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ORIGINAL RESEARCH

Validation of the PROFAD-SSI-SF in Patients with Primary Sjögren's Syndrome with Organ Involvement: Results of Qualitative Interviews and Psychometric Analyses

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ABSTRACT

Introduction: The Profile of Fatigue and Discomfort–Sicca Symptoms Inventory–Short Form (PROFAD-SSI-SF) is a 19-item patient-reported outcome (PRO) measure to assess pain, fatigue, and dryness in patients with primary Sjögren's syndrome (pSS). This analysis identified concepts important to measure, and evaluated the content validity and measurement properties of the PROFAD-SSI-SF, in patients with pSS.

Methods: Qualitative analyses (GSK Study 208396) used transcripts from an online concept elicitation (CE) discussion forum with patients with pSS and interviews with key opinion leaders (KOLs) to finalize a disease model depicting important concepts for patients with pSS. Cognitive debriefing (CD) interviews with patients with pSS were conducted to further evaluate the content validity of the PROFAD-SSI-SF. Quantitative analyses (GSK Study 213253) used post hoc analyses of blinded data from a phase 2 trial to assess PROFAD-SSI-SF measurement properties.

Results: The CE discussion forum ($N = 46$) revealed dryness (oral 87.0%, ocular 73.9%, cutaneous 37.0%, vaginal 23.9%, nasal 15.2%, otic 6.5%), pain (89.1%), and fatigue (87.0%) as the most reported symptoms. KOLs ($N = 5$) found the concepts identified in the disease model accurate and understandable, and confirmed that PROs used in pSS studies should focus on dryness, joint pain, and fatigue. In the CD interviews ($N = 20$), of the 19 participants asked, all found the PROFAD-SSI-SF easy to understand, and 14/19 items were considered relevant by $\geq$ 18/20 participants. The quantitative analyses found an acceptable fit of the PROFAD-SSI-SF factor structure, with adequate internal consistency, test–retest reliability, convergent validity with other PRO measures, known-groups validity with Patient Global Assessment, and ability to detect change in patients with pSS.

Conclusion: The final disease model confirmed that the PROFAD-SSI-SF assesses concepts that are relevant and important to patients with pSS. Our findings support the content validity and measurement properties of the PROFAD-SSI-SF

The affiliation listed for Stephen Maher and Aaron Yarlas was their affiliation at the time of the study.

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as a fit-for-purpose PRO measure appropriate for use in clinical trials in patients with pSS.
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PLAIN LANGUAGE SUMMARY

Primary Sjögren's syndrome (pSS) is a disease where the immune system attacks the body, causing a number of symptoms, most notably dryness (sicca) of the eyes and mouth. The Profile of Fatigue and Discomfort–Sicca Symptoms Inventory–Short Form (PROFAD-SSI-SF) is a questionnaire for patients with pSS that asks about their symptoms. This paper evaluates how relevant the PROFAD-SSI-SF questions are to patients with pSS, and how consistently and accurately the questionnaire can measure changes in their symptoms. We reviewed information about the symptoms and impacts of pSS from an online discussion forum for patients with pSS. Patients said that dryness, fatigue, and pain were the symptoms that most affected their day-to-day lives and well-being. We combined this information with previous research on pSS to design a diagram explaining the key symptoms and day-to-day impacts of pSS, which was reviewed by five experts in pSS. In doing so, we aimed to confirm whether the most important things to patients about living with pSS are asked in the PROFAD-SSI-SF questionnaire. Next, we asked 20 patients with pSS how easy they found the PROFAD-SSI-SF to complete and if any important concepts were missing; they reported that the PROFAD-SSI-SF was easy to fill in and that the important questions were included. Finally, we looked at data from a clinical trial that used the PROFAD-SSI-SF and found it accurately measures changes in symptoms of patients with pSS. This means that the PROFAD-SSI-SF could be used in clinical trials to help assess new medicines for pSS.

Keywords: Autoimmune disease; Content validity; Instrument validation; Patient-reported outcomes; Primary Sjogren's syndrome; PROFAD-SSI-SF; Psychometric properties; Qualitative research

Key Summary Points

Why carry out this study?

The Profile of Fatigue and Discomfort–Sicca Symptoms Inventory–Short Form (PROFAD-SSI-SF) is a 19-item questionnaire for assessing symptoms in patients with primary Sjögren's syndrome (pSS), primarily dryness (sicca), fatigue, and pain.

The development of the questionnaire predates US Food and Drug Administration guidance on patient-reported outcomes; therefore, validation studies are required to confirm that it meets current requirements for use in clinical trials.

What did the study ask/what was the hypothesis of the study?

In addition to refining an existing disease model, this study used qualitative data from patients with pSS and quantitative data (blinded) from a phase 2 clinical trial study of belimumab and rituximab for pSS (NCT02631538) to evaluate the content validity and measurement properties of the PROFAD-SSI-SF to determine whether it is fit for purpose for use in patients with pSS.

What were the study outcomes/conclusions?

The study results support the content validity of the PROFAD-SSI-SF and showed good reliability, construct validity, and ability to detect change, thus confirming its measurement properties and that it is fit for purpose and relevant for use in patients with pSS.

What is learned from the study?

The PROFAD-SSI-SF is a fit-for-purpose patient-reported outcome measure appropriate for use in clinical trials supporting drug development in pSS.

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by mucosal tissue dryness (sicca; e.g., ocular or oral) [1, 2]. Other complications of pSS include: major organ and joint involvement [3, 4]; neuropathies [3, 5]; and increased risk of lymphomas [6, 7].

Key symptoms described by patients with pSS include fatigue [8], dryness, most notably of the mouth and eyes, and pain [2, 9]. Patients also report negative impacts on their health-related quality of life as a result of pSS [10, 11].

Outcome measures typically used in clinical trials in patients with pSS aim to evaluate the symptoms—including mucosal dryness and fatigue [12–14]—and impacts of the disease. The Profile of Fatigue and Discomfort–Sicca Symptoms Inventory–Short Form (PROFAD-SSI-SF) questionnaire is a 19-item patient-reported outcome (PRO) measure divided into eight domains of pSS symptoms (somatic fatigue, mental fatigue, arthralgia, vascular dysfunction, and oral, ocular, cutaneous, and vaginal dryness) scored on an eight-point (0–7) numeric rating scale [15]. The PROFAD-SSI-SF is derived from the 64-item PROFAD-SSI long-form questionnaire; it uses the same eight domains [15] and was developed and validated using a UK cohort of patients with pSS [16, 17]. The PROFAD-SSI-SF has been shown to have a high correlation across all domains (Spearman's p between 0.779 and 0.996; $p < 0.01$) and a similar internal structure to the PROFAD-SSI long-form questionnaire, with the advantage that its shorter length is more convenient in clinical trial settings, as it reduces the reporting burden on patients [15].

The development of the questionnaire predates US Food and Drug Administration (FDA) guidance on patient-reported outcomes [18]. Further validation of the PROFAD-SSI-SF will confirm it meets FDA requirements for PROs [18] and support its use as a clinical trial endpoint. In addition, validation in patients with pSS and organ involvement would encourage the use of the PROFAD-SSI-SF in future clinical trials of new disease-modifying therapies, particularly in light of the interest in biologic therapies for this patient population [19, 20].

This paper describes research that aimed to confirm the key concepts that should be measured in patients with pSS, and to confirm that the PROFAD-SSI-SF assesses these key concepts with the appropriate measurement properties for it to be used in clinical trials in patients with pSS.

METHODS

Study Design

A targeted literature review and qualitative analyses, including a secondary analysis of transcripts from an online concept elicitation (CE) discussion forum, and key opinion leader (KOL) interviews were conducted to develop and refine a previously developed disease model of pSS and identify important concepts to be measured in patients with pSS.

Qualitative cognitive debriefing (CD) interviews with patients with pSS were conducted as a final step to confirm the content validity of the PROFAD-SSI-SF. The quantitative study (GSK Study 213253) evaluated the measurement properties of the PROFAD-SSI-SF using blinded data from a phase 2 randomized, double-blind, placebo-controlled study of belimumab and rituximab in patients with symptomatic and systemically active (European Alliance of Associations for Rheumatology [EULAR] Sjögren's Syndrome Disease Activity Index [ESSDAI] ≥ 5 points) pSS (GSK Study 201842; NCT02631538) [21, 22].

Refining a Disease Model for pSS: Qualitative Analysis

CE Discussion Forum: Secondary Analysis

Transcripts from a previous online CE discussion forum (GSK Study 208399) that gathered information on symptoms, disease impacts, treatment experiences, and goals from 46 patients with pSS [23] were analyzed to confirm and refine the key concepts presented in a draft disease model developed from a targeted

literature review. Findings from the CE study were also used to inform the creation of interview materials for subsequent CD interviews with patients with pSS. For full details, please refer to the Supplementary Material.

KOL Interviews

Ninety-minute, semi-structured telephone interviews were conducted with five KOLs (three rheumatologists and two patient advocates) to further refine the disease model and identify the concepts of the greatest importance to patients with pSS. For full details, please refer to the Supplementary Material.

PROFAD-SSI-SF Evaluation: Qualitative Analyses

CD Interviews

Trained researchers conducted 90-min, one-on-one, semi-structured interviews with patients with pSS to confirm the content validity of the PROFAD-SSI-SF for use in pSS. During the interviews, patients also reviewed and discussed the EULAR Sjögren's Syndrome Patients Reported Index (ESSPRI) [24, 25]—developed to assess patients' symptoms and disease activity—but these findings are not reported here, as this manuscript focuses on the qualitative results of the PROFAD-SSI-SF.

Participants were recruited from a pre-existing patient panel via a non-profit organization that supports patients with pSS. Eligible participants were: adults aged ≥ 18 years; fluent in English (i.e., able to read, write, and fully understand US English); and able to provide a physician-confirmed diagnosis of pSS with organ involvement (to facilitate the future use of PROFAD-SSI-SF in patients with organ involvement). "Organ involvement" was defined as disease activity in ≥ 1 of the following categories based on the ESSDAI [26]: fever of non-infectious origin; lymphadenopathy/lymphoma; arthralgia/synovitis; erythema/vasculitis/purpura; pulmonary involvement; renal involvement; myositis; peripheral/central nervous system involvement; cytopenia of autoimmune origin (with neutropenia) and/or anemia and/or thrombocytopenia and/or lymphopenia. Eligible participants were further screened to select representative members of the target sample, aiming for diversity across disease severity, type of organ involvement, sex, race, education, and time since diagnosis.

CD interviews were conducted either in person at specially equipped locations or remotely using WebEx meeting software. Informed consent was obtained from all participants prior to each interview. Each interview had a four-part structure that included an introduction to the study, initial rapport-building questions, a review of the PROFAD-SSI-SF using the "think-aloud" method as well as targeted questions to address each element of the instrument, and a conclusion (Fig. 1). The CD interview model was not tested in a sample population in this study. However, this model has been widely used and

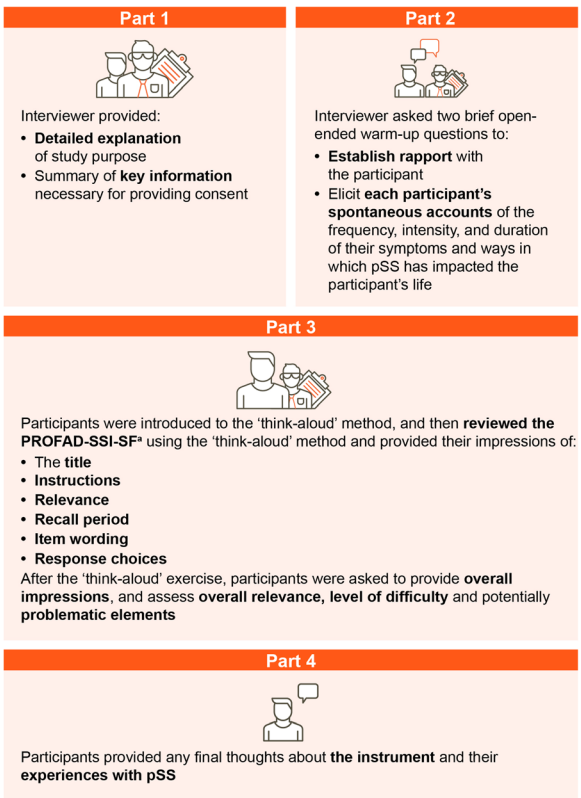

Fig. 1 The four-part structure of the cognitive debriefing interview procedure. [a]ESSPRI was also discussed during the cognitive debriefing interviews. *ESSPRI* European Alliance of Associations for Rheumatology Sjögren's Syndrome Patients Reported Index, *PROFAD-SSI-SF* Profile of Fatigue and Discomfort–Sicca Symptoms Inventory–Short Form, *pSS* primary Sjögren's syndrome

reported previously, including in patients with pSS [27, 28], and is generally considered a robust and reliable approach for qualitative studies that is well received by participants. Furthermore, the think-aloud component of the interview was implemented only after participants were familiar with this approach through practice with an item unrelated to the PROFAD-SSI-SF at the beginning of the interviews. Interviews were transcribed, deidentified, and reviewed for quality against audio recordings. All transcripts were coded and analyzed using a Microsoft Excel workbook. The transcripts were coded to identify any issues or potential problems with each element of the PROFAD-SSI-SF (i.e., the instructions, items, response choices, recall period) with the aim of evaluating the relevance, comprehensibility, and comprehensiveness of the instrument. All responses were evaluated by researchers and assigned codes to capture the type of feedback and whether remarks were spontaneous or prompted after questioning by the interviewer. Rater agreement was evaluated and reached using an iterative process whereby transcripts were coded by a trained analyst and then reviewed by a second researcher. Discrepancies between raters were identified. Follow-up consensus meetings were then held with the raters and study team to discuss any discrepancies and finalize the coding structure and rules. All coding was then reviewed and confirmed by the first author, who was the primary qualitative investigator on the study.

The sample size for CD interviews was determined using the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) PRO Good Research Practices Task Force guidelines and information from the literature [29, 30]. A total sample size of 20 patients was determined to be sufficient to test the understandability and comprehensiveness of the PROFAD-SSI-SF items.

PROFAD-SSI-SF Evaluation: Quantitative Analyses

The quantitative analysis included a post hoc psychometric analysis of blinded data from the phase 2 study described above [21, 22]. Calculations to determine sample size were not performed, as this analysis used existing data.

Test of Structure

Confirmatory factor analysis (CFA) was performed for the items and domains of the PROFAD-SS-SF to provide empirical support for its conceptual framework. An uncorrelated factor structure was used to estimate factors and single-item domains were excluded from models.

A multi-factor multi-visit model combined item responses from the screening, week 24, and week 52 visits to examine the model fit or pattern of factor loadings using data from all visits. This approach was used to increase power with a larger sample size compared with a single-visit model; it was also preferred over other models attempted based on an assessment of model fit. Model fit was evaluated using three indicators: the Comparative Fit Index (CFI), in which values closer to 1 indicate better fit [31]; the Tucker–Lewis Index (TLI), where values closer to 1 indicate a better fit and values ≥ 0.95 are deemed as indicating an acceptable fit [32]; and the root mean square error of approximation (RMSEA), in which a value of 0 indicates a perfect model fit and values < 0.08 are considered to indicate an acceptable fit [33]. Factor loadings of items onto domains and summary scores were examined to interpret the pattern of relationships of the items to domains and summary scores within the context of the hypothesized structure.

Reliability

Internal consistency was assessed with Cronbach's alpha, calculated from screening visit data for each multi-item domain for PROFAD-SSI-SF, with the a priori cutoff of 0.7 indicating adequate internal consistency [34, 35].

For test–retest reliability, intraclass correlation coefficients (ICC) were calculated from two-way mixed-effects models for the PROFAD-SSI-SF domain and summary scores using data from the screening and week 24 visits. Test–retest reliability was examined using each of two different stability criteria. Criterion 1 defined stability as a change of ≤ 1 point on the Patient Global Assessment (PtGA), whereas criterion 2 defined stability as a change of ≤ 1

point on the Physician Global Assessment (PGA). ICC values between 0.50 and 0.75 and between 0.75 and 0.90 indicate moderate and good reliability, respectively [36].

Construct Validity

Convergent/discriminant validity was determined by assessing the convergence between the domains and summary scores of the PROFAD-SSI-SF and similar criterion measures from the ESSPRI (dryness, fatigue, pain, and total score), PtGA, PGA, oral dryness 11-point numeric rating scale (NRS), ocular dryness 11-point NRS, ESSDAI, Schirmer's test, and stimulated and unstimulated salivary flow tests. Only correlation coefficients > 0.30 were considered to be adequately supportive of convergent validity [37].

Known-groups validity analyses compared each of the PROFAD-SSI-SF domain and summary scores with the PtGA, where severity groups were defined as mild (PtGA score of 0–3), moderate (PtGA score of 4–6), and severe (PtGA score of ≥ 7). The analyses used separate one-way between-patient analysis of variance (ANOVA) models. When the omnibus *F*-test was statistically significant, post hoc tests for pairwise comparisons among groups were conducted, using Sidak corrections to control for family-wise type I error due to multiplicity. As very few patients met the criteria for mild severity at screening ($n = 6$), it was decided that data from the week 24 visit would be used instead.

Ability to Detect Change

Correlations between changes in PROFAD-SSI-SF domain and summary scores from screening to weeks 24 and 52 and changes in PGA, PtGA, oral dryness 11-point NRS, ocular dryness 11-point NRS, and ESSDAI during the same time intervals were analyzed. Acceptable levels of concordance were deemed correlations ≥ 0.30.

A second approach assessed the difference in the mean change in PROFAD-SSI-SF domain and summary scores at weeks 24 and 52 across three responder subgroups, defined as those with a large improvement in PtGA (a decrease of ≥ 4 points), a small improvement (a decrease of 2 or 3 points), or no change/worsening (≥ -1 point), as assessed using separate one-way between-patient ANOVA models. When the omnibus *F*-test was statistically significant, post hoc tests for pairwise comparisons among groups were conducted, using Sidak corrections to control for family-wise type I error due to multiplicity.

Analyses of Within-Patient Meaningful Change

Exploratory, anchor-based, participant-meaningful change analyses were conducted by examining standardized response means of PROFAD-SSI-SF summaries when anchored to the PtGA. Several cutoffs were examined in order to identify an inflection point in the summary scores. The definition of meaningful change identified used a PtGA cutoff of ≥ 3 points of improvement (i.e., a change of -3 points) or a $\geq 30\%$ improvement between screening and weeks 24 and 52. Corresponding values were derived using this definition for each scale by examining the respective changes in summary scores across weeks 24 and 52.

In addition, two distribution-based approaches for estimating the magnitude of meaningful change in PRO scores was performed; one approach used one-half of the measure's standard deviation for scores at screening [38], while the other calculated the standard error of measurement [39].

Compliance with Ethical Guidelines

Ethical considerations for the online CE discussion forum and the phase 2 study are summarized elsewhere [21–23].

For the CD interviews, all patients provided informed consent and the study was overseen by an independent review board (IRB) or ethics committee (IRB# 120190199).

RESULTS

Refining a Disease Model for pSS: Qualitative Analysis

CE Discussion Forum: Secondary Analysis

Results from the secondary analysis of the online patient forum discussion transcripts

($n = 46$ participants) centered on symptom experience and burden of illness (e.g., symptoms and physical, social, emotional, and financial impacts) and treatment experience (e.g., prescription and over-the-counter medications taken, effectiveness of treatments, and treatment preferences), and confirmed the concepts of greatest importance for measurement that had been drafted based on the literature. Common symptoms and related comorbidities, impacts, and triggers reported by participants are shown in Fig. 2. According to the forum participants, dryness (oral: 87.0% [$n = 40/46$], ocular: 73.9% [$n = 34/46$], cutaneous: 37.0% [$n = 17/46$], vaginal: 23.9% [$n = 11/46$], nasal: 15.2% [$n = 7/46$], otic: 6.5% [$n = 3/46$]), pain (89.1% [$n = 41/46$]), and fatigue (87.0% [$n = 40/46$]) were the most commonly reported symptoms, affecting almost all aspects of functioning and well-being (Fig. 2).

KOL Interviews

Overall, the KOLs found the key concepts accurate and the disease model appropriate in its representation of the causes, signs, symptoms, triggers, and impacts of pSS. They also confirmed that any PRO used in a pSS-specific study should focus on dryness, joint pain, and fatigue.

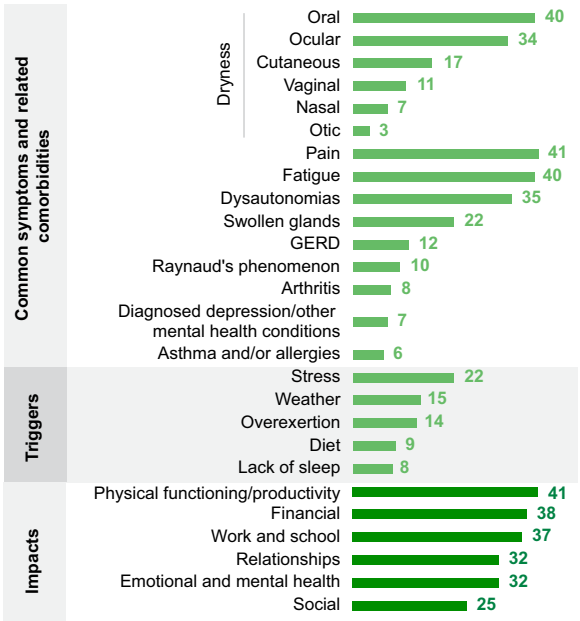

Fig. 2 Concept elicitation forum results showing the number of patients reporting common symptoms of pSS and related comorbidities, triggers, and impacts of pSS ($N = 46$). *GERD* gastroesophageal reflux disease, *pSS* primary Sjögren's syndrome

The final disease model is presented in Fig. S1 in the Supplementary Material. It describes pSS in terms of causes, signs, symptoms, and exacerbating factors or triggers and summarizes the impact of pSS on patients' functioning and well-being.

PROFAD-SSI-SF Evaluation: Qualitative Analyses

CD Interviews

Twenty patients with pSS (Table S2 in the Supplementary Material) took part in the CD interviews; 14 attended the interviews in person and 6 attended remotely. Data analysis did not identify any differences in the findings between these two modes of data collection.

Overall, participants had positive feedback on the PROFAD-SSI-SF; comprehensiveness and relevance were cited as the questionnaire's strengths. All participants asked found the items easy to understand (100.0% [$n = 19/19$]), most (90.0% [$n = 18/20$]) reported no difficulty when choosing answers, and the majority ($\geq 18/20$ participants [$\geq 90.0\%$]) considered 14 of the 19 items relevant to their experiences with pSS. Most participants felt that the questionnaire was an appropriate length (83.3% [$n = 15/18$]) and had an appropriate recall period (70.0% [$n = 14/20$]). Around half thought that it was sufficiently comprehensive (55.0% [$n = 11/20$]), although some suggested additional items for inclusion, such as comorbidities, dry hair, changes in vision, swelling in other places than fingers or wrists, mucus, stomach irritation, dry lips, joint pain, tinnitus, constipation, anxiety, depression, and brain fog. Participants did not report any problems with item content for 11 of the 19 items. Some patients made suggestions for modifications (e.g., revisions or removal) to the remaining eight items; however, these recommendations were not reported consistently across the sample.

PROFAD-SSI-SF Evaluation: Quantitative Analyses

Test of Structure

The domains of the PROFAD-SSI-SF were confirmed by CFA in the multi-factor multi-visit model (Table 1). Evidence supported a good fit with the multi-factor multi-visit model, as indicated by CFI (0.98), TLI (0.99), and RMSEA (0.07), which exceeded the suggested thresholds indicating acceptable fit.

Across all domains, the magnitudes of item-to-factor loadings were large, with all loadings ≥ 0.74 (Table 1). Items for the somatic fatigue and mental fatigue domains had the largest magnitudes over all loading of items, with all ≥ 0.86. The oral dryness domain had the smallest magnitude loadings (0.74–0.85), with difficulty eating the only item within that domain with a loading > 0.80.

Reliability

All domains with multiple items, except for arthralgia, had Cronbach's alpha values of $>$ 0.80, exceeding the suggested threshold indicating adequate fit (Table 2). These findings showed acceptable internal consistency of the PROFAD-SSI-SF.

For test–retest reliability, only a small number of patients (PtGA [criterion 1]: 34.9% [n = 30/86]; PGA [criterion 2]: 20.9% [n = 18/86]) met the criteria for stability. When stability was defined by PtGA, only one PROFAD-SSI-SF domain (vaginal dryness: 0.85) exceeded the a priori ICC value for good test–retest reliability (≥ 0.75); however, the majority of the domain and summary scores had ICCs ≥ 0.50, indicating at least moderate reliability (Table 2). When stability was defined by PGA (criterion 2), four PROFAD-SSI-SF domains (mental fatigue: 0.81, vaginal dryness: 0.93, ocular dryness: 0.76, SSI summary score: 0.87) showed good reliability; the majority of the domain and summary scores had ICCs ≥ 0.50, indicating at least moderate reliability.

Construct Validity

PROFAD-SSI-SF showed convergent validity with measures derived from patient reports.

Table 1 Confirmatory factor analysis of domains of the PROFAD-SSI-SF

	Multi-factor multi-visit model[a]
Domain	
Somatic fatigue	
Item 1 (need rest)	0.88
Item 2 (difficulty starting)	0.88
Item 3 (low stamina)	0.93
Item 4 (weak muscles)	0.86
Mental fatigue	
Item 5 (poor concentration)	0.95[b]
Item 6 (poor memory)	0.95
Arthralgia	
Item 7 (discomfort/pain)	0.79[b]
Item 8 (ache all over)	0.79
Vascular dysfunction[c]	
Item 9 (vascular dysfunction)	–
Cutaneous dryness[c]	
Item 10 (cutaneous dryness)	–
Vaginal dryness[c]	
Item 11 (vaginal dryness)	–
Ocular dryness	
Item 12 (sore eyes)	0.90
Item 13 (eye irritation)	0.78
Item 14 (poor vision)	0.88
Oral dryness	
Item 15 (difficulty eating)	0.85
Item 16 (dry throat)	0.78
Item 17 (bad breath)	0.75
Item 18 (wetting mouth)	0.75
Item 19 (oral problems)	0.74
Model fit statistics	
Sample size[d]	228
Estimator[e]	WLSMV

Table 1 continued

	Multi-factor multi-visit model[a]
RMSEA[f]	**0.07**
CFI[g]	**0.98**
TLI[h]	**0.99**

Models exceeding the threshold for acceptable fit are indicated in bold

CFI Comparative Fit Index, *PROFAD-SSI-SF* Profile of Fatigue and Discomfort–Sicca Symptoms Inventory–Short Form, *RMSEA* root mean square error of approximation, *TLI* Tucker–Lewis index, *WLSMV* weighted least square mean and variance adjusted

[a]Conducted by combining data from screening, week 24, and week 52 administrations of the PROFAD-SSI-SF

[b]A Heywood case (negative residual variance) error was observed with item 5, which may be due to the two-item mental fatigue domain being just identified. To resolve this, factor loadings were kept constant for both two-item domains: mental fatigue and arthralgia

[c]Including single-item domains in the multi-factor models resulted in the underidentification of factors for these domains. Therefore, single-item domains were excluded from the multi-factor models and did not have factor loadings

[d]Patients with ≥ 1 missing item response were excluded from analysis (screening: $n = 1$, week 24: $n = 2$, week 52: $n = 1$)

[e]WSLMV was used instead of maximum likelihood because several polychoric and Pearson correlations differed by > 0.1

[f]Value of 0 indicates a perfect model fit and values < 0.08 are considered to indicate an acceptable fit

[g]Values closer to 1 indicate a better fit

[h]Values closer to 1 indicate a better fit and values ≥ 0.95 are deemed to indicate an acceptable fit

Correlation coefficients > 0.30, indicating acceptable evidence of convergent validity, were observed between other PROs with most PROFAD-SSI-SF domains and summary scores (Table 3). In particular, the PROFAD-SSI-SF fatigue (especially somatic fatigue) domain scores and the PROF summary score were strongly associated with the ESSPRI fatigue scores. Also, the PROFAD-SSI-SF ocular and oral dryness domains showed strong associations with the respective ESSPRI and NRS scales. Associations with other scales measuring dryness were generally weaker for the cutaneous dryness and vaginal dryness domains of the PROFAD-SSI-SF. PROFAD-SSI-SF did not show convergence with clinical measures (PGA, ESSDAI) nor biomarkers (Table 3).

For known-groups validity, all domain and summary scores of the PROFAD-SSI-SF showed statistically significant differences across the three severity groups (all $F \geq 3.72$, all $p \leq 0.03$) with measures derived from patient reports (Table 4). Pairwise Sidak tests showed that, for all domains, the severe group scored statistically significantly worse than the mild group.

Ability to Detect Change

Acceptable levels of concordance (correlations ≥ 0.30) were observed between changes in PROFAD-SSI-SF and changes in other PROs (PtGA, oral dryness NRS, and ocular dryness NRS) from screening to weeks 24 and 52, except for the PROF and PROFAD summary scores with ocular dryness NRS at week 52 (Table 5). The majority of the correlation coefficients (i.e., 31 of 48) for change between the PROFAD-SSI-SF domains and the PROs were ≥ 0.30. No correlations ≥ 0.30 were observed for the cutaneous dryness domain, while only one correlation, with the PtGA at week 24, exceeded 0.30 for the vaginal dryness domain.

All correlation coefficients between changes in the domain and summary scores of the PROFAD-SSI-SF and changes in clinician-rated outcomes—ESSDAI score and PGA—were small (i.e., ≤ 0.33; see Table 5).

In a comparison of responder groups defined by change in PtGA, omnibus tests for all ANOVA models were statistically significant ($p < 0.05$), except for the vascular dysfunction domain at week 24, vaginal dryness domain at week 52, and cutaneous dryness domain at both weeks 24 and 52 (Table 6).

Analyses of Meaningful Change

Corresponding values for meaningful change were approximately 1.5 to 2 points for PROF and PROFAD and 1.5 points for improvement in SSI summary scores (Table 7). The two

Table 2 Internal consistency analysis and test–retest reliability for multi-item domains of the PROFAD-SSI-SF

Domains	Internal consistency analysis[a]			Test–retest reliability (criterion 1)[b]				Test–retest reliability (criterion 2)[c]			
	N	Number of items in domain	Cronbach's alpha[d]	*N*	Screening Mean (SD)	Week 24 Mean (SD)	ICC[e]	*N*	Screening Mean (SD)	Week 24 Mean (SD)	ICC[e]
Somatic fatigue domain	85	4	**0.91**	30	4.42 (1.39)	4.18 (1.46)	0.35	18	4.61 (1.51)	4.47 (1.77)	0.44
Mental fatigue domain	86	2	**0.88**	30	3.70 (1.92)	3.10 (2.20)	0.63	18	3.94 (1.66)	3.42 (2.10)	**0.81**
Arthralgia domain	86	2	**0.74**	30	3.75 (2.08)	3.40 (2.00)	0.56	18	4.11 (1.90)	4.06 (2.01)	0.48
Vascular dysfunction domain	–	–	–	30	3.00 (2.21)	2.40 (2.33)	0.53	18	2.89 (2.22)	3.06 (2.51)	0.61
Cutaneous dryness domain	–	–	–	30	4.00 (2.21)	3.43 (2.18)	0.45	18	3.56 (1.92)	3.72 (2.19)	0.47
Vaginal dryness domain	–	–	–	29	3.14 (2.46)	3.07 (2.28)	**0.85**	18	3.56 (2.33)	3.56 (2.33)	**0.93**
Ocular dryness domain	86	3	**0.83**	30	4.71 (1.46)	4.57 (1.49)	0.50	18	4.83 (1.87)	5.24 (1.72)	**0.76**
Oral dryness domain	86	5	**0.84**	30	4.43 (1.29)	4.02 (1.66)	0.50	18	4.41 (1.40)	4.11 (1.86)	0.67
PROF summary score	–	–	–	30	4.06 (1.44)	3.64 (1.63)	0.52	18	4.28 (1.17)	3.94 (1.53)	0.59
PROFAD summary score	–	–	–	30	3.72 (1.48)	3.27 (1.62)	0.64	18	3.89 (1.27)	3.75 (1.66)	0.68
SSI summary score	–	–	–	30	4.07 (1.26)	3.77 (1.40)	0.68	18	4.09 (1.48)	4.16 (1.58)	**0.87**

ICC intraclass correlation coefficient, *PGA* Physician Global Assessment, *PROF* Profile of Fatigue, *PROFAD-SSI-SF* Profile of Fatigue and Discomfort–Sicca Symptoms Inventory–Short Form, *PtGA* Patient Global Assessment, *SD* standard deviation, *SSI* Sicca Symptoms Inventory

[a]This analysis was conducted at the screening visit only, and for multi-item domains only; single-item domains (vascular dysfunction, cutaneous dryness, and vaginal dryness) were not included

[b]Stable group was defined as patients with a change of ≤ 1 point in PtGA from screening to week 24

[c]Stable group was defined as patients with a change of ≤ 1 point in PGA from screening to week 24

[d]Cronbach's alpha values > 0.70, indicating adequate consistency, are shown in bold

[e]Calculated based on visits at screening and week 24; values > 0.75, indicating good reliability, are shown in bold

Table 3 Correlations among PROFAD-SSI-SF domain and summary scores and scores on criterion measures

Domain	*N*	ESSPRI				PtGA	PGA	11-Point dryness NRS		ESSDAI score	Schirmer's test	Salivary flow	
		Dryness	Fatigue	Pain	Total score			Oral	Ocular			Stimulated	Unstimulated
Somatic fatigue	86	**0.40**	**0.78**	**0.64**	**0.78**	**0.55**	0.12	0.25	**0.34**	− 0.09	–	–	–
Mental fatigue	86	0.26	**0.55**	**0.41**	**0.53**	0.28	− 0.14	0.23	0.22	− 0.26	–	–	–
Arthralgia	86	0.18	**0.46**	**0.82**	**0.66**	**0.44**	− 0.03	0.06	0.14	− 0.02	–	–	–
Vascular dysfunction	86	**0.33**	0.11	**0.31**	**0.32**	0.21	0.08	0.17	0.30	0.07	–	–	–
Cutaneous dryness	86	**0.40**	0.27	**0.35**	**0.44**	0.29	0.14	0.26	0.23	0.12	–	–	–
Vaginal dryness	80	0.26	0.25	0.19	0.29	0.21	0.08	0.15	0.17	− 0.06	–	–	–
Ocular dryness	86	**0.59**	**0.42**	0.21	**0.49**	**0.47**	0.01	**0.47**	**0.67**	− 0.14	0.01	–	–
Oral dryness	86	**0.64**	**0.39**	0.25	**0.52**	**0.52**	− 0.02	**0.54**	**0.42**	− 0.02	–	− 0.33	− 0.29
PROF summary score	86	**0.37**	**0.74**	**0.59**	**0.73**	**0.46**	− 0.02	0.27	**0.32**	− 0.20	–	–	–
PROFAD summary score	86	**0.38**	**0.59**	**0.71**	**0.74**	**0.48**	0.01	0.23	**0.33**	− 0.09	–	–	–
SSI summary score	86	**0.59**	**0.42**	**0.32**	**0.55**	**0.46**	0.07	**0.44**	**0.46**	− 0.03	0.01	− 0.15	− 0.20

Correlation coefficients > 0.30, indicating acceptable evidence of convergent validity, are shown in bold

ESSDAI EULAR Sjögren's Syndrome Disease Activity Index, *ESSPRI* EULAR Sjögren's Syndrome Patient Reported Index, *EULAR* European Alliance of Associations for Rheumatology, *NRS* numeric rating scale, *PGA* Physician Global Assessment, *PROF* Profile of Fatigue, *PROFAD-SSI-SF* Profile of Fatigue and Discomfort–Sicca Symptoms Inventory–Short Form, *PtGA* Patient Global Assessment, *SSI* Sicca Symptoms Inventory

Table 4 Known-groups validity analysis: severity classified by PtGA at week 24

	Mild (PtGA 0–3)		Moderate (PtGA 4–6)		Severe (PtGA 7–10)		*F*	*p* value[a]
	N	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)		
Domain								
Somatic fatigue	17	1.91 (1.56)	28	3.30 (1.66)	29	4.55 (1.44)	15.70	< **0.001**[x,y,z]
Mental fatigue	17	0.97 (1.02)	28	2.73 (2.08)	29	3.00 (2.09)	6.68	**0.002**[x,y]
Arthralgia	17	1.85 (1.67)	29	2.57 (1.91)	29	3.62 (1.91)	5.25	**0.007**[y]
Vascular dysfunction	17	0.35 (0.86)	29	1.59 (1.82)	29	2.93 (2.53)	9.35	< **0.001**[y,z]
Cutaneous dryness	17	1.24 (1.48)	29	3.24 (1.83)	29	3.90 (2.37)	9.83	< **0.001**[x,y]
Vaginal dryness	15	1.73 (2.25)	27	2.37 (2.15)	28	3.61 (2.50)	3.72	**0.030**[y]
Ocular dryness	17	2.14 (1.74)	29	3.70 (1.87)	29	4.68 (1.73)	10.84	< **0.001**[x,y]
Oral dryness	17	1.69 (1.29)	28	2.94 (1.64)	29	4.12 (1.88)	11.52	< **0.001**[y,z]
PROF summary score	17	1.44 (1.03)	28	3.02 (1.65)	29	3.78 (1.42)	14.09	< **0.001**[x,y]
PROFAD summary score	17	1.27 (0.92)	28	2.52 (1.44)	29	3.53 (1.52)	14.53	< **0.001**[x,y,z]
SSI summary score	17	1.68 (1.30)	28	3.02 (1.33)	29	4.07 (1.67)	14.19	< **0.001**[x,y,z]

PROF Profile of Fatigue, *PROFAD-SSI-SF* Profile of Fatigue and Discomfort–Sicca Symptoms Inventory–Short Form, *PtGA* Patient Global Assessment, *SD* standard deviation, *SSI* Sicca Symptoms Inventory

[a]Bold values show that the Sidak test result was significant ($p < 0.05$) for pairwise comparisons: [x]mild versus moderate; [y]mild versus severe; [z]moderate versus severe

distribution-based approaches of meaningful change generally showed agreement, indicating an approximately meaningful change of approximately 1 point.

DISCUSSION

Overall, these analyses support the content validity and measurement properties of the PROFAD-SSI-SF for use among patients with pSS.

The final disease model confirmed that the items and content of the PROFAD-SSI-SF assess the most relevant and important concepts to patients with pSS. The results of the CE forums and KOL interviews emphasized the importance of the impact of dryness, pain, and fatigue when evaluating burden of disease and treatment benefits in patients with pSS. Dryness, pain, and fatigue have previously been reported as symptoms central to pSS [25, 40–42], and key expert panel discussions have also highlighted fatigue as a particularly important outcome domain in relation to patients' disease experiences [43, 44].

In this study, the CD interviews confirmed that the concepts contained within the PROFAD-SSI-SF were appropriate to measure dryness, pain, and fatigue in patients with pSS and were understandable, with most items considered relevant by most patients. Problems with the questions reported by participants in the CD interviews were infrequent and generally focused on the redundancy of some items or personal preferences (e.g., changing "hard to see ATM or computer screen" in item 14's list of examples to reflect cell phone screens). However, because feedback about redundancies was inconsistent and none of the issues impacted participants' ability to understand the items as intended, no changes to the instrument are proposed. Some patients reported concepts (e.g., gastrointestinal issues, changes in vision, dry hair) related to their experience with pSS

Table 5 Change score correlations at weeks 24 and 52

	PtGA	PGA	Oral dryness NRS	Ocular dryness NRS	ESSDAI score	Lacrimal function (Schirmer's)	Unstimulated salivary flow	Stimulated salivary flow
Week 24								
PROFAD-SSI-SF domain								
Somatic fatigue	**0.60**	0.28	**0.31**	**0.40**	0.22	− 0.09	− 0.05	0.04
Mental fatigue	**0.41**	0.16	**0.39**	**0.37**	0.14	− 0.09	− 0.12	0.07
Arthralgia	**0.48**	0.29	**0.33**	**0.32**	0.27	− 0.08	− 0.02	0.17
Vascular dysfunction	0.23	0.27	0.23	**0.37**	0.25	− 0.24	− 0.13	− 0.07
Cutaneous dryness	0.18	0.00	0.28	0.27	0.07	− 0.05	0.04	0.21
Vaginal dryness	**0.34**	0.22	0.29	0.17	0.01	− 0.05	− 0.22	− 0.01
Ocular dryness	**0.39**	0.28	**0.41**	**0.62**	0.08	− 0.12	− 0.12	0.06
Oral dryness	**0.43**	0.09	**0.47**	**0.44**	0.18	− 0.15	− 0.13	0.09
PROF summary score	**0.57**	0.25	**0.40**	**0.44**	0.21	− 0.10	− 0.10	0.07
PROFAD summary score	**0.56**	**0.33**	**0.40**	**0.48**	**0.33**	− 0.17	− 0.12	0.06
SSI summary score	**0.42**	0.17	**0.46**	**0.48**	0.15	− 0.11	− 0.14	0.11
Week 52								
PROFAD-SSI-SF domain								
Somatic fatigue	**0.52**	0.22	**0.39**	0.21	0.08	0.10	− 0.18	0.00
Mental fatigue	**0.43**	0.14	**0.44**	0.23	0.00	− 0.08	− 0.12	− 0.05
Arthralgia	**0.41**	0.13	0.24	− 0.03	0.11	0.12	0.10	0.17
Vascular dysfunction	**0.36**	0.24	**0.43**	**0.32**	0.06	0.02	0.04	0.05
Cutaneous dryness	0.11	0.21	0.08	0.10	0.22	− 0.04	− 0.03	0.06
Vaginal dryness	0.25	0.07	0.29	0.17	− 0.09	− 0.15	− 0.07	0.14
Ocular dryness	**0.50**	0.20	**0.41**	**0.48**	− 0.05	0.04	− 0.24	0.04
Oral dryness	**0.49**	0.03	**0.53**	**0.35**	0.05	− 0.10	− 0.08	− 0.03
PROF summary score	**0.54**	0.20	**0.46**	0.25	0.04	0.02	− 0.17	− 0.03
PROFAD summary score	**0.58**	0.25	**0.51**	0.25	0.09	0.06	− 0.04	0.07
SSI summary score	**0.45**	0.19	**0.44**	**0.37**	0.06	− 0.08	− 0.12	0.08

Acceptable levels of concordance (correlation ≥ 0.30) are indicated in bold

ESSDAI EULAR Sjögren's Syndrome Disease Activity Index, *EULAR* European Alliance of Associations for Rheumatology, *NRS* numeric rating scale, *PGA* Physician Global Assessment, *PROF* Profile of Fatigue, *PROFAD-SSI-SF* Profile of Fatigue and Discomfort–Sicca Symptoms Inventory–Short Form, *PtGA* Patient Global Assessment, *SSI* Sicca Symptoms Inventory

that they felt were missing from the PROFAD-SSI-SF. However, the use of the PROFAD-SSI-SF in combination with other PRO instruments that assess those concepts not included in the PROFAD-SSI-SF has the potential to facilitate a comprehensive holistic assessment of the experience of patients with pSS.

Importantly, the CD interviews were conducted in patients with pSS and organ involvement. This allowed the PROFAD-SSI-SF to be validated in this group of patients. While a minority of patients have high disease activity and/or severe organ involvement [45], pain, fatigue, and dryness are cardinal symptoms of pSS, and are the aspects patients most wish to improve [23].

In our quantitative analysis, patients were evaluated at weeks 24 and 52, in line with the interim and primary analysis data available, respectively, from the phase 2 study (GSK Study 201842) that assessed the efficacy and safety of belimumab and rituximab in patients with pSS [21, 22]. The PROFAD-SSI-SF, PtGA, and PGA were not performed after week 52. However, none of the described analyses considered treatment manipulations, and the intent was to evaluate the measurement properties of the PROFAD-SSI-SF. Where stratification of participants was performed, stratification was based on indications of change as indicated by other specified assessment variables such as the PtGA or disease activity as measured by ESSDAI. The quantitative analyses confirmed an acceptable fit of the factor structure of the PROFAD-SSI-SF, as well as good internal consistency, construct validity, and ability to detect change in patients with pSS. Consistent with our findings, a previous study performed to validate the SSI—a component of the PROFAD-SSI-SF—also reported that it was a measure with good construct validity that captured some of the most important symptoms associated with pSS [17]. Another study reported that the PROFAD had a similar structure to the Multidimensional Fatigue Inventory (MFI), but with better resolution of somatic fatigue facets than the MFI [40]. Similarly, results of a previous study assessing the sensitivity of the questionnaire in distinguishing fatigue in patients with pSS, systemic lupus erythematosus, and rheumatoid arthritis indicated that the PROFAD-SSI-SF was an appropriate tool to assess whether the severity of fatigue is pathological in patients with pSS [16]. The sensitivity of the PROFAD-SSI-SF was greater than the Medical Outcome Study 36-Item Short-Form Health Survey in the measurement of patient status [16, 46].

In terms of concordance between the PROFAD-SSI-SF and clinical assessments (such as the PGA, ESSDAI, and Schirmer test), the quantitative analysis revealed no or poor concordance between these measures, whereas there was acceptable concordance between the PROFAD-SSI-SF and other PROs; for example, the oral dryness NRS and ocular dryness NRS. This is comparable with several studies in pSS that have reported only weak or moderate correlations between PRO measures and clinical assessments but relatively high correlations with other PROs [17, 47–50]. Also, a recent randomized controlled trial found that clinical measures improved with the study drug, whereas ESSPRI and PtGA did not [51]. The consistency of this observation across different PROs and studies points to a disconnect between patients' and clinicians' assessments of symptom severity in pSS, rather than patients having difficulties with a particular measure or being inconsistent in their reporting. Altogether, this suggests that the PROFAD-SSI-SF captures patient experiences of the disease that are potentially not well reflected in clinical measures. Therefore, to get a complete picture of patient burden and treatment benefits, it could be beneficial to utilize a complementary measure such as the PROFAD-SSI-SF along with clinical measures.

The ESSDAI and the ESSPRI were developed to measure disease activity and key pSS symptoms, respectively, in clinical trials, and have become commonly used when investigating the effectiveness of new therapies [48, 52, 53]. While the ESSPRI uses a single visual analogue scale per symptom or concept, the multi-question PROFAD-SSI-SF may reveal more information while being of an appropriate length for use as an outcome measure in clinical trials.

This study has some limitations. The secondary analysis of the CE discussion forum was performed on a pre-existing dataset, making it

Table 6 Analysis of ability to detect change at weeks 24 and 52

	No change/worsening in PtGA[a]		Small improvement in PtGA[b]		Large improvement in PtGA[c]		*F*	*p* value[d]
	N	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)		
Week 24								
PROFAD-SSI-SF domain								
Somatic fatigue	38	0.04 (1.64)	21	− 1.05 (1.81)	14	− 2.74 (1.75)	13.77	< **0.001**[y,z]
Mental fatigue	38	− 0.26 (1.98)	21	− 1.38 (2.16)	14	− 1.50 (1.59)	3.22	**0.046**
Arthralgia	38	− 0.04 (2.07)	22	− 1.64 (2.42)	14	− 1.79 (1.96)	5.45	< **0.006**[x,y]
Vascular dysfunction	38	− 0.37 (2.11)	22	− 1.36 (3.02)	14	− 1.21 (2.08)	1.41	0.250
Cutaneous dryness	38	− 0.26 (2.36)	22	0.14 (2.95)	14	− 1.36 (2.90)	1.41	0.252
Vaginal dryness	36	0.03 (1.36)	20	− 0.50 (2.01)	13	− 1.46 (2.18)	3.55	**0.034**[y]
Ocular dryness	38	0.10 (1.48)	22	− 0.88 (2.14)	14	− 1.48 (2.39)	4.25	**0.018**[y]
Oral dryness	38	− 0.18 (1.54)	21	− 0.85 (1.57)	14	− 1.83 (1.85)	5.48	**0.006**[y]
PROF summary score	38	− 0.11 (1.60)	21	− 1.21 (1.69)	14	− 2.12 (1.45)	8.96	< **0.001**[x,y]
PROFAD summary score	38	− 0.16 (1.39)	21	− 1.42 (1.87)	14	− 1.81 (1.17)	8.37	**0.001**[x,y]
SSI summary score	38	− 0.08 (1.15)	21	− 0.59 (1.80)	14	− 1.57 (1.83)	5.08	**0.009**[y]
Week 52								
PROFAD-SSI-SF domain								
Somatic fatigue	39	0.06 (1.62)	18	− 1.06 (1.54)	14	− 2.56 (2.18)	12.27	< **0.001**[y]
Mental fatigue	39	0.21 (1.42)	18	− 0.89 (1.75)	14	− 1.79 (2.04)	8.42	**0.001**[y]
Arthralgia	39	− 0.06 (1.94)	18	− 1.19 (2.24)	14	− 1.57 (2.39)	3.44	**0.038**
Vascular dysfunction	39	0.67 (2.22)	18	− 1.33 (2.14)	14	− 1.36 (2.95)	6.39	< **0.003**[x,y]
Cutaneous dryness	39	− 0.03 (2.31)	18	− 0.83 (2.38)	14	− 1.00 (2.15)	1.31	0.277
Vaginal dryness	35	− 0.57 (1.38)	18	− 0.78 (1.86)	13	− 1.69 (2.50)	1.91	0.157
Ocular dryness	39	0.14 (1.43)	18	− 1.22 (0.99)	14	− 1.48 (1.97)	9.03	< **0.001**[x,y]
Oral dryness	39	− 0.11 (1.25)	18	− 1.31 (1.34)	14	− 1.71 (1.63)	9.52	< **0.001**[x,y]
PROF summary score	39	0.13 (1.33)	18	− 0.97 (1.53)	14	− 2.17 (1.63)	13.89	< **0.001**[x,y]
PROFAD summary score	39	0.22 (1.12)	18	− 1.12 (1.55)	14	− 1.82 (1.60)	14.34	< **0.001**[x,y]

Table 6 continued

	No change/worsening in PtGA[a]		Small improvement in PtGA[b]		Large improvement in PtGA[c]		*F*	*p* value[d]
	N	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)		
SSI summary score	39	− 0.11 (0.92)	18	− 1.04 (1.18)	14	− 1.45 (1.61)	8.72	< **0.001**[x,y]

PtGA decrease indicates an improvement in health status

PGA Physician Global Assessment, *NRS* numeric rating scale, *PROF* Profile of Fatigue, *PROFAD-SSI-SF* Profile of Fatigue and Discomfort, *PtGA* Patient Global Assessment, *SSI* Sicca Symptoms Inventory

[a]Change ≥ − 1 in PtGA from screening to week 24 or 52

[b]Decrease of 2 or 3 points in PtGA from screening to week 24

[c]Decrease of 4 or more points in PtGA from screening to week 24

[d]Bold values show that the Sidak test result was significant ($p < 0.05$) for pairwise comparisons: [x]no change/worsening versus small improvement; [y]no change/worsening versus large improvement; [z]small improvement versus large improvement

impossible to ask follow-up questions, and furthermore, the sample size of the phase 2 trial was based on the primary study objective (to investigate safety and tolerability); therefore, it was not sized for the purpose of the current quantitative analyses. In addition, the method used to collect CE discussion forum data meant that consistent information was not always collected for all participants. Nonetheless, analysis confirmed that saturation of concepts was achieved. In addition, the KOL interviews served to add information and insight to the outcomes of the discussion forum. The test–retest reliability results should be interpreted with caution due to the relatively long 6-month time interval between test and retest, which is longer than typically applied in psychometric validations of PROs [54]. Given this longer time interval, few patients would be expected to remain stable in a clinical trial setting. As expected, only a small number of patients met the criteria for stability, and those analyses were underpowered due to small sample sizes, increasing the likelihood of imprecise ICC estimates.

Despite some limitations, results from this study provide valuable information from a patient perspective about dryness, pain, and fatigue associated with pSS. Moreover, it has been argued that randomized controlled trials should use specific and validated definitions of endpoints and use evidence-based selection of the most treatment-responsive pSS domains [55]. The results presented here support the use of the PROFAD-SSI-SF in such clinical trials.

CONCLUSIONS

Findings from this study support the content validity and measurement properties of the PROFAD-SSI-SF, a fit-for-purpose PRO measure appropriate for use among patients with pSS in clinical trials supporting drug development. The content validity of PROFAD-SSI-SF was further demonstrated by the final disease model, where it was confirmed that PROFAD-SSI-SF assessed the most relevant and important concepts to patients with pSS. The results of this study highlight the importance of including PRO measures such as the PROFAD-SSI-SF in clinical trials and clinical practice, as clinical ratings are not sufficient by themselves to capture patient health and treatment benefit.

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Table 7 Results of anchor-based meaningful change analyses at weeks 24 and 52

	Change in PtGA cut[a]	*N*	Mean change	SD of change	Median (IQR)	SRM[b]
Week 24						
PROF summary score	− 3	7	− 1.84	1.51	− 1.75 (− 3.63, − 0.63)	− 1.22
	≤ − 3	21	− 2.03	1.44	− 2.38 (− 3.50, − 0.56)	− 1.41
	≤ − 30%	26	− 1.85	1.45	− 1.94 (− 2.81, − 0.44)	− 1.28
PROFAD summary score	− 3	7	− 2.06	1.81	− 1.38 (− 3.69, − 0.56)	− 1.14
	≤ − 3	21	− 1.89	1.37	− 1.63 (− 2.97, − 0.88)	− 1.38
	≤ − 30%	26	− 1.67	1.41	− 1.44 (− 2.75, − 0.52)	− 1.19
SSI summary score	− 3	7	− 0.53	2.17	0.13 (− 3.37, 0.60)	− 0.24
	≤ − 3	21	− 1.22	1.96	− 0.97 (− 3.31, 0.28)	− 0.62
	≤ − 30%	26	− 1.16	1.87	− 0.73 (− 3.28, 0.25)	− 0.62
Week 52						
PROF summary score	− 3	12	− 1.42	1.41	− 1.75 (− 2.53, − 0.13)	− 1.01
	≤ − 3	26	− 1.82	1.55	− 1.94 (− 2.91, − 0.63)	− 1.18
	≤ − 30%	27	− 1.75	1.56	− 1.88 (− 2.88, − 0.5)	− 1.12
PROFAD summary score	− 3	12	− 1.40	1.39	− 1.06 (− 2.67, − 0.28)	− 1.01
	≤ − 3	26	− 1.62	1.49	− 1.22 (− 2.36, − 0.42)	− 1.09
	≤ − 30%	27	− 1.59	1.47	− 1.13 (− 2.31, − 0.44)	− 1.08
SSI summary score	− 3	12	− 1.42	1.12	− 1.01 (− 2.32, − 0.55)	− 1.27
	≤ − 3	26	− 1.44	1.38	− 1.07 (− 2.23, − 0.53)	− 1.04
	≤ − 30%	27	− 1.39	1.38	− 1.03 (− 2.18, − 0.51)	− 1.01

PtGA decrease indicates an improvement in health status

IQR interquartile range, *NRS* numeric rating scale, *PGA* Physician Global Assessment, *PROF* Profile of Fatigue, *PROFAD* Profile of Fatigue and Discomfort, *PtGA* Patient Global Assessment, *SD* standard deviation, *SRM* standardized response mean, *SSI* Sicca Symptoms Inventory

[a]Change from screening to week 24 or 52

[b]SRM = (week 24 or 52 score − screening score)/(SD of change distribution)

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Compliance with Ethics Guidelines. Ethical considerations for the online CE discussion forum and the phase 2 study are summarized elsewhere [21–23]. For the CD interviews, all patients provided informed consent and the study was overseen by an independent review board (IRB) or ethics committee (IRB# 120190199).

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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