The Hidradenitis Suppurativa Symptom and Impact Diary: Development and psychometric evaluation of a novel set of patient reported outcomes for hidradenitis suppurativa

Running head: The Hidradenitis Suppurativa Symptom and Impact Diary

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Data availability: Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible trials. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymised to respect the privacy of patients who have participated in the trials in line with applicable laws and regulations. For any enquiries relating to use of the Hidradenitis Suppurativa Symptom and Impact Diary, please contact novartisprorequest@rws.com.

Ethics statement: Study data was acquired as part of two phase 3 randomised controlled trials which received standard IRB approval. The study protocol for the phase 3 trials and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each centre. The phase 3 study was performed according to The International Conference

on Harmonisation Guidelines for Good Clinical Practice that have their origin in the Declaration of Helsinki. Written informed consent was obtained from each patient during the screening visit and before any study-specific procedure was carried out. All study materials for the development study were reviewed and approved by an RTI International institutional review board (IRB) committee.

Patient consent: Written patient consent for publication was obtained.

What is already known about this topic?

- Hidradenitis suppurativa (HS) is a difficult-to-treat, chronic, recurring, inflammatory skin disease associated with a high burden of disease and a substantial negative impact on patient quality of life. Patient-reported outcome (PRO) measures are important to ensure that the patient experience is captured when evaluating efficacy of treatments in clinical trials

What does this study add?

- The Hidradenitis Suppurativa Symptom and Impact Diary (HSSID) is a novel PRO measure that has demonstrated strong cross-sectional psychometric measurement properties for all HSSID items. The HSSID can be used in clinical trials to assess the symptoms and impacts of HS in adult patients

Abstract

Background Hidradenitis suppurativa (HS) is associated with a substantial disease burden. Given the complex nature of HS-related symptoms, patient-reported outcome (PRO) measures are important to ensure that the patient experience is captured when evaluating the efficacy of treatments in clinical trials.

Objectives To develop the Hidradenitis Suppurativa Symptom and Impact Diary (HSSID©), a novel PRO measure for use in clinical trials to assess the symptoms and impacts of HS in adult patients, and to validate its psychometric properties.

Methods The development phase involved patients with HS and clinicians with HS expertise and included three sequential stages: (1) concept elicitation interviews (*N*=8), (2) item development, and (3) cognitive debriefing interviews (*N*=12). Psychometric properties of the

HSSID were evaluated using data from a subset of patients participating in the SUNSHINE (NCT03713619) and SUNRISE (NCT03713632) trials, and included assessments of reliability, validity, and ability to detect change. Anchor-based methods to estimate meaningful change thresholds were explored.

Results The HSSID comprises 11 items; five relate to HS symptoms (lesion-related pain, lesion-related itching, lesion drainage, odour, and physical fatigue) and six relate to HS impacts (ability to walk, ability to move [other than walking], sleep disturbance, time spent with other people, negative impact on emotions, and ability to complete work). Patients found the HSSID items easy to understand and reported no difficulties recalling symptoms/impacts experienced in the prior 24 hours. Overall, 478 patients from SUNSHINE and SUNRISE were included in the psychometric evaluation phase. Good association with low redundancy was observed among HSSID items with moderate (>0.30) to strong (>0.50) inter-diary item correlations among symptoms and impact items, and across groups. Test-retest reliability estimates in stable subsets were high across SUNSHINE and SUNRISE, ranging from 0.78 to 0.96. Construct validity analysis confirmed that each HSSID item correlated with ≥1 targeted support variable. HSSID item scores demonstrated satisfactory responsiveness to detect change, however, anchor-based meaningful change thresholds could be established for the worst lesion-related pain item only.

Conclusions The HSSID appropriately assesses the symptoms and impacts of HS in adults, and HSSID items demonstrated generally robust psychometric properties.

Introduction

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory, follicular skin disease characterised by deep dermal inflammatory nodules, abscesses, and tunnels.[1-4] HS is associated with a substantial disease and comorbidity burden[5,6] and can have a profound psychosocial impact on patients' lives, driven by pain, reported to be the most disturbing symptom,[7-10] depression, anxiety, self-consciousness, and sexual dysfunction.[11-14] The impact on quality of life (QoL) is reportedly worse in HS than other dermatological conditions, such as atopic dermatitis, and other major non-dermatological conditions.[15,16] Difficult-to-treat cutaneous

complications of HS are often accompanied by malodorous and purulent drainage, which further contribute to the negative impact on QoL experienced by patients.[17,18]

Given the complex nature of HS-related symptoms, patient-reported outcome (PRO) measures are important to ensure that the patient experience is captured when evaluating treatment effect in clinical trials. The HIdradenitis SuppuraTiva cORe outcomes set International Collaboration (HISTORIC) identified pain, HS-specific QoL, and the symptoms of drainage and fatigue as core domains relevant to stakeholders, including patients, for use in HS clinical trials.[19]

The SUNSHINE and SUNRISE phase 3 trials demonstrated sustained efficacy of secukinumab, alongside a favourable safety profile, in patients with moderate to severe HS.[20] When the SUNSHINE and SUNRISE trials were initiated, HS-specific PRO measures were in development, but none were fully validated, readily available, or recommended for use in clinical trials.[21] Therefore, Novartis, supported by RTI Health Solutions (RTI-HS), developed the Hidradenitis Suppurativa Symptom and Impact Diary (HSSID) to assess the *symptoms* and *impacts* of HS in adult patients, for use in the SUNSHINE and SUNRISE trials. The HSSID was developed to capture concepts of interest for treatment efficacy (e.g. worst lesion-related pain) and concepts important to other aspects of the patient experience (e.g. drainage, odour). Here, we report on the development and psychometric evaluation of the HSSID.

Methods

Study design

SUNSHINE (NCT03713619) and SUNRISE (NCT03713632) were identical, double-blind, randomized, multicentre, placebo-controlled clinical trials, which assessed the clinical efficacy

and safety of secukinumab in patients with moderate to severe HS.[20] The study design and results of SUNSHINE and SUNRISE have been published.[20]

The development and evaluation of the psychometric properties of the HSSID were conducted in two phases. The first phase included development of the HSSID with the objective of creating a tool that could be used in SUNSHINE and SUNRISE; the second phase included evaluation of the psychometric properties of the HSSID, which was conducted using data from a subset of patients participating in SUNSHINE (*N*=233) and SUNRISE (*N*=245).

Development phase of the HSSID

The HSSID was developed in accordance with the United States (US) Food and Drug Administration PRO Guidance for Industry 2009.[22] The HSSID development process included three stages: (1) concept elicitation, (2) item development, and (3) qualitative evaluation (cognitive debriefing interviews). All materials for the concept elicitation and cognitive debriefing interviews were approved by an RTI International institutional review board (IRB), and all patients provided informed consent.

Concept elicitation

Interviews were conducted with four clinical dermatologists with expertise in HS to gain their perspective on treating patients with HS to inform development of the interview guide for the concept elicitation patient interviews. Telephone interviews were then conducted with eight patients to elicit information on important symptoms and impacts of HS. Patients were identified via the Hidradenitis Suppurativa Foundation (HSF), an advocacy group in the United States. Participant criteria were developed to identify patients with moderate to severe HS, the target population for future Novartis clinical trials. Included patients were aged 18–65 years, diagnosed with HS for at least 1 year prior to the study, had HS symptoms consistent with Hurley stage II/III, had a prior history of surgical or laser procedures related to HS, were currently on or had

been treated with systemic medications, but still experiencing HS symptoms, and had ≥3 current lesions (defined as lesions causing pain and/or drainage). Patients were excluded if they were taking biologics or had used them within the last year. Interviews were conducted by two experienced RTI-HS team members, including SM, with training in qualitative methodology and more than two decades of qualitative experience. Each interview lasted approximately 60 minutes and was audio recorded and transcribed verbatim. See **Appendix S1** for interview guide.

Conceptual model

A conceptual model was developed based on input from clinicians and patients with HS (based on the results of the concept elicitation interviews) and further refined based on feedback from two dermatologists in the United States who had extensive clinical and research experience in dermatologic diseases, including HS **(Figure S1).**

Item development

Based on the results of the clinician interviews and the concept elicitation interviews, a draft item pool was developed using standard survey methodology. The items were developed to incorporate the terminology used by the participants, and alternative item wording and response options (i.e., numerical rating scales [NRS] and verbal rating scales [VRS]) were developed for further evaluation with participants. In addition, the draft item pool was reviewed by two clinical experts prior to finalising the items for the cognitive debriefing interviews.

Qualitative evaluation

Cognitive debriefing interviews were conducted with 12 adults with HS (different from those who participated in the concept elicitation interviews) in two iterative rounds to refine the items. All cognitive debriefing interviews were conducted via telephone by two experienced members of

the RTI-HS team following an interview guide. Patients were identified via HSF, and eligibility criteria were the same as the concept elicitation interviews, except that the exclusion criteria regarding biologic use was omitted. Interviews began with open-ended concept elicitation of symptoms and impacts of HS experienced by patients. Participants were then asked to engage in cognitive debriefing of the draft measure. A 'think aloud' format was used to gather information about patients' interpretation of each item. Interviewers also asked probing questions to gain further information on interpretation of the questions and response options, to identify any need for modifications to improve comprehension and ease of response. After discussing each item individually, participants were asked to identify which items were most and least relevant to their experience with HS, whether any item(s) could be omitted, and if any concepts were missing. The results of the first round of interviews (*N*=6) were analysed to identify any patterns in how patients interpreted each item and determine how well the items captured relevant concepts; the revised instructions and items were evaluated in a second round of interviews (*N*=6). Each interview lasted approximately 60 minutes and was audio recorded and transcribed. Transcripts were verified through an iterative process of technical and editorial review. The recordings were destroyed once the transcripts were finalized. See **Appendix S2** for interview guide.

Psychometric evaluation phase of the HSSID

Data source

The psychometric evaluation analysis used data from the SUNSHINE and SUNRISE phase 3 clinical trials. Patients included in the psychometric analysis were ≥18 years, had received ≥1 dose of the study treatment, and had a baseline HSSID item score. In addition, as part of the inclusion criteria for SUNSHINE and SUNRISE, patients had moderate to severe HS (defined as ≥5 inflammatory lesions affecting ≥2 distinct anatomical areas) for ≥1 year and agreed to daily

use of topical over-the-counter antiseptics on the areas affected by HS lesions while on study treatment.

Measures

Patient instruments to support the evaluation of the HSSID included the Dermatology Life Quality Index (DLQI), European Quality of Life 5-dimension 3-levels (EQ-5D-3L), Work Productivity and Activity Impairment – Specific Health Problem (WPAI-SHP), pain Numeric Rating Scale (NRS), Patient Global Impression of Change (PGI-C), and Patient Global Impression of Severity (PGI-S) questionnaires.

Clinical measures to support the evaluation of the HSSID were HS Clinical Response (HiSCR; ≥50% reduction in AN count with no increase in the number of abscesses and/or draining tunnels relative to baseline), AN50 (50% reduction in abscess and inflammatory nodule count relative to baseline), modified HS Score (mHSS), and the HS Physician's Global assessment (HS-PGA).

Analytical methods

Table 1 provides an overview of the analytical methods used to evaluate the psychometric properties of the HSSID.

Results

Development phase

Concept elicitation

Of the eight patients who completed the concept elicitation interviews, seven were female and the mean (range) age was 33.9 (25.0–41.0) years **(Table 2).** The mean (range) time since diagnosis was 9.9 (0.5–19.0) years, and six patients had Hurley stage III. Pain and a lack of

general knowledge/awareness about HS were the most frequently reported difficult aspects of having HS (each 37.5%; *n*=3), followed by impact on life and daily activities (25%; *n*=2), and feeling of hopelessness, scarring, discolouration of skin, and passing disease on to offspring (each 12.5%; *n*=1). All patients spontaneously reported pain and redness as one of their HS symptoms. Other commonly reported HS symptoms were draining (spontaneous report [S], *n*=7; probed report [P], *n*=1), fatigue (S, *n*=3; P, *n*=4), scarring (S, *n*=2; P, *n*=5), swelling/inflammation (S, *n*=1; P, *n*=5), warmth around lesions (S, *n*=1; P, *n*=7), and odour (S, *n*=4; P, *n*=2). Patients most frequently reported pain as the most bothersome symptom **(Figure 1);** a summary of the most representative patient quotes related to the most bothersome symptoms of HS is provided in **Table 3.** In terms of impacts of HS, all patients spontaneously reported limitations on the ability to walk due to pain. Other commonly reported physical impacts included difficulty with moving (besides walking) and difficulty with other physical activities.

Draft item pool

The most frequently reported concepts by patients (reported by 3 or more patients) were included in the draft item pool, along with those that were reported as bothersome and which had the potential to improve with treatment. The draft item pool included 29 items for further evaluation.

Cognitive debriefing interviews

The initial item pool was evaluated and refined through two iterative rounds of interviews conducted with 12 patients **(Table 2)**, who provided feedback on their understanding of instructions, questions, response options, and the recall period. Participants found the items easy to understand and simple to answer. They reported no difficulty recalling HS symptoms and impacts experienced in the previous 24 hours. In relation to the impact items, participants were probed on the appropriateness of a 24-hour recall period to assess whether a longer time period, such as a week, could be implemented. When probed, each participant stated that they

experienced day-to-day variation in the impact concepts included and therefore the use of a longer recall period was not recommended.

HSSID

The final HSSID is a self-administered eDiary, which measures HS symptoms and impacts during the previous 24 hours. The HSSID comprises 11 items; five relating to symptoms of HS (lesion-related pain, lesion-related itching, lesion drainage, odour, and physical fatigue) and six relating to impacts (ability to walk, ability to move [other than walking], sleep disturbance, time spent with other people, negative impact on emotions, and ability to complete work) (**Appendix S3**).

Psychometric evaluation of the HSSID

Baseline patient characteristics

Overall, 233 patients in SUNSHINE and 245 patients in SUNRISE were included in the psychometric analysis of the HSSID **(Table 4).** Most patients were female (SUNSHINE [62.7%]; SUNRISE [59.2%]); mean age was 36.1 and 37.2 years, and mean time since diagnosis was 8.6 and 9.2 years in SUNSHINE and SUNRISE, respectively.

Descriptive statistics

Daily responses (which were incorporated into a weekly score calculated as the average of the 7 daily scores; requiring at least 4 daily scores or the weekly score was recorded as missing) showed a general trend towards lower scores (improvement) from baseline to week 2 and week 2 to week 16 in SUNSHINE and SUNRISE. The greatest mean (SD) changes for weekly HSSID item scores from baseline to week 16 were for the items 'worst pain' (SUNSHINE, −1.2 [2.2];

SUNRISE, −1.1 [2.3]) and 'worst itching' (SUNSHINE, −1.2 [2.1]; SUNRISE, −1.1 [2.3]) **(Table S2).**

Distributions of weekly mean scores did not show floor or ceiling effects across any of the HSSID items. This provided evidence that the proposed weekly scores had sufficient ranges to show detriment and improvement, given that a ceiling effect occurs when a large proportion of the sample provides responses using the highest/best score category, leaving limited room for score increase/improvement, and a floor effect occurs when a large proportion of the sample provides responses using the lowest/worst score category, leaving limited room for score decrease/deterioration.

Structure

Inter-item correlations among daily HSSID items at baseline (week 0), week 2, and week 16 were generally similar across timepoints in SUNSHINE and SUNRISE **(Tables S3 and S4).** The correlations among the symptom items all exceeded 0.30. A small number of correlations exceeded 0.80, which could indicate redundancy; lesion drainage and odour from drainage were highly associated, although not exactly redundant. Correlations among the impact items ranged from large to very large (using the criteria outlined in **Table 1**) and correlations between symptoms and impacts items were moderate to large. The analysis did not identify any items that needed to be removed due to redundancy. Correlations among the weekly item scores were generally similar to the daily item scores.

Test-retest reliability

Test-retest reliability was conducted in both the overall sample and in two separate stable subsamples identified by (1) stable (equivalent) PGI-S scores at baseline and week 2, and (2) by a 'No Change' PGI-C week 2 response. Test-retest statistics all exceeded the criterion of 0.70, indicating adequate reliability in both the overall sample and stable subsamples. The

greatest intraclass correlation coefficients (ICCs) were for worst fatigue item across SUNSHINE and SUNRISE and across the overall and stable subsamples (ICC range 0.90–0.96) **(Table S5).**

Construct validity

The HSSID items and supporting measures describing similar symptoms or impacts were anticipated to be more strongly associated versus items describing less similar symptoms or impacts; all hypotheses predicted at least moderate (r≥0.30) correlations between HSSID items and supporting measures. Hypotheses were met, except for two assessments; in these cases, the failures were both in SUNSHINE and the misses were not large (r=0.28 for symptom item on worst lesion-related itching; r=0.29 for impact item on ability to complete work) **(Table S6).**

Known group validity

The known group analysis demonstrated that the hypothesis of statistically significant group mean differences was met, except in one case (HS-PGA group; worst fatigue item in SUNRISE). The analysis showed that group means were appropriately ordered among the known groups, except for three cases (HS-PGA group; HSSID worst lesion-related pain, worst lesion-related itching, and worst fatigue items in SUNRISE).

Ability to detect change

A priori hypotheses were defined based on change from baseline to week 16 according to external support variables (PGI-S, PGI-C, HiSCR, AN50, DLQI, and HS-PGA). In SUNSHINE, all HSSID item scores were responsive to change when change groups were defined by patient-reported measure scores (PGI-S [*P* <0.0001 to 0.0002], PGI-C [*P* <0.0001 to 0.0028], and DLQI symptoms and feelings [*P* <0.0001 to 0.0015]) and the primary clinical endpoint (HiSCR [*P* <0.0001 to 0.0270]) **(Table S7).** In SUNRISE, all HSSID scores detected change identified by PGI-C score (*P* <0.0001 to 0.0261) and change in DLQI symptoms and feelings score (*P*

<0.0001 to 0.0099). HiSCR score-related changes were identified by 9 of the 11 HSSID item scores (exceptions were lesion drainage and drainage odour) **(Table S8).**

Meaningful change threshold estimations

The anchor method is often used to establish meaningful within-patient change thresholds. In this type of analysis, an external reference is used to examine the relationship between scores. In this study, the analysis to confirm adequate association between target scores and candidate clinical anchors (including PGI-S changes [between baseline and week 16], week 16 PGI-C scores, patients achieving HiSCR, and AN50 at week 16) and to confirm alignment between mean change group scores and candidate anchor change group definitions to support their appropriateness for serving as anchors, detected deficiencies with the functioning of key candidate anchor measures. These included insufficient item change score correlations (HiSCR and AN50); in addition, some HSSID items did not exhibit ordered means/medians across the anchor change groups. Following review of the correlations, descriptive statistics, empirical cumulative distribution functions, and probability density functions, the evidence fully supported estimating anchor-based meaningful change thresholds for the worst-lesion–related pain item only.

Discussion

Patients with HS experience a substantial negative impact on their lives.[13,14] HS-specific PRO measures capture the patient experience of living with HS when evaluating treatment effects in clinical trials. No suitable measures were validated or readily available for use when the SUNSHINE and SUNRISE trials were planned and initiated, therefore, the HSSID was developed for use in these trials.

Recognition of the need for HS-specific PRO measures has resulted in the recent development of a number of HS-specific tools, for which the limitations and strengths have been described.[21,23] Additional measures include the HS Patient Global Assessment of QoL (HS PtGA),[24] a single-item PRO for HS-specific HRQoL; the nine-item Hidradenitis Suppurativa Symptom Assessment (HSSA); 17-item Hidradenitis Suppurativa Impact Assessment (HSIA);[25] 17-item HiSQOL,[26] including three subdomains; and the 23-item QoL in HS (QoL-HS) questionnaire.[27] The HiSQOL instrument has a 7-day recall period and includes 17 items that are grouped into symptom, psychosocial and functional domains.[26] In contrast, the HSSID has a 24-hour recall period and includes 11 items categorised according to symptoms and impacts. Both instruments share several core items, such as those addressing HS symptoms and the impact on walking, sleep, and work/study – underscoring the relevance of these concepts to people living with HS. However, they also differ in scope: the HiSQOL includes items on sexual activity/desire, while the HSSID uniquely captures fatigue and social interaction. The HSSID was purpose-built to assess HS symptoms and patient-perceived impact of secukinumab treatment in the context of the SUNSHINE and SUNRISE trials, and its development preceded the publication of the HiSQOL.

The findings of the psychometric evaluation in this current study provided support for test-retest reliability, construct validity, discriminate validity (known groups), and the ability to detect change (responsiveness) in the HSSID.

A strength of the study was the robust development process and psychometric analysis conducted with the rigor described in regulatory guidance. A limitation of the study was the performance of the anchors in the anchor-based threshold estimation. The distal relationship between these anchors and the target scores made estimation of the meaningful change thresholds in this study challenging. The proposed global anchors, which were clinical measures, were not aligned well enough with the individual constructs underlying the target

scores to be used to define meaningful change in the different symptom items. In other words, the most suitable available candidate anchors invoked general constructs such as the patient's HS 'symptoms' or 'overall status', but a strong association between these more general measures with specific individual HS symptom items did not materialise in this study. Change in pain appeared to drive the more general assessments of change but did not always align closely with other specific symptom change. Consideration of the related qualitative results revealed that most patients considered worst lesion-related pain to be the most important symptom when considering their overall HS severity, a finding that is consistent with previous literature and the limitations observed for the meaningful change analyses.[7,9,19] It should be noted that the HSSID was developed and evaluated in a population of adult patients with moderate to severe HS; the concepts of importance may be different for patients who have mild HS. Further, the HSSID was developed for use in clinical trials; while it is relevant for use in clinical practice, its performance was not evaluated outside of the clinical trial setting.

In conclusion, the HSSID adequately and appropriately assesses the symptoms and impacts of HS in adult patients. The HSSID demonstrated strong cross-sectional psychometric measurement properties for all HSSID items. The HSSID can be used by patients with moderate to severe HS in a clinical trial setting. Further research is warranted using more specific anchors to better define meaningful change for the different symptom and impact items.

References

1 Goldburg SR, Strober BE, Payette MJ. Hidradenitis suppurativa: Epidemiology, clinical presentation, and pathogenesis. *J Am Acad Dermatol* 2020; **82**: 1045-58.

2 Sabat R, Jemec GBE, Matusiak L *et al.* Hidradenitis suppurativa. *Nat Rev Dis Primers* 2020; **6**: 18.

3 Scholl L, Hessam S, Bergmann U *et al.* Surgical Treatment of Sinus Tracts and Fistulas in Perianal Hidradenitis Suppurativa. *J Cutan Med Surg* 2018; **22**: 239-41.

4 Jemec GB. Clinical practice. Hidradenitis suppurativa. *N Engl J Med* 2012; **366**: 158-64.
5 Ingram JR, Bettoli V, Espy JI *et al.* Unmet clinical needs and burden of disease in hidradenitis suppurativa: real-world experience from EU5 and US. *J Eur Acad Dermatol Venereol* 2022; **36**: 1597-605.
6 Marvel J, Vlahiotis A, Sainski-Nguyen A *et al.* Disease burden and cost of hidradenitis suppurativa: a retrospective examination of US administrative claims data. *BMJ Open* 2019; **9**: e030579.
7 Smith HS, Chao JD, Teitelbaum J. Painful hidradenitis suppurativa. *Clin J Pain* 2010; **26**: 435-44.
8 Patel ZS, Hoffman LK, Buse DC *et al.* Pain, Psychological Comorbidities, Disability, and Impaired Quality of Life in Hidradenitis Suppurativa [corrected]. *Curr Pain Headache Rep* 2017; **21**: 49.
9 Matusiak L, Szczech J, Kaaz K *et al.* Clinical Characteristics of Pruritus and Pain in Patients with Hidradenitis Suppurativa. *Acta Derm Venereol* 2018; **98**: 191-4.
10 Hasan SB, Gendra R, James J *et al.* Pain measurement in painful skin conditions and rheumatoid arthritis randomized controlled trials: a scoping review to inform pain measurement in hidradenitis suppurativa. *Br J Dermatol* 2022; **187**: 846-54.
11 Thorlacius L, Cohen AD, Gislason GH *et al.* Increased Suicide Risk in Patients with Hidradenitis Suppurativa. *J Invest Dermatol* 2018; **138**: 52-7.
12 Machado MO, Stergiopoulos V, Maes M *et al.* Depression and Anxiety in Adults With Hidradenitis Suppurativa: A Systematic Review and Meta-analysis. *JAMA Dermatol* 2019; **155**: 939-45.
13 McKenzie SA, Harview CL, Truong AK *et al.* Physical symptoms and psychosocial problems associated with hidradenitis suppurativa: correlation with Hurley stage. *Dermatol Online J* 2020; **26**.
14 Kimball AB, Kirby J, Ingram JR *et al.* Burden of Hidradenitis Suppurativa: A Systematic Literature Review of Patient Reported Outcomes. *Dermatol Ther (Heidelb)* 2024; **14**: 83-98.
15 Mortimore AM, Bullen A, McMeniman EK. The impact of hidradenitis suppurativa on quality of life is worse than inflammatory bowel disease and myocardial infarction. *Australas J Dermatol* 2022; **63**: 505-8.
16 Balieva F, Kupfer J, Lien L *et al.* The burden of common skin diseases assessed with the EQ5D: a European multicentre study in 13 countries. *Br J Dermatol* 2017; **176**: 1170-8.

17 Yuan JT, Naik HB. Complications of hidradenitis suppurativa. *Semin Cutan Med Surg* 2017; **36**: 79-85.
18 Molina-Leyva A, Cuenca-Barrales C. Pruritus and Malodour in Patients with Hidradenitis Suppurativa: Impact on Quality of Life and Clinical Features Associated with Symptom Severity. *Dermatology* 2020; **236**: 59-65.
19 Thorlacius L, Ingram JR, Villumsen B *et al.* A core domain set for hidradenitis suppurativa trial outcomes: an international Delphi process. *Br J Dermatol* 2018; **179**: 642-50.
20 Kimball AB, Jemec GBE, Alavi A *et al.* Secukinumab in moderate-to-severe hidradenitis suppurativa (SUNSHINE and SUNRISE): week 16 and week 52 results of two identical, multicentre, randomised, placebo-controlled, double-blind phase 3 trials. *Lancet* 2023; **401**: 747-61.
21 Chernyshov PV, Zouboulis CC, Tomas-Aragones L *et al.* Quality of life measurement in hidradenitis suppurativa: position statement of the European Academy of Dermatology and Venereology task forces on Quality of Life and Patient-Oriented Outcomes and Acne, Rosacea and Hidradenitis Suppurativa. *J Eur Acad Dermatol Venereol* 2019; **33**: 1633-43.
22 Administration USDoHaHSFaD. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. In. 2009.
23 Kaur AP, Laing ME, Griffin L *et al.* Quality of life in Hidradenitis Suppurativa (Acne Inversa): A scoping review. *Skin Health Dis* 2023; **3**: e214.
24 Kirby JS, Hereford B, Thorlacius L *et al.* Validation of global item for assessing impact on quality of life of patients with hidradenitis suppurativa. *Br J Dermatol* 2021; **184**: 681-7.
25 Kimball AB, Sundaram M, Banderas B *et al.* Development and initial psychometric evaluation of patient-reported outcome questionnaires to evaluate the symptoms and impact of hidradenitis suppurativa. *J Dermatolog Treat* 2018; **29**: 152-64.
26 Kirby JS, Thorlacius L, Villumsen B *et al.* The Hidradenitis Suppurativa Quality of Life (HiSQOL) score: development and validation of a measure for clinical trials. *Br J Dermatol* 2020; **183**: 340-8.
27 Otten M, Augustin M, Blome C *et al.* Measuring Quality of Life in Hidradenitis Suppurativa: Development and Validation of a Disease-specific Patient-reported Outcome Measure for Practice and Research. *Acta Derm Venereol* 2023; **103**: adv00859.

Figure Legends

Figure 1. Findings from the patient concept elicitation interviews on the most bothersome symptoms of HS (*N*=8)

*The total for this category is 7 because one patient reported an issue that was not a sign or symptom (costs associated with purchasing bandages).

HS, hidradenitis suppurativa.

Table 1. Analytical methods used to evaluate the psychometric properties of the HSSID

Analysis	Purpose	Brief description of key methods
Descriptive statistics	• Summarize sample characteristics • Assess the use and appropriateness of response scales and identify possible floor and ceiling effects (defined as observed endorsements at twice the expected probability in an extreme category than would be expected under a uniform distribution (i.e. ≥18% in an extreme category for an 11-point, 0-to-10 rating item and ≥40% or ≥50% for 5-item or 4-item ordinal response items, respectively) • Assess missing data	• Key daily HSSID response frequencies • Key weekly item score statistics (HSSID items) • Key support variable statistics

Structure	• Evaluate the correlations among the HSSID items	• Daily and weekly inter-item correlations*
		• Thresholds:
		  ○ Moderate correlation: ≥0.30 to <0.50
		  ○ Large correlation: ≥0.50 to <0.80

		○ Very large correlation: ≥0.80 •
Test-retest reliability	• Assess agreement of scores to ensure that HSSID scores are consistent across time when no change has occurred	• 2-way mixed-effects ANOVAs with absolute agreement for single measures were used to compute ICC estimates of test-retest reliability using data for baseline and week 2 for each item ○ Estimated using the full sample and stable subsamples ○ ICC values of ≥0.70 indicated adequate reliability
Construct validity	• Assess whether HSSID scores measure what each item is expected (hypothesized) to measure	• Correlations (Pearson/polychoric) between HSSID scores and other study measures (e.g. DLQI domain scores, WPAI-SHP activity domain scores, and mHSS) • The *a priori* hypothesis regarding the directions and magnitudes of correlations was that positive correlations are predicted between the HSSID scores and the DLQI, EQ-5D-3L, WPAI-SHP, HS-PGA, and mHSS scores • Moderate-to-strong correlations hypothesized between HSSID item scores and support measures are presented in **Table S1** • The test of construct validity for the HSSD scores was dependent on meeting levels of pre-specified correlation: ○ ≥0.50: strong ○ 0.30–0.49: moderate ○ 0.10–0.29: small
Known groups validity	• Evaluate whether HSSID scores can distinguish between groups that are hypothesized to differ	• ANOVA by groups defined using other study measures (e.g. HiSCR, HS-PGA, PGI-S, and EQ-5D-3L Mobility, Usual activities, and Anxiety/Depression domains)

Ability to detect change (sensitivity to change)	• Evaluate whether HSSID scores can detect change where change is expected (hypothesized)	• ANOVA by groups of known change ○ Patients reporting more improvement based on the grouping variable were hypothesized to have more negative (i.e., improved) HSSID change scores • Correlation between change in HSSID scores and other study change measures (e.g. those related to DLQI symptoms domain and HS-PGA change score groups, and HiSCR and PGI-C week 16 score groups)
Meaningful within-patient change (meaningful improvement, threshold for improvement)	• Develop thresholds of meaningful within-patient change of HSSID scores	• Anchor-based method using other study measures as anchors (descriptive statistics; CDF and PDF plots with 95% CIs) • Candidate anchors: PGI-S, PGI-C, HiSCR, AN50 • ROC analysis estimates • Distribution-based methods: Half-SD and standard error of measurement

*Suggested minimum correlation value=0.30; specified correlation value to identify redundancy=0.80.

AN50, ≥50% reduction in abscess and inflammatory nodule count; ANOVA, analysis of variance; CDF, cumulative distribution function; CI, confidence interval; DLQI, Dermatology Life Quality Index; EQ-5D-3L, European Quality of Life 5-dimension 3-level; HiSCR, Hidradenitis Suppurativa Clinical Response; HSSID, Hidradenitis Suppurativa Symptom and Impact diary; HS-PGA, Hidradenitis Suppurativa Physician's Global Assessment; ICC, intraclass correlation coefficient; mHSS, modified Hidradenitis Suppurativa Score; PDF, probability density function; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; ROC, receiver-operating characteristic; SD, standard deviation; WPAI-SHP, Work Productivity and Activity Impairment – Specific Health Problem.

Note: The clinical trial study design did not incorporate a test-retest time period. Baseline and week 2 were selected and stable subsamples were identified to provide data for the test-retest evaluation. In addition, the evaluation of internal consistency and factor analysis was not pursued given that the scales were formative.

Table 2. Demographic and clinical characteristics of patients in the concept elicitation and cognitive debriefing stages of the HSSID development*

Characteristic	Concept elicitation (*N*=8)	Cognitive debrief interviews		
		Round 1 (*N*=6)	Round 2 (*N*=6)	Total (*N*=12)
Age in years, mean (range)	33.9 (25–41)	34.7 (22–49)	36.2 (21–59)	35.5 (21–59)
Sex, n (%)				
Male	1 (12.5)	0 (0.0)	1 (16.7)	1 (8.3)
Female	7 (87.5)	6 (100)	5 (83.3)	11 (91.7)
Race/ethnicity, n (%)				
White	5 (62.5)	5 (83.3)	4 (66.7)	9 (75.0)
Black	2 (25.0)	1 (16.7)	1 (16.7)	2 (16.7)
Indian	1 (12.5)	–	–	–
Hispanic	–	0 (0.0)	1 (16.7)	1 (8.3)
Highest level of education, n (%)				
High school or lower	1 (12.5)	2 (33.3)	1 (16.7)	3 (25.0)
Some college	2 (25.0)	1 (16.7)	3 (50.0)	4 (33.3)
College	3 (37.5)	1 (16.7)	0 (0.0)	1 (8.3)
Postgraduate	2 (25.0)	2 (33.3)	2 (33.3)	4 (33.3)
Employment				
Full-time	5 (62.5)	4 (66.7)	1 (16.7)	5 (41.7)
Part-time	0 (0.0)	1 (16.7)	3 (50.0)	4 (33.3)
Not employed	3 (37.5)	1 (16.7)	2 (33.3)	3 (25.0)
Time since diagnosis, years				
Mean	9.9	11.2	11.3	11.3
Range	0.5–19	5–22	4–20	4–22
Hurley stage, n (%)				
Stage II	2 (25.0)	1 (16.7)	1 (16.7)	2 (16.7)
Stage III	6 (75.0)	5 (83.3)	5 (83.3)	10 (83.3)
Currently using biologics, n (%)				
Yes	2 (25.0)	3 (50.0)	2 (33.3)	5 (41.7)
No	6 (75.0)	3 (50.0)	4 (66.7)	7 (58.3)

*Different participants undertook the concept elicitation and cognitive debriefing interviews.
HSSID, Hidradenitis Suppurativa Symptom and Impact Diary; N, number of patients in group; n, number of patients with outcome.

Table 3. Selected verbatim patient quotes from the concept elicitation interviews related to the most bothersome symptoms of HS

Symptom	Verbatim patient quotes
Pain	*"Because it affected my everyday living. If I was in too much pain, I would have to not participate in things. It affected me emotionally. Um…I wasn't as social as I was when I wasn't flaring."*
	"Just because I can't get away from it. It's just something that…I'm in pain every single day of my life."
	"It's difficult to find, first of all, physicians that understand how significant the pain is. And then when nobody really understands the disease, then nobody really understands what's going on. It seems to me like the pain is atrocious, but then it's also downplayed by everyone else, like you're making too big of a deal out of it. It's just a form of acne, when it's not. And so, the pain first of all, it limits movement or any activities I can be a part of, I have to cancel plans often due to the pain."
Draining	*"You have this pus and blood and all that. You have to cover it. It takes a lot of time. Changing the bandages. It's not like you…it's just all of it. It's time consuming."*
	"Because it's something your body is exiting out and you have to take care of it. And it's not something like sweat. It's, yeah, you just take a shower and you feel clean. But this, it's natural substance on your skin. You can feel when it dries up, its foul smell."
	"If that [drainage] wasn't there, this disease [could] be a lot [more] controllable. Because now you're not worried about going into public and your shirt getting wet from the pus and you're looking at your shirt. You sat down and you're not constantly checking out your buttocks to see if there's a blood stain or anything, and you're walking around because it's embarrassing."
General appearance (discoloration, pigmentation, scarring)	*"So, the discoloration, you can have a cyst or a boil, and it's over and done with 7 days tops. Then it leaves a discoloration and it leaves scarring that lasts for years."*
	"It's because…like, if I want to wear a bathing suit. I'm not comfortable in a bathing suit because I have scars all on my thighs and on my underarms."
Restriction due to pain	*"If the soreness and the tenderness wasn't there, it'd be a lot easier because then you can sit down. You can go to sleep. You can play sports."*
Fatigue	*"I would say that the fatigue affects me the most just because I've got two kids, and they notice that I'm tired all the time."*

Bleeding	*"Because I bleed everywhere. When I go to the bathroom, I bleed all over the toilet. I stain my clothes. My friend [laughter], my best friend was worried that I was going to bleed on her new couch. I can't wear colored leggings because I'm going to bleed on them and they're going to see it."*
Burning sensation	*"For me it would be the burning. That deep burning sensation when it's starting to form."*

1 HS, hidradenitis suppurativa.

Table 4. Baseline patient characteristics of the psychometric analysis population in the SUNSHINE and SUNRISE trials

Characteristic	SUNSHINE (*N*=233)	SUNRISE (*N*=245)
Age in years, mean (SD)	36.1 (11.9)	37.2 (11.5)
Sex, n (%)		
Male	87 (37.3)	100 (40.8)
Female	146 (62.7)	145 (59.2)
Race, n (%)		
American Indian or Alaska Native	1 (0.4)	0 (0.0)
Asian	2 (0.9)	3 (1.2)
Black or African American	30 (12.9)	32 (13.1)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.4)
White	198 (85.0)	207 (84.5)
Multiple	2 (0.9)	2 (0.8)
Country, n (%)		
Germany	62 (26.6)	67 (27.3)
Spain	26 (11.2)	26 (10.6)
France	56 (24.0)	69 (28.2)
Italy	9 (3.9)	10 (4.1)
United States	80 (34.3)	73 (29.8)
Time since diagnosis of HS, years, mean (SD)	8.6 (8.4)	9.2 (8.3)
Hurley stage, n (%)		
Stage I	16 (6.9)	5 (2.0)
Stage II	136 (58.4)	142 (58.0)
Stage III	81 (34.8)	98 (40.0)
Weight, kg, mean (SD)	99.0 (25.1)	96.3 (23.8)

HS, hidradenitis suppurativa; N, number of patients in group; n, number of patients with outcome; SD, standard deviation.

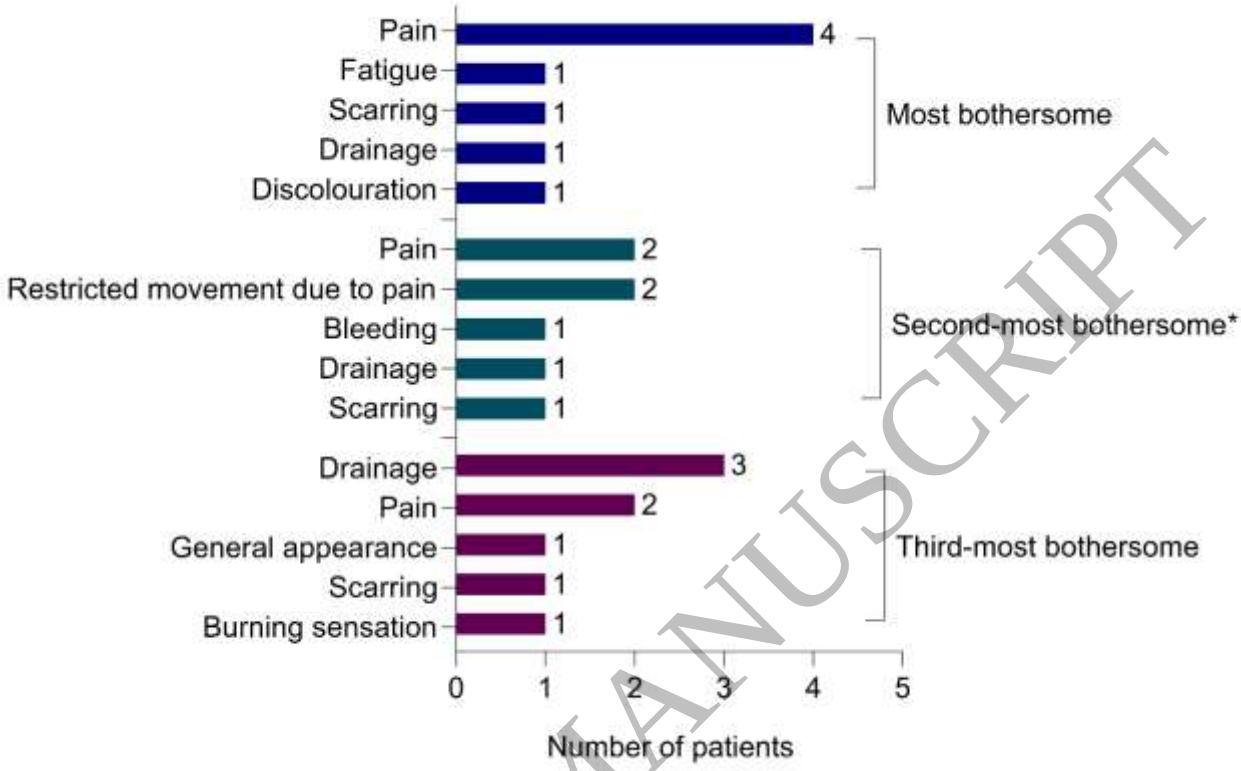

Figure 1
168x111 mm (x DPI)