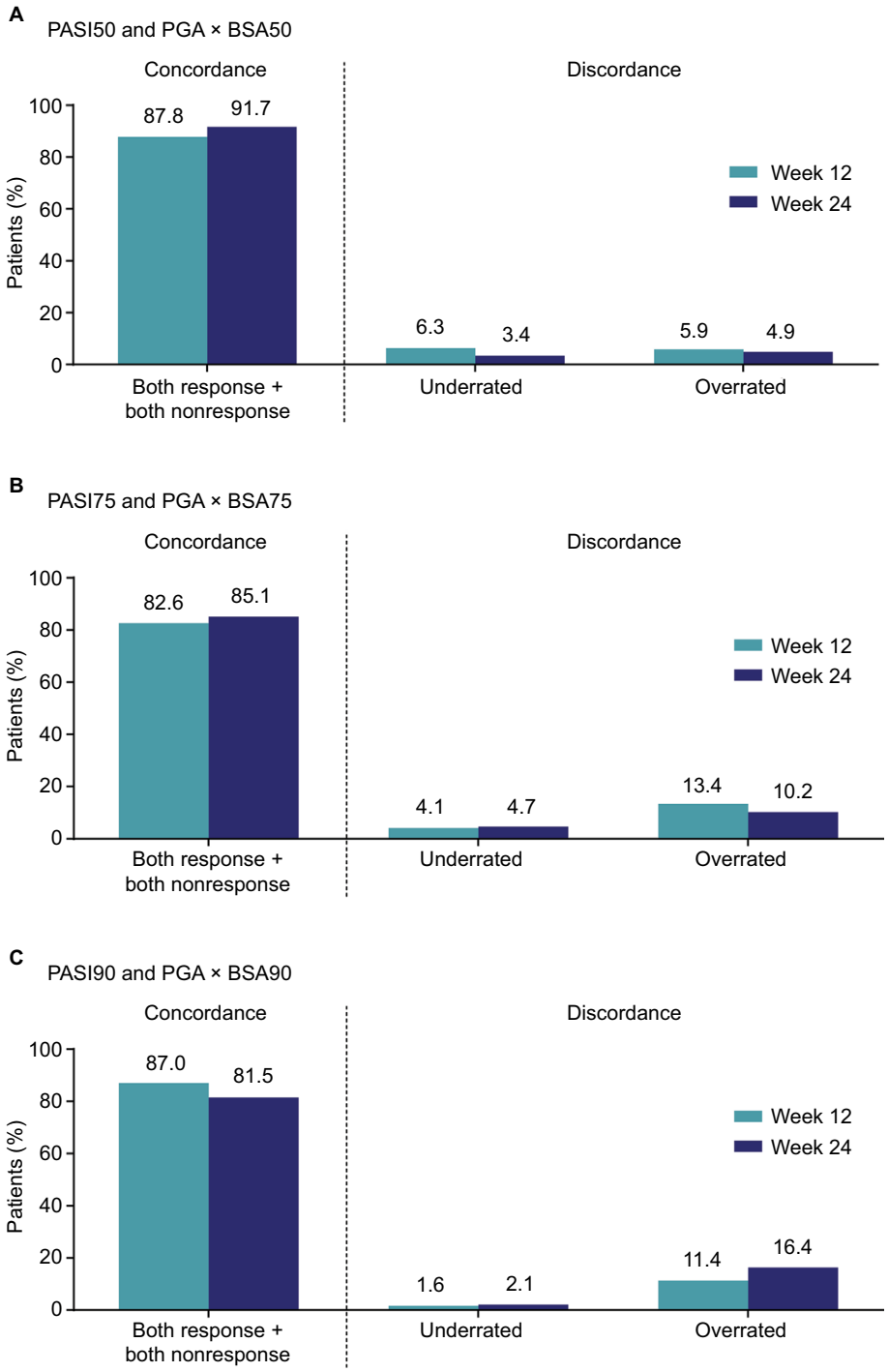


**Figure 3** Concordance and discordance between PASI50 and PGA × BSA50 **(A)**, PASI75 and PGA × BSA75 **(B)**, and PASI90 and PGA × BSA90 **(C)**. Concordance included the total number of patients who achieved both PASI and PGA × BSA response or both PASI and PGA × BSA nonresponse, underrated responses included patients who achieved PASI response and PGA × BSA nonresponse, and overrated responses included patients who achieved PASI nonresponse and PGA × BSA response.
**Abbreviations:** BSA, Body Surface Area; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment.

erythema 3, induration 3, and desquamation 3 and a BSA of 1%, and patient 2 had identical lesion severity scores but a BSA of 9%; they would have an identical PASI score of 9 as both BSA values would come under the <10% range and thus be considered equal in the calculation.[2] In contrast, PGA × BSA scores would reflect their different disease states, with a score of 3 for patient 1 and 27 for patient 2. This sensitivity is most pronounced with mild disease, since there is a larger relative difference between 9% and 1% BSA (9× greater BSA) than between 29% and 21% BSA (1.4× greater BSA). PASI is limited by unequally distributed area score groupings that are not consistently sensitive

**Table 3** Correlations between other measures of psoriasis severity and PGA × BSA

| Time | BSA versus PGA × BSA | | PGA versus PGA × BSA | | PtGA versus PGA × BSA | | DLQI versus PGA × BSA | |
|---|---|---|---|---|---|---|---|---|
| | n | *r* | n | *r* | n | *r* | n | *r* |
| Baseline | 510 | 0.96 | 510 | 0.51 | 505 | 0.19 | 508 | 0.17 |
| Week 12 | 495 | 0.95 | 495 | 0.80 | 495 | 0.40 | 493 | 0.37 |
| Week 12 CFB | 495 | 0.88 | 495 | 0.59 | 490 | 0.24 | 493 | 0.22 |
| Week 24 | 472 | 0.97 | 472 | 0.88 | 471 | 0.52 | 470 | 0.51 |
| Week 24 CFB | 472 | 0.91 | 472 | 0.49 | 466 | 0.26 | 470 | 0.21 |

**Notes:** *P*<0.001 for all Spearman correlations. Data are for observed cases. Week 12/24 CFB in PGA × BSA was calculated as week 12/24 PGA × BSA – baseline PGA × BSA. The scale for PtGA in the PRESTA study was converted from 0–100 to 0–5 by dividing by 20.
**Abbreviations:** BSA, Body Surface Area; CFB, change from baseline; DLQI, Dermatology Life Quality Index; PGA, Physician Global Assessment; PtGA, Patient Global Assessment; *r*, Spearman correlation coefficient.

to clinically meaningful differences in area involvement (for example, 1 for up to 10% BSA, 2 for 10%–29%, 3 for 30%–49%, 4 for 50%–69%, 5 for 70%–89%, and 6 for ≥90%). With PGA × BSA, this limitation is avoided with a continuous area score (for example, 0%–100%), which enables improved monitoring of treatment efficacy over time in clinical practice. Under some circumstances, the PGA × BSA score may be the same despite different combinations of PGA and BSA: for example, a PGA of 5 and BSA of 4 versus PGA of 1 and BSA of 20 (PGA × BSA is 20 for both). For such patients, the PGA × BSA score can easily be deconstructed into component scores to facilitate clinical judgment.

## Conclusion

In conclusion, PGA × BSA is a sensitive tool for assessing psoriasis severity and response to therapy. While not interchangeable, PGA × BSA and PASI had high agreement, and PGA × BSA has the advantage of being practical for use in both clinical practice and clinical trials.

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## Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to be accountable for all aspects of the work.

## Disclosure

Jessica A Walsh has received honoraria for serving as a consultant for Novartis. Heather Jones is an employee of Pfizer and has a financial interest in Pfizer. Lotus Mallbris was employed by Pfizer at the time of the analysis and has a financial interest in Pfizer. Kristina Callis Duffin/her institution has received a salary for serving as an investigator for AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, and Stiefel, honoraria for serving as a consultant for AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, and Stiefel, and fellowship funding for serving as a consultant for AbbVie. Gerald G Krueger has received honoraria for serving as an advisory board member or consultant or speaker for AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Genentech, Janssen, Eli Lilly, L'Oreal, Novartis, Pfizer, UCB, and Valeant. Daniel O Clegg has received honoraria as a consultant for Janssen Pharmaceuticals. Annette Szumski is an employee of inVentiv Health and was contracted by Pfizer to provide statistical support for the development of this paper. The authors report no other conflicts of interest in this work.

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# Supplementary materials

**Table S1** PRISTINE Trial (NCT00663052): names and addresses of IRBs or IECs

| Country<br>IRB/IEC name and address | Investigational site(s) No. |
|---|---|
| **Argentina** | |
| CEPI Comité de Ética de Protocolos de Investigación,<br>Hospital Italiano de Buenos Aires<br>Gascon 450, Capital Federal, Zip code: C1199ABB, Argentina | 014 |
| Comité de Ética Independiente para Ensayos en Farmacología Clínica<br>J.E Uriburu 774 Ipiso Zip code: C1027AAP, Capital Federal, Argentina | 013, 045 |
| **Austria** | |
| Etikkommission der Stadt Wien<br>Thomas - Klestil Platz 8<br>Town Town 1. Stock, 1030 Wien | 036, 037 |
| **Belgium** | |
| Commission d'Éthique Biomédicale Hospitalo-Facultaire<br>Avenue Hippocrate 55.14 Tour Harvey - niveau 0<br>1200 Bruxelles | 041 |
| Leading EC is the EC of Ghent (site 002): Ethics Committee UZ Ghent<br>De Pintelaan 185<br>9000 Ghent | 002, 041 |
| **Czech Republic** | |
| Etická Komise Nemocnice Jihlava Vrchlickeho 59, 586 33, Jihlava, Czech Republic | 016 |
| Lokalni Eticka Komise Fakultni nemocnice Plzen Edvards Benese 13,<br>305 99 Plzen-Bory, Czech Republic | 008 |
| Multicentrieka eticka Komise Fakultni nemocnice u sv. Anny v Brne<br>Pekarska 53, 656 91, Brno, Czech Republic | 008, 016 |
| Germany | |
| Ethikkommission des Fachbereichs Medizin der Johann Wolfgang von Goethe-Universität Frankfurt Haus 1<br>Theodor-Stern-Kai 7 60590 Frankfurt am Main | 032, 033, 034, 039, 040, 048, 049 |
| Greece | |
| National Ethics Committee 284 Mesogeion Ave., 155 62 Holargos | 018 |
| **Hungary** | |
| Debreceni Egyetem Orvos-és Egészségfudományi Centrum<br>Tudományos Bizottságának Regionális és Intézményi Etikai Bizottsága<br>Nagyerdei Krt. 98. H-4012, Debrecen, Hungary | 007 |
| Egészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottsága<br>Arany János utca 6-8. Budapest, H-1051 Hungary | 006, 007, 046, 047 |
| Miskolci Egészségügyi Központ és Egyetemi Oktatókórház<br>Intézeti Kutatásetikai Bizottság<br>H-3501, Miskolc, Csabai kapu 9-11., Hungary | 006 |
| Semmelweis Egyetem<br>Intézményi Kutatásetikai Bizottsága 1091, Budapest, Üllöi út 93 Hungary | 047 |
| Szegedi Tudományegyetem Szent-Györgyi Albert Klinikai Központ<br>Regionális és Intézményi Humán Orvosbiológiai Kutatásetikai Bizottsága<br>6720, Szeged, Korányi fasor 8-10 Hungary | 046 |
| **Italy** | |
| Comitato Etico<br>Azienda USL 4 L'Aquilla<br>P.O. San Salvatore<br>loc. Coppito 67100 - L'Aquila Italy | 021 |
| **Korea** | |
| Institutional Review Board Samsung Medical Center<br>B111, Annex, Samsung Medical Center,<br>50 Ilwon-dong, Kangnam-gu,<br>Seoul, 135-710 Korea | 028 |
| Seoul National University College of Medicine/Seoul National University Hospital Institutional Review Board<br>IRB, Clinical Research Institute, Seoul National University Hospital, 28 Yeongeon-dong,<br>Jongno-gu, Seoul, 110-744 Korea | 029 |
| **Mexico** | |
| Comité de Ética de la Facultad de Medicina de la UANL y<br>Hospital Universitario "Dr. José Eleuterio González" UANL (Dermatology Department)<br>Av. Francisco I. Madero poniente s/n y Av. Gonzalitos Col. Mitras Centro, Monterrey, Nuevo León CP 64460 | 042 |
| Comité de Ética del Instituto Dermatologico de Jalisco "Dr. José Barba Rubio".<br>Av. Federalismo Nte. No. 3102 Atemajac del Valle CP. 45190<br>Zapopan Jalisco Mexico | 011 |
| Unidad de Investigacion Clinica e Medicina SC Edificio Delta<br>Av. La Clinica # 2520 Despacho 520 Monterrey NL, CP 64710<br>Mexico | 012 |
| **Spain** | |
| CEIC del Hospital de la Santa Creu I Sant Pau Av. San Antonio Mª Claret, 167<br>08025 Barcelona | 022, 023 |
| **Taiwan** | |
| Research Ethics Committee of National Taiwan University Hospital,<br>B4 Floor, No.7, Chung-San South Rd, Taipei 100, Taiwan | 030 |
| The Institutional Review Board of Taipei Medical University Hospital<br>252, Wu Hsing Street, Taipei, Taiwan, ROC | 031 |

(*Continued*)

(*Continued*)

**Table S1** (*Continued*)

| Country<br>IRB/IEC name and address | Investigational site(s) No. |
|---|---|
| **Thailand** | |
| Ethical Clearance Committee On Human Rights To Researches Involving Human Subjects Faculty Of Medicine,<br>Ramathibodi Hospital, Mehidol University<br>3rd Floor, Research And Welfare Building,<br>Ramathibodi Hospital, Rama 6 Road,<br>Rajthevi, Bangkaok 10400<br>Thailand | 027 |
| Reserarch Affairs Faculty Of Medicine<br>Division Of Research Affairs<br>3rd Floor, Anandha Mahidol Building<br>Faculty OF Medicine,<br>Chulalongkorn University<br>Rama 4 Road, Pathumwan,<br>Bangkok 10330,<br>Thailand | 026 |

**Note:** This post hoc analysis utilised data from old studies. IRB/EC names could be recovered for the PRISTINE (NCT00663052), but not PRESTA trial (NCT00245960).
**Abbreviations:** IRB, Institutional Review Boards; IEC, Independent Ethics Committees.