Evaluation of sPGA × BSA as an Outcome Measure and Treatment Target for Clinical Practice

Joseph F. Merola1, David A. Amato2, Kyoungah See2, Russel Burge2,3, Craig Mallinckrodt2, Clement K. Ojeh2 and Alice Gottlieb4

Clinical outcome measures are becoming more important in psoriasis treatment. Reliable and standardized measures of severity feasible for clinical practice are needed. Our objective was to investigate body surface area (BSA) and the product of BSA and static Physician Global Assessment (sPGA) (ie, BSA × sPGA) as potential proxy measures for PASI scores. Data were pooled from three multicenter, randomized, double-blind, placebo-controlled, phase 3 trials of ixekizumab in patients with moderate to severe psoriasis (UNCOVER-1, -2, -3; N = 3,866). Assessments included the Psoriasis Area and Severity Index (PASI), BSA, and BSA × sPGA. Rank correlations between BSA × sPGA and PASI were stronger than between BSA and PASI (baseline, \( r = 0.759 \) vs. \( r = 0.707 \); week 12, \( r = 0.959 \) vs. \( r = 0.924 \)). Week 12 concordance rates with PASI responses were as follows: for 75% reduction in PASI: BSA, 86.2%; BSA × sPGA, 93.8%; for 90% reduction in PASI: BSA, 86.9%; BSA × sPGA, 88.2%. The 75% reduction in PASI positive and negative predictive values were higher for BSA × sPGA versus BSA; for 90% reduction in PASI, positive predictive value was lower and negative predictive value was higher for BSA × sPGA versus BSA. Receiver operating characteristic curve analyses identified the most accurate percentage changes in BSA and BSA × sPGA as 66% and 83% for a 75% reduction in PASI cutoff and 84% and 94% for a 90% reduction in PASI, respectively. These results suggest that BSA and BSA × sPGA are viable tools for use as a PASI proxy by real-world practitioners and may be appropriate measurements for use in clinical practice for treat-to-target strategies.

RESULTS

Patient demographics

In this pooled sample of 3,886 patients, the average age was 45.5 years, 68% were male, and 93% were white. Mean

INTRODUCTION

In early 2017, the Medical Board of the National Psoriasis Foundation published specific treatment goals for psoriasis that make achieving clear or almost clear skin the new standard of care (Armstrong et al., 2017). Similar treat-to-target paradigms first used in cardiology and subsequently in endocrinology and rheumatology resulted in improved patient outcomes (Atar et al., 2010). Therefore, the need exists for a reliable and standardized measure of psoriasis severity that can be implemented in routine clinical practice.

The Psoriasis Area and Severity Index (PASI) has been used for clinical practice decisions (National Institute for Health and Care Excellence, 2012). A 75% improvement (PASI 75) is a common primary endpoint in clinical trials. However, the PASI is not ideal for clinical practice (Schmitt and Wozel, 2005) because it is too cumbersome. The PASI requires separate and detailed assessments of body surface area (BSA), redness, thickness, and scaliness separately for four body regions. In addition, the PASI has been shown to be inaccurate in patients with low levels of psoriasis (Gourraud et al., 2012), which are the majority of those seen clinically (Schmitt and Wozel, 2005).

Other measures of disease severity for psoriasis include the static Physician Global Assessment (sPGA) and BSA. The sPGA is a measure of the severity of skin lesions, but in contrast to the PASI, it does not account for BSA involvement. The BSA is easily evaluated and well known to dermatologists but does not distinguish between thin, nonscaly and thick, scaly lesions. BSA is common to all three metrics: BSA, sPGA × BSA, and PASI. Although the product of BSA and sPGA (BSA × sPGA) has been evaluated as a possible proxy for the PASI (Duffin et al., 2017; Walsh et al., 2013), it has not been evaluated in large-scale, double-blind, randomized clinical trials for biologic therapies.

The purpose of this investigation was to assess BSA and BSA × sPGA as potential proxy measures for PASI to support treat-to-target strategies in patients with moderate to severe psoriasis who are treated with biologics.

RESULTS

Patient demographics

In this pooled sample of 3,886 patients, the average age was 45.5 years, 68% were male, and 93% were white. Mean
baseline values for PASI, BSA, and sPGA were 20, 27%, and 3.6, respectively.

**Correlation analyses**

Spearman rank correlations showed strong and statistically significant associations between week 12 (primary endpoint) absolute PASI and change in PASI and absolute and change in both proxy PASI measures, BSA and BSA × sPGA (Table 1 and Table 2). Correlations were similar across active treatment groups (etanercept and ixekizumab) but somewhat lower for placebo. Correlations were stronger for absolute PASI compared with changes in PASI, and correlations were slightly stronger for BSA × sPGA compared with BSA alone.

Table 3 compares Spearman rank correlation across time points and across low, medium, and high levels of disease involvement. The low, medium, and high categories are based on BSA subgroups only. At week 12, both proxy measures and PASI were strongly correlated, but correlations were considerably lower for earlier time points (week 4, week 8), during which full clinical response was not achieved. Similarly, correlations were stronger among patients with low residual levels of disease severity, indicating excellent clinical response, than among patients with medium and high levels of residual disease severity remaining despite treatment.

**Sensitivity and specificity analyses**

Table 4 shows sensitivity and specificity of the association between the percentage change in both proxy measures with PASI 75 and 90% improvement in PASI (PASI 90) at week 12. For PASI 75, a 66% change in BSA provides the maximum association (based on Youden index), whereas an 83% change in BSA × sPGA had the maximum association. These proxy measures had significant associations with PASI (P < 0.001) after 12 weeks of treatment. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were higher for BSA × sPGA than for BSA based on PASI 75. An 84% improvement in BSA value and a 94% improvement in BSA × sPGA provide the maximal associations with PASI 90. Based on PASI 90, BSA had higher specificity but lower sensitivity compared with BSA × sPGA.

**Concordance**

Concordance assessed the agreement between PASI and proxy measures in patients obtaining or not obtaining at least PASI 75 (PASI 90) at week 12. When outcomes were discordant, they were classified as overrated or underrated. Overrating occurred if the proxy measure indicated PASI 75 (PASI 90) but the PASI did not show 75% (90%) improvement. Underrating occurred if BSA did not improve by 75% (90%) but the PASI did improve by 75% (90%). The overall concordance rates for PASI 75 and PASI 90 changes in BSA and PASI were 86.2% and 86.9%, respectively. The overall concordance rates for BSA × sPGA were 93.8% and 88.2% for PASI 75 and PASI 90, respectively (data not shown).

Figure 1 (top panel) shows the concordance of BSA and PASI improvements within residual BSA subgroups (low, medium, and high) for PASI 75 and PASI 90 after 12 weeks of treatment. For PASI 75, BSA and PASI were 98.4% concordant in low-BSA patients (who are mostly high clinical responders) at week 12. For PASI 90, BSA and PASI were 87.3% concordant, with roughly equal likelihoods of overrating or underrating. In the medium BSA subgroup, concordance was 64.6% and 73.6% for 75% and 90% change thresholds. The level of underrating was 32.6% for the 75% change threshold. In the high BSA subgroup, concordance was 83.4% for PASI 75 and 94.8% for PASI 90.

**Regression analyses**

Scatterplots of scores at week 12 with absolute PASI on the y-axis and BSA or BSA × sPGA on the x-axis, with a regression line with correlation coefficient, are shown in Figures 2a and 2b, respectively. These plots provide a visual representation of the correlations between PASI and proxy measures. The scatterplot for BSA (Figure 2a) shows a wider spread than the plot with BSA × sPGA, which appears more dense (Figure 2b). These graphs show that 93% of the data are located between PASI less than 25.2 and BSA less than 45% (Figure 2a), whereas 94% of the data are located between PASI less than 25.2 and BSA × sPGA less than 150 (Figure 2b). The regression line indicates how the observed proxy measure (BSA or BSA × sPGA) maps to PASI scores at week 12. The fitted regression equations are the average predicted PASI value based on the BSA and BSA × sPGA proxy values.

Observed BSA × sPGA values within ranges are mapped to mean PASI scores based on week 12 data and shown by residual disease severity group (see Supplementary Table S1 online). For example, patients with an observed BSA × sPGA in the range of 10 to less than 20 in the mild disease severity group had a mean absolute PASI of 4.1 (standard deviation = 2.18), with a 95% confidence interval of 3.9 to 4.3. Patients with an observed BSA × sPGA of 80 to less than 90 in the severe disease severity group had a mean PASI of 17.1 (standard deviation = 4.37; 95% confidence interval = 16.0–18.1).

Figure 3 provides ROC curves for both proxy measures, using PASI 75 and PASI 90 cutoffs. The ROC curves compare sensitivity versus specificity across the ranges of proxy values for the ability to predict PASI 75 and PASI 90 after 12 weeks of treatment. The area under the ROC curve is another measure of test performance for these proxy measures. In panel A, ROC curves for BSA and BSA × sPGA to predict PASI 75 are shown. Based on Youden index, a percentage change in BSA of 66% was determined to be the best predictor for PASI 75, whereas the corresponding value for BSA × sPGA was 83%. In panel B, the most accurate BSA and BSA × sPGA percentage change values for predicting PASI 90 were determined to be 84% and 94%, respectively.
DISCUSSION

Evidence-based treat-to-target goals have the promise of cost savings and better patient outcomes (Vermeer et al., 2013). The nation’s largest payer, Medicare, has implemented the Physician Value-Based Modifier, a multiplier to Medicare reimbursement that will financially reward physicians who provide care that is high value—both high in quality and lower in cost (Chien and Rosenthal, 2013). The quality aspect will rely on specialty-specific physician- and practice-reported metrics, and dermatologists are taking action to define those metrics. With the increasing public demand for quality, transparency, and dermatologists are taking action to define those metrics. The quality aspect will rely on specialty-specific physician- and practice-reported metrics, and dermatologists are taking action to define those metrics. With the increasing public demand for quality, transparency, and accountability in health care and new treat-to-target goals in dermatology, providers need a clinically useful severity measure that, like the PASI, incorporates both the extent and quality of lesions.

Two measures are presently receiving significant attention as potential outcome measures for use in clinical practice and are tied to effective treatment. The BSA measurement has been suggested as a target goal by the National Psoriasis Foundation in a recent publication (Armstrong et al., 2017). The target response definitions were based on a consensus panel of dermatologists with specific expertise in psoriasis treatment. Alternatively, the International Dermatology Outcomes Measures has worked to develop and validate measures for skin diseases by using the Delphi survey process (Perez-Chada et al., 2017). The consensus opinion for the International Dermatology Outcomes Measures is focused on the BSA × sPGA measurement, which captures more clinical information than BSA alone, as a potential outcome that can be used consistently across clinical trials and in real-world practice.

In our comparison of BSA and BSA × sPGA to PASI in the UNCOVER clinical trials program, BSA and BSA × sPGA were highly correlated with PASI scores among patients with low residual disease severity (high response to treatment), but the correlations were more moderate in magnitude among patients with moderate or severe residual disease (low response to treatment). Concordance between PASI and proxies based on categorical measures of improvement (PASI 75 and PASI 90) followed a similar pattern. This is consistent with Duffin et al. (2017), who report high levels of concordance between BSA × sPGA at week 16 in the pivotal Apremilast clinical trials for moderate to severe psoriasis (Duffin et al., 2017). Consistent with Lane et al. (2016), data from our analysis suggest that BSA measurement alone also showed good correlation to the PASI, but less so at higher BSA levels for patients after 12 weeks of treatment.

With respect to concordance, disagreement between proxies and PASI can arise because the PASI uses a nonlinear assessment of BSA, whereas proxy BSA is a linear assessment. That is, continuous BSA scores are mapped to a 0 to 6 range for the PASI such that the impact of a 1-unit change in BSA does not always have the same impact on the PASI. In contrast, a 1-unit change in BSA always has the same effect on proxy scores.

Furthermore, the most severe patients at baseline who had good responses (PASI 75 and PASI 90) after 12 weeks often continued to have BSA greater than 10%, suggesting that relying on BSA changes alone does not fully capture the benefit or amount of clinical improvement. Thus, in patients with the most severe disease, the one-dimensional measure

<table>
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<tr>
<th>Table 1. Correlations and 95% confidence intervals for absolute PASI with BSA and BSA × sPGA proxy measures at week 12</th>
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<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Etanercept</td>
</tr>
<tr>
<td>Ixekizumab Q2W¹</td>
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<td>Ixekizumab Q4W¹</td>
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</tbody>
</table>

For all values, P < 0.001.

Abbreviations: BSA, body surface area; CI, confidence interval; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks (weeks 0–12); Q4W, every 4 weeks (weeks 0–12); sPGA, static Physician Global Assessment.

¹Patients received a 160-mg starting dose of ixekizumab at week 0 before receiving 80 mg ixekizumab (Q2W or Q4W).

<table>
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<tr>
<th>Table 2. Correlations and 95% confidence intervals for change in PASI with change in BSA and BSA × sPGA proxy measures at week 12</th>
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<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Placebo</td>
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of BSA is not as accurate in reflecting the multifactorial aspects of psoriasis as captured by the PASI. In addition, the underlying results for changes in BSA suggest that among those high-BSA patients who achieved high PASI responses at week 12 (n = 201 for PASI 75 and n = 64 for PASI 90 [Figure 1]), PASI improvements were more likely driven by changes in reductions in thickness, redness, and scaliness than changes in BSA. Despite the shortcomings of relying on BSA alone, BSA measurement among dermatologists is much less of an issue than measuring PASI and is common to PASI and sPGA metrics.

For both proxy measures, concordance rates for PASI 75 were strongest among low residual BSA patients (comprising mostly high clinical responders), whereas for PASI 90, the highest concordance rates occurred in high residual BSA patients. Concordance rates were the lowest for both BSA and BSA × sPGA for the medium residual BSA group. For each of the three residual BSA groups, BSA × sPGA had higher concordance for PASI 75 and PASI 90 compared with BSA alone.

ROC analyses were conducted to estimate the percentage change in BSA and BSA × sPGA values that would optimize the association with PASI changes (PASI 75 and PASI 90). An observed percentage change in BSA of 66% from baseline to week 12 was determined to most accurately reflect PASI 75, whereas an 84% change represented PASI 90 improvement. When using BSA × sPGA, after 12 weeks of treatment, a change in BSA and BSA × sPGA of 83% and 94%, respectively. In practice, these observed percentage changes after 12 weeks of treatment should be relatively easy for clinicians to perform. The use of BSA × sPGA has the added advantage of describing more patients and their unobserved likely PASI improvement for a given level of residual disease severity. For

### Table 3. Correlations of absolute PASI with BSA and BSA × sPGA: overall and by BSA subgroup by week

<table>
<thead>
<tr>
<th>Measure</th>
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<tr>
<td>BSA Subgroup</td>
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<tr>
<td>Overall</td>
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<tr>
<td>n</td>
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<tr>
<td>BSA</td>
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<td>BSA × sPGA</td>
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### Table 4. Sensitivity, specificity, positive predictive value, and negative predictive value at week 12 for PASI 75 and PASI 90 improvement and proxy percentage improvement for BSA and BSA × sPGA (using PASI 75 and PASI 90 commonly used in randomized controlled trials), all treatment groups combined

<table>
<thead>
<tr>
<th>Proxy Improvement</th>
<th>BSA Improvement</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
<th>McNemar Test, P-value</th>
<th>Gamma Coefficient, (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI % Improvement</td>
<td>BSA Improvement</td>
<td>Sensitivity, %</td>
<td>Specificity, %</td>
<td>PPV, %</td>
<td>NPV, %</td>
<td>McNemar Test, P-value</td>
<td>Gamma Coefficient, (95% CI)</td>
</tr>
<tr>
<td>BSA</td>
<td>66</td>
<td>75</td>
<td>86.32</td>
<td>93.34</td>
<td>95.93</td>
<td>78.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>90</td>
<td>86.35</td>
<td>89.92</td>
<td>88.34</td>
<td>88.16</td>
<td>0.061</td>
</tr>
<tr>
<td>BSA × sPGA</td>
<td>83</td>
<td>75</td>
<td>92.38</td>
<td>95.10</td>
<td>97.17</td>
<td>87.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>94</td>
<td>90</td>
<td>90.16</td>
<td>88.49</td>
<td>87.38</td>
<td>91.05</td>
<td>0.006</td>
</tr>
</tbody>
</table>
example, a baseline BSA × sPGA value of 60 could include patients with a baseline BSA of 20% and sPGA of 3, a BSA of 15% and sPGA of 4, or a BSA of 12% and sPGA of 5. An observed BSA × sPGA of 10.2 (83% decrease) after 12 weeks would represent PASI 75, whereas an observed value of 3.6 (94% improvement) would reflect PASI 90.

There are several strengths and limitations to consider when interpreting the present investigation. The data pool was large (N = 3,866) and included two biologic therapies, and the study designs were consistent with most clinical trials in psoriasis. In this analysis, several analytic approaches were used to describe various aspects of the association between PASI and the proxy measures, including assessments within and across time and disease severity. However, this investigation was based on patients with moderate to severe psoriasis at baseline, and it is unclear how these results would generalize to less severe populations in general clinical practice. Nevertheless, the
proxies performed most similarly to the PASI in patients with low residual disease severity after 12 weeks of treatment. In addition, these results used 12-week data for the primary endpoints in these studies.

In aggregate, the results of this study suggest that BSA and BSA \times sPGA are adequate proxies for PASI, especially with targets for a high degree of clinical response (i.e., low residual levels of disease severity). Using both as a multiple provided improved concordance with all PASI measures over BSA alone; these results suggest that BSA \times sPGA may be the preferred tool for use as a PASI proxy for real-world practitioners and may be appropriate measurements for use in clinical practice for treat-to-target strategies.

**MATERIALS AND METHODS**

**Data source**

Data were taken from three multicenter, randomized, double-blind, placebo- and active-controlled phase 3 trials of ixekizumab in patients with moderate to severe psoriasis: UNCOVER-1 (NCT01474512, N = 1,296), UNCOVER-2 (NCT01597245, N = 1,224), and UNCOVER-3 (NCT01646177, N = 1,346). Results of these studies have been reported previously (Gordon et al., 2016; Griffiths et al., 2015). The studies included patients 18 years and older, with a history of psoriasis longer than 6 months, and at least moderate disease severity (sPGA score \geq 3 or PASI score \geq 12 at screening and baseline), with 10% or more of their BSA affected (Gordon et al., 2016). Patients were randomized to placebo or 80 mg of ixekizumab every 2 or every 4 weeks after a starting dose of 160 mg at week 0. The UNCOVER-2 and -3 studies also included etanercept 50 mg twice weekly. Co-primary efficacy endpoints for all studies were the proportion of patients achieving an sPGA score of 0 or 1 and 75% or greater improvement in PASI at week 12.

**Analysis endpoints and assessments**

Assessments of disease severity included PASI, BSA, and sPGA, which were administered according to the protocols of the UNCOVER studies. All investigators were trained in the techniques to be used in the trials to optimize consistency.

PASI involves determining the area and severity of lesions in four body regions (head, trunk, arms, and legs) to establish subscores for each region that are combined through a multistep mathematical equation to provide a single score in the range from 0 (no disease) to 72 (maximal disease) (Fredriksson and Pettersson, 1978). Clinical severity is estimated by signs of erythema, induration, and scaling, each with scores from 0 (no involvement) to 4 (severe involvement) and multiplied by a factor based on the area of involvement for each region. The scores for each region are then combined as a weighted sum, with weights roughly proportional to the percentage of the total body represented by the region, to determine the final PASI score.

The sPGA uses a Likert scale of scores between clear (0) to severe or very severe (ranging from 5 to 8) and is derived from the severity of erythema, desquamation (Feldman and Krueger, 2005), and induration. The sPGA is the physician’s determination of the patient’s overall lesion severity at a given time point. It is simple and quick but is less objective and does not explicitly reflect the extent of involved skin (Chow et al., 2015). In UNCOVER, the three components are graded using a 6-point scale, and the patient’s psoriasis is assessed as clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5). Scores between whole numbers were rounded to the next highest number.

BSA is a physician rating of the percentage of involvement of psoriasis and is assessed on a scale from 0% (no involvement) to 100% (full involvement), where each 1% corresponds roughly to the size of the participant’s handprint. BSA measures have traditionally been divided into low (\leq 3%), medium (3% to \leq 10%), and high (>10%) and were used in this analysis.
CONFLICT OF INTEREST
Joseph Merola is a consultant, advisor, and/or investigator for Biogen IDEC, AbbVie, Eli Lilly and Company, Novartis, Pfizer, Janssen, UCB, Samumed, Science 37, Celgene, Sanofi Regeneron, Merck, Incyte, and GS&K and a speaker for AbbVie. David A. Amato, Kyoungha See, Russell Burge, Craig Mallinckrodt, and Clement K Ojeh are employees and minor stockholders of Eli Lilly and Company. Alice Gottlieb is a consultant/member of the advisory board for Janssen, Inc.; Celgene Corp.; Bristol Myers Squibb Co.; Beiersdorf, Inc.; Abbvie; UCB; Novartis; Incyte; Pfizer; Lilly; Xenophor; Development Crescendo Bioscience; Aclars; Amicus; Reddy Labs; Valeant; Dermira; Allergan; CSL Behring; Merck; and Sun Pharmaceutical Industries and has received research/educational grants from Janssen Incyte. The study was sponsored by Eli Lilly and Company.

Statistical analysis
Analyses were conducted on the overall population and by BSA subgroups (low, medium, and high) using SAS, version 9.4 (SAS Institute, Cary, NC). Spearman rank correlations assessed the strength of the association between PASI scores and PASI changes from baseline with the proxy measures for PASI. McNemar test and the gamma coefficient assessed the sensitivity and specificity at week 12 of 75% and 90% improvements in BSA and BSA × sPGA versus the corresponding PASI 75 and PASI 90, which are commonly used in randomized clinical trials.

Concordance rates were calculated as the percentage of patients with agreement between PASI and proxy measures in patients obtaining or not obtaining at least PASI 75 (PASI 90) at week 12. When outcomes were discordant, they were classified as overrated or underrated. Overrating occurred if the proxy measure indicated PASI 75 (PASI 90) but the PASI did not show 75% (90%) improvement, whereas underrating occurred if the proxy measure did not indicate PASI 75 (PASI 90) but the PASI did show 75% (90%) improvement. Percentages of patients in these two discordant categories were calculated similarly as in the concordance category.

Sensitivity (true positive rate) measures the proportion of patients determined to be responders based on the PASI who also were identified by the proxy measures as being responders. Specificity (true negative rate) measures the proportion of patients determined to be nonresponders based on the PASI who also were identified by the proxy measures as being nonresponders.

For concordance, a proxy overrated severity if the response threshold was achieved for the proxy but not for PASI; the proxy underrated severity if the response threshold was achieved for PASI but not the proxy. PASI means and 95% confidence intervals were calculated for specified BSA × sPGA ranges. PASI means and 95% confidence intervals were calculated for specified BSA × sPGA ranges.

ROC analyses were conducted to compare sensitivity versus specificity across the ranges of proxy values for the ability to predict the PASI cutoff (PASI 75 and PASI 90). The ROC figures display the sensitivity along the y-axis versus its 1-specificity of the test along the x-axis for all possible values of the proxy measures. The length of the vertical line of equality (where sensitivity equals 1-specificity) to the ROC curve depicts the highest Youden index value, which indicates the best cutoff for the association with the proxy values compared with those commonly used in randomized controlled trials (PASI 75 and PASI 90 rates). The best cutoff has the highest sum of sensitivity and specificity.

REFERENCES